The Chemistry of Quinonoid Compounds, Vol. II
Edited by S. Patai and Z. Rappoport

The chemistry of the **quinonoid compounds** Volume 2

Part 1

THE CHEMISTRY OF FUNCTIONAL GROUPS

A series of advanced treatises under the general editorship of Professor Saul Patai

The chemistry of alkenes (2 volumes)
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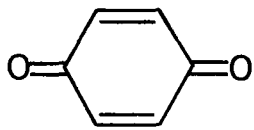

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Edited by

SAUL PATAI

ZVI RAPPOPORT

The Hebrew University, Jerusalem

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SAUL PATAI
ZVI RAPPOPORT

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The Chemistry of the Metal–Carbon Bond (four volumes)
The Chemistry of Peroxides
The Chemistry of Organic Se and Te Compounds Vol. 1
The Chemistry of the Cyclopropyl Group (two parts)
The Chemistry of Organic Se and Te Compounds Vol. 2

Titles in press

The Chemistry of Sulphones and Sulphoxides
The Chemistry of Organosilicon Compounds
The Chemistry of Enones
Supplement A2: The Chemistry of the Double-Bonded Functional Groups, Volume 2.

Titles in Preparation

The Chemistry of Enols
The Chemistry of Sulphinic Acids, Esters and Derivatives
The Chemistry of Sulphenic Acids and Esters.

Advice or criticism regarding the plan and execution of this series will we welcomed by the Editor.

The publication of this series would never have started, let alone continued, without the support of many persons. First and foremost among these is Dr Arnold Weissberger, whose reassurance and trust encouraged me to tackle this task. The efficient and patient cooperation of several staff-members of the Publisher also rendered me invaluable aid (but unfortunately their code of ethics does not allow me to thank them by name). Many of my friends and colleagues in Israel and overseas helped me in the solution of various major and minor matters, and my thanks are due to all of them, especially to Professor Z. Rappoport. Carrying out such a long-range project would be quite impossible without the non-professional but none the less essential participation and partnership of my wife.

The Hebrew University
Jerusalem, ISRAEL SAUL PATAI

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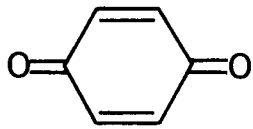

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The Chemistry of Amidines and Imidates
The Chemistry of the Hydrazo, Azo and Azoxy Groups (*two parts*)
The Chemistry of Cyanates and their Thio Derivatives (*two parts*)
The Chemistry of Diazonium and Diazo Groups (*two parts*)

The Chemistry of the Carbon–Carbon Triple Bond (*two parts*)
Supplement A: The Chemistry of Double-bonded Functional Groups (*two parts*)
The Chemistry of Ketenes, Allenes and Related Compounds (*two parts*)
Supplement B: The Chemistry of Acid Derivatives (*two parts*)
Supplement C: The Chemistry of Triple-Bonded Functional Groups (*two parts*)
Supplement D: The Chemistry of Halides, Pseudo-halides and Azides (*two parts*)
Supplement E: The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulphur Analogues (*two parts*)
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The Chemistry of the Metal–Carbon Bond (*four volumes*)
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Titles in press

The Chemistry of Sulphones and Sulphoxides
The Chemistry of Organosilicon Compounds
The Chemistry of Enones
Supplement A2: The Chemistry of the Double-Bonded Functional Groups, Volume 2.

Titles in Preparation

The Chemistry of Enols
The Chemistry of Sulphinic Acids, Esters and Derivatives
The Chemistry of Sulphenic Acids and Esters.

Advice or criticism regarding the plan and execution of this series will we welcomed by the Editor.

The publication of this series would never have started, let alone continued, without the support of many persons. First and foremost among these is Dr Arnold Weissberger, whose reassurance and trust encouraged me to tackle this task. The efficient and patient cooperation of several staff-members of the Publisher also rendered me invaluable aid (but unfortunately their code of ethics does not allow me to thank them by name). Many of my friends and colleagues in Israel and overseas helped me in the solution of various major and minor matters, and my thanks are due to all of them, especially to Professor Z. Rappoport. Carrying out such a long-range project would be quite impossible without the non-professional but none the less essential participation and partnership of my wife.

The Hebrew University
Jerusalem, ISRAEL SAUL PATAI

Contents

The Chemistry of Quinonoid Compounds, Vol. II
Edited by S. Patai and Z. Rappoport

CHAPTER 1

General and theoretical aspects of quinones

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LIST OF ABBREVIATIONS

A. Names of Chemical Compounds

DDQ	2,3-dicyano-5,6-dichlorobenzoquinone
MBQDM	*meta*-benzoquinodimethane
MBQM	*meta*-benzoquinomethane
NMP	*N*-methylphenazine
OBQ	*ortho*-benzoquinone
OQDI	*ortho*-quinone diimine
OQDM	*ortho*-quinodimethane
OQI	*ortho*-quinone imine
OQM	*ortho*-quinomethane
PBQ	*para*-benzoquinone
PQDI	*para*-quinone diimine
PQDM	*para*-quinodimethane
PQI	*para*-quinone imine
PQM	*para*-quinomethane
TCNQ	tetracyanoquinodimethane
TTF	tetrathiofulvalene

B. Names of Experimental and Theoretical Methods

AO	atomic orbital
MO	molecular orbital
SCF	self-consistent field
ΔSCF	difference in SCF energy between different species or different states of a given species
CBL	constant bond length
VBL	variable bond length
REPA	resonance energy per atom
REPE	resonance energy per electron
HOMO	highest occupied molecular orbital
LUMO	lowest unoccupied molecular orbital
LCAO	linear combination of atomic orbitals
FMO	frontier molecular orbital
CI	configuration interaction
STO-3G	minimum Gaussian basis set used in *ab initio* calculations
4-31G	medium-sized Gaussian basis set used in *ab initio* calculations
CNDO	semi-empirical molecular orbital methods
MNDO	
INDO	
MINDO	
HAM	
HMO	
EHMO	
PPP	
IR	infrared
UV	ultraviolet
EPR	electron paramagnetic resonance
NMR	nuclear magnetic resonance
PES	photoelectron spectroscopy

VTPES	variable temperature electron spectroscopy
ETS	electron transmission spectroscopy
ENDOR	electron nuclear double resonance

I. INTRODUCTION

Molecules exhibiting a quinonoid structure constitute a large and important class in the chemistry of organic compounds. Extensive treatments of chemical and physical properties of quinonoid compounds are available in the literature. The two volumes on these compounds edited by Patai[1] give a broad survey of the state-of-the-art in the field up to 1974, and the bibliography in the series *Houben-Weyl* also has two volumes dedicated to quinones[2].

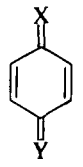
We will focus on contributions to the field that have appeared after the publication of the first relevant volume in this series[1]. Furthermore our presentation will put emphasis on general and theoretical aspects of the chemistry of quinonoid compounds. For detailed discussions of particular aspects of specific groups within the family of these compounds, we refer to subsequent chapters of the present volume.

The outline of our presentation will be the following. In section II we give a brief survey of the available experimental data on the molecular structures of quinonoid systems. Section III contains a short discussion of symmetries and orbital topologies for the appropriate symmetry groups (D_{2h} and C_{2v}). In Section IV we focus on physical properties of molecular ground states, and discuss explicitly resonance energies and aromaticity, thermodynamic and kinetic stabilities. We also include a brief discussion of electron affinities, and a comparative study of open and bicyclic forms in the case of *ortho*-compounds. In this section we also touch briefly on the problem related to the description of the *meta*-form, referring to Chapter 10 for a full treatment of this class of compounds. A few comments on molecular polarizabilities are included. In Section V we give a short presentation of certain aspects of the spectroscopy of some of the quinonoid compounds focusing on the interesting problem of Koopmans and shake-up states which are of vital importance in the interpretation of photoelectron spectra (PES). For a full account of this topic we refer to Chapter 5 of this volume. However, UV and IR spectra are also discussed to some extent, the main theme being current interpretations of the properties of the near-degenerate $n\pi^*$ states of *para*-benzoquinone (PBQ). In Section VI we give some brief comments on current models used in the interpretation of cycloaddition reactions, referring to separate chapters for comprehensive presentations of chemical reactions in general. Finally in Section VII we describe some of the current contributions to polymerization reactions.

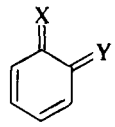
We emphasize that our list of references does not pretend to be exhaustive. In the selection of papers to be quoted we have adopted the following guidelines: (1) as a rule attention is given mainly to recent papers; (2) the papers should allude to theoretical aspects of the molecular properties and not be of a purely technical nature; (3) extensive lists of papers referring to any particular special issue should be looked for in the pertinent chapters of this volume.

The types of compounds included in our treatment has been limited. We have put emphasis on molecules containing one benzene ring, and have included naphtho- and anthraquinones only when demanded in comparative discussions. The same applies to other derivatives of compounds containing a single benzene ring.

The main theme of our presentation will be a discussion of chemical and physical properties of the *para*-compounds (**1a–1g**) and the corresponding *ortho*-compounds (**2a–2g**):



(1)

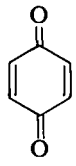


(2)

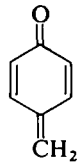
where

Y \ X	O	CH_2	NH	S
O	a	b	d	f
CH_2		c		
NH			e	
S				g

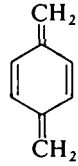
The entries in the table above indicate compounds that have been synthesized and/or detected as highly reactive intermediates. We have adopted the following names in full and abbreviated forms for the *para*-compounds.



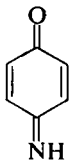
p-benzoquinone
PBQ
(**1a**)



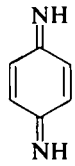
p-quinomethane
PQM
(**1b**)



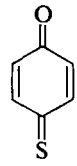
p-quinodimethane
PQDM
(**1c**)



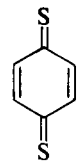
p-quinone imine
PQI
(**1d**)



p-quinone diimine
PQDI
(**1e**)



monothio-PBQ
(**1f**)



dithio-PBQ
(**1g**)

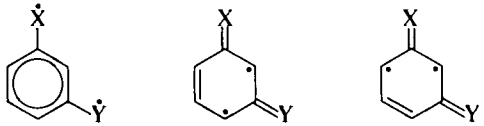
For the *ortho*-compounds (**2a–2g**) and the *meta*-compounds (**3a–3g**) a completely analogous naming and labelling system has been adopted (the letter P substituted by O and M respectively).

Of the compounds listed above PBQ (**1a**) and OBQ (**2a**) are comparatively stable solids at room temperature[3–5]. The remaining species are very unstable and highly reactive. PQM (**1b**) has been produced by flash thermolysis and isolated as a solid film at 77 K[6],

whereas the isomer OQM (**2b**) has been trapped as a solid at liquid nitrogen temperature[7]. More recently this molecule has also been detected in the vapour phase by the VTPES technique[8]. The hydrocarbon PQDM (**1c**) was known only as a reactive intermediate[9,10] until it was isolated in the solid state at 77 K[11]. The other isomer OQDM (**2c**) has not been isolated but observed in rigid glass at 77 K as a result of photolysis[12–14] and trapped in an argon matrix in the temperature range 8–30 K[15]. It has also been postulated to occur as an intermediate in a sonochemical reaction in solution at room temperature[16]. The unsubstituted species PQI (**1d**) and PQDI (**1e**) are rather unstable at room temperature[2], and their *ortho* counterparts OQI (**2d**) and OQDI (**2e**) are even more reactive. However, due to the basic character of the imine nitrogen, stable salts, e.g. chlorides, have been prepared and studied[17]. The sulphur-containing analogues monothio-PBQ (**1f**) and dithio-PBQ (**1g**) have recently been detected as products by pyrolysis[18].

The monothio OBQ (**2f**) has been postulated as a possible intermediate in the pyrolysis of 1,2,3-benzoxadithiole-2-oxide and 1,3-benzoxathiole-2-one[19]. MNDO calculations[19] indicate that the molecule has a strong preference for a closed shell polyene structure as opposed to a bicyclic isomer.

The *meta* analogues of (**1**) and (**2**) are expected to have diradical nature since no classical



(3)

Kekulé structure may be written for these cases. Some of their properties will be commented on briefly in Section IV. For a full account we refer to Chapter 10 in this volume.

II. GEOMETRICAL STRUCTURES

A limited number of experimental investigations on the molecular structures of quinones and quinonoidal systems are available.

PBQ has been studied by electron diffraction in the vapour phase[20–22], and by X-ray diffraction in the crystal[23]. The geometries obtained from the crystal data[23] and from the most recent electron diffraction data[22] are in very good agreement except for the C=C bond which is found to be somewhat longer in the vapour experiment (see Table 1). The

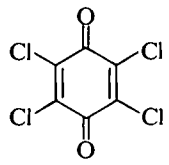
TABLE 1. Geometrical parameters for PBQ (**1a**) obtained by electron diffraction[22] and X-ray diffraction[23]

Parameter[a]	Electron diffr.[b]	X-ray diffr.[c]
C=O	1.225 ± 0.002	1.222 ± 0.008
C=C	1.344 ± 0.003	1.322 ± 0.008
C–C	1.481 ± 0.002	1.477 ± 0.006
C–H	1.089 ± 0.011	—
∠C(2)C(1)C(6)	118.1 ± 0.3	117.8 ± 0.6

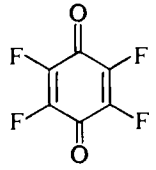
[a] Distances in Ångstrom, angles in degrees.
[b] Error estimates are 2σ.
[c] Error estimates are σ.

length of this bond is a good indicator to the possible importance of benzenoid contributions to the structure of this molecule. As revealed by the data in Table 1, the molecule displays a pronounced single-bond double-bond alternation both in the vapour phase and in the solid state, the C=C bond in the solid state being even shorter than the one in ethylene which is 1.336 Å[24]. These data indicate clearly that in using structural information as an indicator, this molecule has a typical quinonoid structure. In both investigations[22,23] the molecule was found to have a planar structure displaying D_{2h} symmetry.

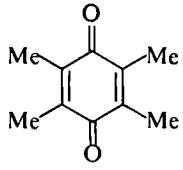
Also for derivatives of PBQ, structural investigations have confirmed an alternation between typical single and double carbon–carbon bonds in the ring. This is the case for reported studies of *p*-chloranil[25], *p*-fluoranil[26,27] and duroquinone[27,28].



p-chloranil

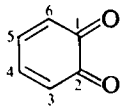


p-fluoranil



duroquinone

OBQ has been reported to exist in two different forms[4]. The red crystalline form that is stable at room temperature has been determined structurally by X-ray crystallographic methods[5]. This is the quinonoid form **2a** with pronounced single-bond double-bond alternation in the ring. However, as revealed by Table 2, two of the distinct single bonds in the ring are significantly longer than in PBQ. This is an indication of a slightly more



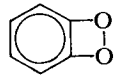
benzenoid-like structure of this molecule. The single bond C(1)–C(2) is found to be abnormally long considering trigonally hybridized carbon atoms. Moreover, small, but significant deformations from planarity have been observed in this molecule, the ring having adopted a slightly twisted boat conformation with the oxygen atoms displaced on either side of the mean ring plane[5].

TABLE 2. Geometrical parameters for OBQ obtained by X-ray diffraction[5]

Parameter[a]	Value[b]
C=O	1.220 ± 0.002
C=C	1.341 ± 0.002
C(1)–C(6)	1.469 ± 0.002
C(4)–C(5)	1.454 ± 0.004
C(1)–C(2)	1.552 ± 0.003

[a] Distances in Ångstrom.
[b] Error estimates are σ.

A microwave study of OBQ in the vapour phase did not result in a set of structural parameters[29]. However rotational constants derived from the spectrum were in agreement with the corresponding constants derived from the X-ray analysis[5]. This excludes the presence of significant amounts of the valence tautomer



in the vapour phase (*vide infra*).

Even for the very unstable PQDM, which has been detected as a reactive intermediate in the polymerization of the pyrolysis product of *p*-xylene[9] and of [2.2]paracyclophane[10], and which has been isolated in the solid state only at 77 K[11], electron diffraction data from the vapour phase are available[30]. The structural parameters obtained by this study do support a model having an alternation between long and short carbon–carbon bonds although not as pronounced as in the case of PBQ. The value reported for the long C–C bond is 1.451 Å as opposed to an average value of the C–C short bonds of 1.381 Å[30]. The latter value, which is larger than one corresponding to a normal double bond, demonstrates that PQDM, although having an alternating structure, is not composed of pure single-bond and double-bond fragments.

With the exception of the slight distortion of OBQ observed in the crystalline state[5], we may conclude that the structural information quoted above support the idea of planar quinonoid molecules. This has an important bearing on any discussion related to the distribution of the outer valence electrons, making possible a clear-cut distinction between σ and π electrons.

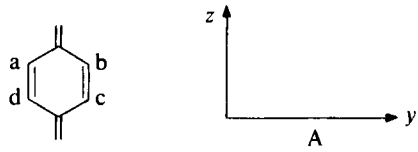
III. SYMMETRIES AND ORBITAL TOPOLOGIES

Referring to the experimental results discussed in the previous section we assume that the *para*-compounds (**1**) all belong to the symmetry group D_{2h} whereas the *ortho*- (**2**) and *meta*-compounds (**3**) are classified according to the group C_{2v}.

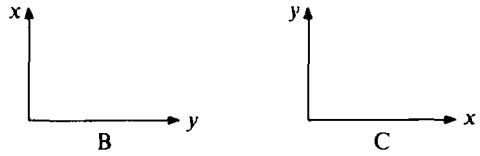
The atomic orbitals (AOs) constituting the basis for the π-electron system span the following representations in the group D_{2h}.

$a_u(\pi)$: a − b + c − d
$b_{2g}(\pi)$: a + b − c − d
$b_{1g}(\pi)$: a − b − c + d
$b_{3u}(\pi)$: a + b + c + d

where orientation of coordinate system and labelling of AOs are as follows.



If we employ the alternative coordinate systems also used in the literature

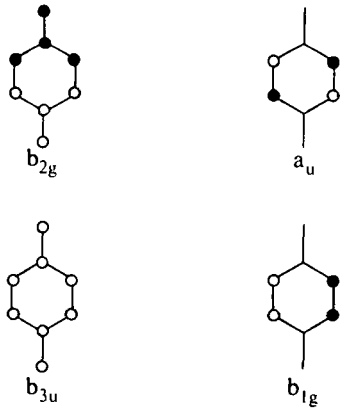


we obtain the following relations between the irreducible representations.

A	B	C
$a_u(\pi)$	$a_u(\pi)$	$a_u(\pi)$
$b_{2g}(\pi)$	$b_{2g}(\pi)$	$b_{3g}(\pi)$
$b_{1g}(\pi)$	$b_{3g}(\pi)$	$b_{2g}(\pi)$
$b_{3u}(\pi)$	$b_{1u}(\pi)$	$b_{1u}(\pi)$

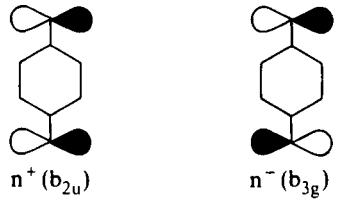
In our presentation we will label our symmetry orbitals according to reference system A.

Qualitative lobe diagrams giving the phases of the AOs in the different representations are shown below. It is worth mentioning that the exocyclic AOs of π symmetry do not



participate in the molecular orbitals (MOs) belonging to the representations b_{1g} and a_u.

In PBQ and analogues having the same symmetry (D_{2h}), AOs describing the exocyclic lone pairs constitute symmetry orbitals belonging to the representations $b_{2u}(n_1 + n_2)$ and $b_{3g}(n_1 - n_2)$:



This implies that for symmetry reasons the lone-pair orbitals are prevented from mixing with the π system. The lone-pair orbitals are usually labelled as:

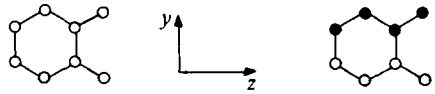
$$n^+ = \frac{1}{\sqrt{2}}(n_1 + n_2)\ b_{2u}$$

$$n^- = \frac{1}{\sqrt{2}}(n_1 - n_2)\ b_{3g}$$

By employing the rotated coordinate systems described above we obtain the following relations between the representations to which the lone-pair orbitals belong.

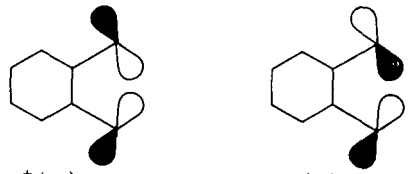
A	B	C
$b_{2u}(n)$	$b_{2u}(n)$	$b_{3u}(n)$
$b_{3g}(n)$	$b_{1g}(n)$	$b_{1g}(n)$

For the *ortho* and *meta* isomers the appropriate outer valence orbitals of π type span the following representations of the symmetry group C_{2v}.



b_1 a_2

where the *ortho* isomer has been chosen to illustrate the phases of the AOs. In the case of quinones and analogues having exocyclic lone pairs we obtain the following lobe diagrams:



$n^+(a_1)$ $n^-(b_2)$

where

$$n^+ = \frac{1}{\sqrt{2}}(n_1 + n_2)\ a_1$$

$$n^- = \frac{1}{\sqrt{2}}(n_1 - n_2)\ b_2$$

IV. PHYSICAL PROPERTIES OF GROUND STATES

Aspects of ground state properties relevant for molecular spectra are presented in Section V (*vide infra*).

A. Relative Stabilities

1. Aromaticity and resonance energies

A measure of the relative stabilities of the quinones and quinodimethanes would be their relative resonance energy or aromatic character. The former may be taken relative to hypothetical structures defined on the basis of experimental data. A study by Herndon[31] aiming at determining resonance energies on the basis of photoelectron spectra and graph theoretical methods gives us a starting point for this discussion, since both series of compounds have been investigated by the same procedure. In that work the arbitrariness in the choice of reference structure is avoided by using the same experimental data for parametrization of both the reference and parent system. For a series of hydrocarbon systems there is a reasonable agreement with experimental counterparts. A resonance energy of +0.10 eV for PQDM puts this species in the category of non-aromatic compounds. In a similar way a value of −0.27 eV is assigned to PBQ, placing it among the anti-aromatic compounds. It must be remarked, however, that the presence of a heteroatom does make an extra uncertainty here. This point was taken up in some detail in a previous chapter in this series[32].

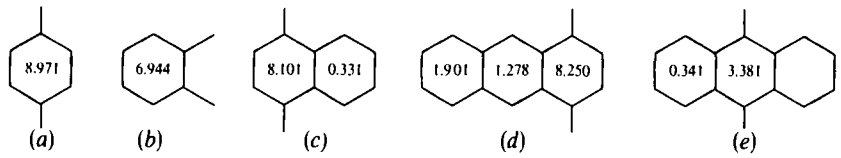
Gleicher[33] has calculated stabilities of various hydrocarbon quinonoid compounds following the method of Hess and Schaad[34, 35]. This method is based on the Hückel wave function, and a measure of the resonance energy, REPE (resonance energy per π electron) is obtained by introducing a localized structure characterized by standard bond energies for various carbon–carbon single and double bonds.

Whereas earlier calculations on the quinodimethane series tended to predict a substantial thermodynamic stabilization for quinodimethanes[36, 37] the calculation by Gleicher[33] moderated this view, since REPE values of only 0.005 β and 0.006 β were found for the 1,2 and 1,4 isomer respectively. These results are in accordance with the prediction by Herndon for the 1,4 isomer. Another interesting result emerged from the calculations by Gleicher: annelation of benzenoid units to the basic structures seemed to have a strongly stabilizing effect. For instance, 9,10-anthracenequinodimethane was found to have a REPE value of 0.040 β, and similar values were reported for other systems where both ring double bonds from the prototype were incorporated in the aromatic unit. Because of an apparent inconsistency for derivatives of the 1,2 isomer, the same authors also carried out SCF CBL calculations in a slightly modified version of the method of Dewar and Gleicher[38, 39]. The results predicted an anti-aromatic character to all quinodimethanes for which only a single classical structure may be written. However, a third set of calculations by these authors based upon the SCF VBL technique of Dewar (where the σ energies of the carbon–carbon bonds are calculated explicitly, avoiding implementation of empirical parameters) finds the 1,4 isomer to be slightly anti-aromatic (REPE = $-0.004\,\beta$) while the 1,2 isomer is predicted to be somewhat aromatic (REPE = $0.012\,\beta$).

In the same line, Gutman and Bosanac[40] have calculated the 'cycle energy' as a measure of thermodynamic stability. Their approach is based upon a graph theoretical treatment of the Hückel π-electron energy. In that work, only the *meta* and *para* quinodimethanes were considered, both showing some aromatic stabilization, but less than other systems of the $(4n+2)$ ring size. The cycle energies reported were $+0.0958\,\beta$ and $+0.0612\,\beta$ respectively. Note the more stabilized *meta* form.

In an investigation of the aromatic properties of polycyclic benzenoid compounds, Kruszewski[41] has assigned an index of aromaticity to each ring. The index is based upon

Julg's definition of aromaticity[42] although instead of a distance criterion, a bond order criterion is used. The bond orders were calculated by HMO technique. In this scheme the reference molecule benzene is assigned an index value of zero, and an increase in the index value implies a decrease in aromaticity. We present below some results of interest. Note the large difference between *d* and *e*. (The single bonds emanating from the rings indicate



double bonds to CH_2). In *e*, the substituted ring has a lower degree of aromaticity than the side ring, but the index value of 3.381 is a moderate value. In this respect this series of compounds differs from many polycyclic aromatic hydrocarbons, where the central rings are so reactive that they are prone to undergo reactions that will remove them from conjugation[43]. The findings pertaining to the quinodimethanes seem to agree qualitatively with the previously mentioned findings by Gleicher[33] where aromatic stabilization was predicted when two bonds of the basic structures were shared with benzene rings. One might conclude from the works by Herndon[31], Gleicher[33] and Gutman[40] that both OQDM and PQDM should be nearly non-aromatic. As for the *meta* isomer, having no classical structures, we have treated this species separately (see Section IV.D).

The predicted thermodynamic stability of the quinodimethanes relative to the quinones seems to be in contrast with the ease of formation of these compounds. Whereas the *ortho* and *para* quinones are stable compounds, the corresponding quinodimethanes are highly unstable having resisted isolation until recently trapped at 77 K[11].

2. *Kinetic vs. thermodynamic stability*

As pointed out by Hess and Schaad[44], the ease of isolation of a system depends not only on its thermodynamic stability, but also on its kinetic stability. Thus, a high energy compound may be isolable if it has no favourable conversion routes, and, vice versa, a stable compound may not be isolable if it has favourable routes to still more stable compounds. The kinetic instability of a series of non-benzenoid hydrocarbons has been discussed in detail by Aihara[45], who pointed out several examples of kinetic instability in thermodynamically stable compounds.

As a measure of kinetic stability towards electrophiles and nucleophiles, Aihara has calculated reactivity indices based upon Wheland's localization energy[46,47] and Fukui's superdelocalizability[48,49].

The line of reasoning involves a characterization of the transition state. For instance, an electrophilic substitution results in a new conjugated system of one less atom and two less electrons (a σ complex or Wheland intermediate). The localization energy is then a measure of the energy in going from a given hydrocarbon to the σ complex. The smaller the localization energy, the more susceptible the carbon, and an index is assigned to each non-equivalent carbon in the system.

When applied as a measure of the reactivity towards nucleophilic substitution and addition reactions, the localization energy is calculated for a σ complex having a -1 formal charge. For alternant hydrocarbons (like the *o*- and *p*-quinodimethanes) predictions based upon localization and superdelocalizability leads to an equal amount of nucleophilic and electrophilic reactivity because of the symmetry of the π-orbital energies.

The work of Aihara predicts both *o*- and *p*-quinodimethanes to fall in the category of non-aromatic compounds having a small per cent resonance energy. All carbon atoms were predicted to be susceptible, the ring carbons to the same extent and slightly more so than the exocyclic carbons.

From a very different approach, Jug has reached the conclusion that PBQ should be non-aromatic[50]. His method is based upon the ring current concept. A bond order is defined as the weighted sum of eigenvalues of the two-centre parts of the density matrix of the pair of atoms considered. The minimal bond order in a ring system in its equilibrium is then defined as an index of aromaticity.

Table 3 summarizes some of the predictions regarding aromaticity.

TABLE 3. Aromatic properties of PQDM, OQDM and PBQ predicted in literature

Method[a]	PQDM	OQDM	PBQ	Ref.
PES + graph theory	Non-arom.		Anti-arom.	31
Huckel ('REPE')	Non-arom.	Non-arom.		33
SCF-CBL	Anti-arom.	Anti-arom.		33
SCF-VBL	Anti-arom. (slightly)	Aromatic		33
Huckel ('cycle energy')	Aromatic (slightly)			40
Localization energy	Non-arom.	Non-arom.		45
Ring current concept			Non-arom.	50

[a] See text.

None of the cited theoretical works has compared the stability of OBQ to the other systems in the table, but evidence from experimental electrochemistry gives us some information on this point. Indeed, experimental redox potentials offer a straightforward way of comparing stabilities of quinone derivatives. Since the *ortho* species has a higher electrode potential (0.792 V) than the *para* form (0.715 V), the former species should be the less stable of the two[51]. The redox potentials for a series of quinones have been measured[51] and calculated values have been obtained by Schmand and coworkers[52] who made use of the postulated (by Dewar and Trinajstic[53]) linear relationship between the redox potentials and the difference in the heat of atomization between the quinone and the hydroquinone. There is a good overall agreement between the experimental and calculated values. A particularly low redox potential was found for 9,10-anthraquinone (calculated value 0.25 V, experimental value 0.154 V). This is in line with the previously mentioned high REPE value for 9,10-anthracenequinodimethane and the general trend extracted from the work of Gleicher[33] that annelation of benzene rings has a stabilizing effect.

Of interest in this context is also the stability considerations carried out in a work by Banks and coworkers[54]. On the basis of an *ab initio* STO-3G calculation PQDM is found to be more stable than the most stable conformer of the open-chain cross-conjugated isomer 3-methylene-1,4-pentadiene by 4.35 kcal mol^{-1}. From arguments involving homodesmotic criteria (comparisons between compounds having an equal number of carbon atoms with a particular hybridization and an equal number of carbon atoms with a given number of hydrogens attached), PQDM was found to be slightly stabilized as compared to other open-chain systems, leaving no doubt that the strain energy of PQDM must be negligible.

B. Electron Affinities and Properties of Anionic States

Much interest has been focused on the electron affinities of this class of compounds. This is due to the ability of quinonoid systems to form charge transfer complexes by acting as

electron acceptors. Several of these complexes are good conductors.

The electron affinity of PBQ has been calculated by *ab initio* ΔSCF calculations augmented by a semiempirical estimation of correlation energy by Millefiori and Millefiori[55]. The latter contribution was calculated according to a method proposed by Sinanoglu[56] and is based upon CNDO/2 wave functions. The molecular electron correlation energy is given in terms of matrix elements that may be partitioned into one- and two-centre terms. The electron affinities for PBQ as calculated at different levels of sophistication were: on the basis of Koopmans' theorem, −0.07 eV; on the basis of ΔSCF calculations (taken as the difference in total energy between PBQ and the corresponding anion), 0.81 eV; and ΔSCF augmented by electron correlation contribution as explained above, 2.20 eV. All these calculations were carried out at the 4-31G level. An experimental value of the electron affinity of PBQ is found by Cooper and coworkers[57] by caesium ion electron impact to be 1.89 eV. These authors also provide evidence for the existence of a long-lived metastable state of the PBQ^- ion at 1.4 eV. This ion is claimed to be generated by direct attachment of the incident electron into the b_{3u} orbital followed by internal conversion to the $^2B_{2g}$ ground state of the anion[57]. Electron affinity values of 1.98 eV and 1.83 eV have furthermore been inferred from half-wave reduction potential and charge transfer complex data[58]. Millefiori and Millefiori also were able to deduce a value for the disproportionation energies of the reaction

$$2PBQ^{1-} \rightarrow PBQ + PBQ^{2-}$$

including the correlation term to be 6.43 eV at the 4-31G level, in reasonable agreement with the value of 5.97 eV that may be inferred from electrochemical data[59–61].

MNDO calculations by Dewar and Rzepa[62] yielded an adiabatic electron affinity value of 1.88 eV and a vertical value of 1.51 eV. This large difference is in itself indicative of a substantial geometry change in going from the neutral molecule to the anion. Indeed, the calculated geometry of the anion reported in the work by Dewar and Rzepa shows a more benzenoid character for this species than for the neutral molecule.

The high electron affinity of PBQ is enhanced by suitable substitution. As pointed out by Cooper and coworkers[63], the perhalo derivatives, i.e. *p*-fluoranil, *p*-chloranil and *p*-bromanil, should have stronger affinity for electrons than PBQ, and indeed values of 2.92 ± 0.2 eV, 2.76 ± 0.2 eV and 2.44 ± 0.2 eV were found for these systems by means of collision technique. Electron affinities for a number of substituted quinones have been found also on the basis of gas phase equilibrium constants for reactions of the type $A^- + B = A + B^-$ using an electron beam high ion source pressure mass spectrometer[64]. The electron affinity for PBQ determined in this way was found to be 1.81 eV. Annelation of one benzene ring to PBQ was found to reduce the electron affinity slightly, while chlorine substitution was found to increase the electron affinity. For chloranil, the value was found to be 2.68 eV. These values are comparable to the values for electron affinity which have been reported for TCNQ. Much attention has been focused on this latter species because of its potential as a superconductor and its tendency to form charge transfer complexes. Two *ab initio* calculations have been carried out on this species[65, 66]. These works predict electron affinities for TCNQ of 2.83 eV and 2.63 eV respectively, the latter value being determined with a slightly larger basis set and a structure closer to the X-ray structure of the species[67].

In conjunction with electron transmission spectroscopy (ETS) measurements of PBQ, PBQ derivatives, and related molecules Modelli and Burrow[68] have used MO theory in order to pin down the sequence of the virtual orbitals of PBQ. They find the LUMO to be of b_{2g} symmetry, and the subsequent π orbitals to follow in the order b_{3u}, a_u, b_{2g} with energies of 0.69 eV, 1.41 eV and 4.37 eV, respectively. The sequence b_{3u}, a_u is apparently not unequivocally established, as the metastable state at 1.4 eV reported by Cooper and coworkers[57] was assigned to be a $^2B_{3u}$ state. Semiempirical calculations of PPP-type[69], of CNDO-type[70] and Xα calculations[72] indicate a larger stability of the b_{3u} orbital.

A curious point in this connection is mentioned in a review article on crystalline π compounds by Herbstein[73]. According to data given in that article, it looks as if mixing substituents produces the most powerful acceptors, thus 2,3-dicyano-5,6-dichlorobenzoquinone (DDQ) is reported to be a better acceptor than either chloranil or cyananil (all of which are more powerful than PBQ). Although there are large uncertainties and small differences in electron affinity reported in that article (0.25 eV between cyananil and DDQ), it may be that unsymmetrical substitution favours the formation of molecular complexes due to dispersion forces and dipole moments in addition to electrostatic forces. However, the usefulness of this in forming charge transfer complexes may be limited due to an increased tendency for DDQ to form complexes with itself.

Although the high electron affinity is involved in any rationalization of the conductivity properties of these systems, single molecule calculations alone or calculations on corresponding anions are apparently not sufficient to explain the high conductivities, and at least two units would have to be considered to predict the collective behaviour in the crystalline phase[66]. The work by Johansen[66] gives an interestingly low value of 4.50 eV for the disproportionation reaction

$$2\mathrm{TCNQ}^- \rightarrow \mathrm{TCNQ} + \mathrm{TCNQ}^{2-}$$

and suggests that these data and the change from quinonoid to benzenoid structure in going from the neutral species to the anion are among factors responsible for the high conductivity.

A review by Andre and coworkers[74] summarizes the existing data up to 1976 on physical properties of highly anisotropic systems like the charge transfer complexes formed with TCNQ (e.g. TTF–TCNQ and NMP–TCNQ).

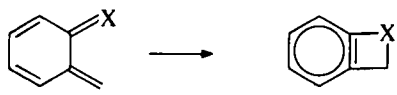
Within the framework of EHMO/LCAO-MO-CI Zhang and Yan[75] have calculated the energy band structure of the triclinic crystal form of NMP–TCNQ. This form is reported to have an electric conductivity comparable to a metal[76] whereas the monoclinic form is reported to be a semiconductor[77].

A study by Mirek and Buda[78] gives MNDO values for adiabatic electron affinities, LUMO energies and ionization potentials for a number of polycyano compounds, among them the di- and tetra-substituted cyano derivatives of PQDM. An increase in electron affinities and ionization potentials and a decrease in LUMO energies was found as the number of cyano groups was increased.

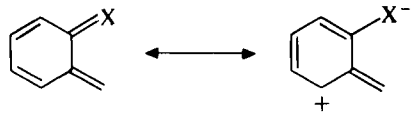
The relative electron affinities of a number of molecules including substituted quinones have been reported by Fukuda and McIver[79]. The results were derived from pulsed ion cyclotron resonance spectrometry. For a whole series of molecules, there is a marked additivity in substituent effects. Thus, there is a decrease in electron affinity of PBQ upon successive methylation, and an increase upon fluorination. The effect of successive chlorination upon the electron affinity is somewhat more complex, since steric factors are also important.

C. *Ortho* Form vs. Bicyclic Form

The *ortho* forms of the quinonoid systems pose a special structural problem, because of the possible conversion to benzocyclobutene:



The intramolecular $(2\pi + 2\sigma)$ cycloaddition of **2** may be useful in synthetic chemistry. Kolshorn and Meier[80] have calculated relative stabilities of **1** and **2** for the cases X = CH_2, NH, O and S using EHMO technique. For all these systems, the quinonoid form was found to be the more stable one, and increasing thermodynamic stabilities were found when going from X = CH_2 to S, NH and O. Furthermore, the activation energy for the ring-closure process was particularly high for the oxa compound. In other words, the more electronegative X favours the open, quinonoid structure because of resonance stabilization of the dipole form



Ring-closure from the first excited singlet was predicted to occur for X = CH_2 and S but not for NH or O. Although these results are inferred from calculations neglecting configuration interaction, it is worth noticing that several derivatives of the closed form for X = CH_2, S and NH are known, but derivatives of the oxa analogue are hitherto unknown.

Kinetic work by Roth and coworkers[81] unambiguously favours the closed form of the hydrocarbon, and the energy profile for the conversion is deduced from thermochemical data. The enthalpy of formation of the closed form was found to be 47.7 kcal mol^{-1}, the corresponding values for OQDM and the transition state were 58.2 and 86.6 kcal mol^{-1} respectively, all values referring to the gas phase. The data were only slightly modified in a later shock tube technique work by the same group[82]. MINDO/3 calculations by Bingham and coworkers[83] yielded a value of enthalpy of formation of benzocyclobutene of 59 kcal mol^{-1}, but complete geometry optimization using the same procedure[78] yielded a value of 48.5 kcal mol^{-1} in excellent agreement with existing experimental values.

A novel application of the open form–closed form equilibrium is found in a flash vacuum pyrolysis experiment of benzocyclobutene by Trahanovsky[84]. The reaction was found to give anthracene among other high molecular weight products, the reaction is proposed to go via the (4 + 4) dimer form of OQDM followed by loss of two carbon atoms and six hydrogens. The reaction is highly regiospecific.

D. The *Meta* Isomers

As mentioned in Section I we will allude only briefly to the properties of the *meta* isomers (**3**), as their characteristic features are discussed extensively in a separate chapter.

The *meta* species most thoroughly discussed in the literature appears to be the hydrocarbon *meta*-benzoquinodimethane (MBQDM), on which a series of both experimental and theoretical investigations have been carried out. However, *meta*-benzoquinomethane (MBQM) has also been claimed to occur as a result of irradiation of 6-methylenebicyclo[3.1.0]hex-3-ene-2-one in a solution of 2-methyltetrahydrofuran at 11 K[85].

The hydrocarbon MBQDM has been prepared from dehydro-*m*-quinodimethane in a host matrix at 77 K[86]. Very recently Goodman and Berson were able to isolate the hydrocarbon at low temperature, and to study its reactivity in solution[87].

The dominant feature of the *meta* isomers as compared to the *ortho* and *para* counterparts is their diradical nature. This has been confirmed experimentally by electron paramagnetic resonance (EPR) spectra[85,86] demonstrating triplet ground states. Furthermore, theoretical calculations at different levels of sophistication have predicted a triplet ground state of MBQDM[14,88–90]. The only *ab initio* study[90] among these

calculations led to a $^3B_2$ ground state of the molecule, the $^1A_1$ state being 10 kcal mol^{-1} higher in energy. The predicted energy difference between the $^3B_2$ ground state of MBQDM and the ^1A_g ground state of PQDM was found to depend strongly on the method used for recovering the molecular correlation energy. A lower bound of 24 kcal mol^{-1} to the energy difference $^3B_2 - {}^1A_g$ was suggested[90]. This value is in accordance with a value of 26 kcal mol^{-1} estimated indirectly by Hehre and coworkers[91].

The electronic and fluorescence spectra of MBQDM have been recorded at 77 K[92], and electronic transitions have been estimated by accompanying MO calculations[92].

E. Polarizabilities

In a series of papers Hameka and coworkers have calculated both linear and third-order non-linear electric susceptibilities of aromatic and conjugated hydrocarbons[93-97], among which both PBQDM and OBQDM were included. The numerical values obtained for these species were dramatically different between the Hückel and the PPP methods[97]. The discrepancies were interpreted in terms of different estimates of the lowest excitation energies within these two approximations.

Electric polarizabilities and diamagnetic susceptibilities have been related to the quinonoid character of some conjugated systems in papers by Luzanov's group[98,99]. In the studies, which were performed within the π-electron approximation, it was found that molecules having quinonoid features as measured by other properties, also displayed comparatively large π-electron polarizabilities[99]. Thus for PBQDM a value of 11.35 Å^3, and for PBQ a value of 6.94 Å^3 were obtained. The corresponding value for benzene is 4.0 Å^3. Furthermore, a pronounced anisotropy of the π-electron polarizability was predicted for the quinonoid compounds. This has been interpreted in terms of double bonds located along the long axis of the molecules. The slightly lower value for PBQ as compared with PBQDM has been attributed to the high electronegativity of oxygen[99]. It should, however, be mentioned that a polarizability study based on the δ-function model[100] does not lead to significant anisotropy of the π-electron polarizability of PBQ[101].

V. SPECTROSCOPIC PROPERTIES AND EXCITED STATES

A. General Considerations

Experimental results available for the molecules belonging to the *ortho* and *para* groups, (1) and (2), respectively indicate pronounced polyene structures, and closed shell electronic ground states. Thus for PQDM electron diffraction data[30], photoelectron spectra[102], low temperature IR and UV spectra[11], NMR spectrum at low temperature of pyrolysis product[103], and other spectroscopic studies[104,105], all support the assumption of a closed shell ground state as opposed to the alternative biradical form. An estimate made by homodesmotic reactions indicates that there is no strain in the molecule[54]. Molecular orbital calculations within the CNDO/S and INDO approximations lead to the conclusion that the energetically favourable configuration is a spin-paired singlet[106]. PPP calculations with full CI in the π space do, however, indicate a certain amount of biradical character[89]. A similar conclusion is obtained by valence-bond calculations[107].

The species PQM is very reactive and unstable. It has been characterized by low temperature NMR, IR, and UV spectra[6]. Its UV spectrum in dilute solutions has also been recorded[108]. The spectra confirm the quinonoid structure of the molecule. So do semiempirical calculations both of Hückel type and at the SCF level[109,110]. Its UV spectrum has been rationalized by semiempirical SCF calculations[111].

The species OQDM has not been isolated. It has been studied in organic matrices by fluorescence, by fluorescence excitation and by UV absorption[12-14]. Spectra with higher

resolution have been obtained in Shpolskii matrices[92], and in argon matrices IR, Raman, UV, fluorescence and fluorescence excitation spectra have been obtained[15]. The spectroscopic data are consistent with a closed shell molecular ground state. This conclusion has furthermore been confirmed both by Hückel-type calculations[80] and by SCF studies within the PPP approximation[88, 112].

For the isomer OQM an IR spectrum has been observed of the matrix isolated molecule[113]. A UV photoelectron spectrum of the molecule has also been recorded in the temperature range 100–600°C, and its electronic structure has been discussed[8]. The data available support the assumption of a closed shell structure with alternating single and double bonds.

For the very unstable species PQI a UV spectrum has been recorded in solution[114]. Similar spectra are available also for PQDI[114, 115], for which also IR information[115] and NMR data are available[115]. For the *ortho* counterparts OQI and OQDI, UV spectra in solution have been recorded[116].

Very recently monothio-PBQ and dithio-PBQ have been produced[18], and their photoelectron spectra have been recorded[18]. Both IR and UV spectra of these compounds have been obtained in argon matrices[18]. The results of MNDO calculations indicate an electron configuration analogous to PBQ[18].

B. Photoelectron Spectra, Koopmans' Theorem and Shake-up States

An important source of information regarding the occupancy and sequence of the outer valence orbitals is provided by photoelectron spectra (PES) in conjunction with theoretical calculations. Of central importance in the interpretation of PES is the assumed validity of Koopmans' theorem[117] which implies a frozen orbital approximation in the description of the ionization process. As pointed out by Richards[118] the success of Koopmans' theorem in quantitative discussions of vertical ionization energies may be traced back to a fortuitous cancellation of errors due to reorganization of electrons and neglect of electronic correlation effects. In a series of recent investigations, strong evidences for a breakdown of Koopmans' theorem have been accumulated[119–122]. An example of particular importance in this context is the case of PQDM. The PES of this molecule and its 3,7-dimethyl derivative were recorded and interpreted by Koenig and coworkers[102, 123]. The samples of the compounds were generated by flash vacuum pyrolysis of [2.2]paracyclophane and its dimethyl derivative, respectively, and the spectra were analysed in terms of the structure representation (SR) method[124–126]. The first band peaking at around 7.9 eV was assigned to a pure Koopmans' configuration ($^2B_{3u}$) of the ion, and the second observed peak at around 9.7 eV was interpreted in terms of an ionic Koopmans' configuration of symmetry $^2B_{1g}$[102]. Arguments in support of this assignment were found by comparison with observed spectra for related molecules[127]. The third band at about 10 eV having an apparently low intensity was rationalized by an ionization process of a non-Koopmans nature. It was suggested that this band could be described by a $^2B_{2g}$ ionic state having a large coupling between $1b_{2g}(\pi)^{-1}$ Koopmans hole state and the non-Koopmans valence orbital excitation $2b_{3u}(\pi)^{-1} \rightarrow 2b_{2g}(\pi^*)$[102]. Support for this interpretation was obtained by a photoelectron study of the 2,5-dimethyl derivative of PQDM[123]. This highly unconventional assignment invoking a HOMO–LUMO shake-up state was challenged by Dewar[128]. On the basis of MNDO calculations it was claimed that the energy difference between the hole state and the non-Koopmans excitation was too large for an effective coupling[128]. Results of additional recent calculations[129–132], however, have given support to the original assignment of Koenig and coworkers[102, 123].

The sequence of the outer valence orbitals in PBQ is still somewhat uncertain in spite of a series of experimental and theoretical investigations. The PES of PBQ and many of its derivatives have been recorded by different groups[71, 133–138]. A UV spectrum of PBQ in

the vapour phase has also been reported[70]. A multitude of semiempirical methods have been applied in efforts made to pin down a unique assignment of the highest filled orbitals[71, 136–145]. Several *ab initio* studies have been made on the electronic ground state of PBQ[146–148], but they have only partially settled questions related to the assignment of the low energy bands in the PES. However, the rather extensive calculations by Ha[148] have shown that a striking change in the ordering of state energies takes place after inclusion of configurational mixing. This is a demonstration of the insufficiency of the orbital model.

Interestingly, the supposedly best quality *ab initio* calculation[145] on PBQ agrees with CNDO/2[130, 134, 141] and HAM/3 calculations[71] in placing the n states at higher energies than the π states. One of the crucial requirements in the assignment of the orbital sequence, imposed by the UV spectrum[70], is that the energy splitting between $n^+(b_{2u})$ and $n^-(b_{3g})$ should not exceed 0.3 eV[137].

TABLE 4. Suggested sequences for the four highest filled orbitals of PBQ*

Method	I(1)	I(2)	I(3)	I(4)	Ref.
CNDO/2	$n^-(b_{3g})$	$n^+(b_{2u})$	$\pi_1(b_{3u})$	$\pi_2(b_{1g})$	133, 137, 144
INDO	$n^-(b_{3g})$	$\pi_1(b_{3u})$	$n^+(b_{2u})$	$\pi_2(b_{1g})$	136, 142, 144
CNDO + CI[a]	$^2B_{3g}(n^-)$	$^2B_{2u}(n^+)$	$^2B_{3u}(\pi_1)$	$^2B_{1g}(\pi_2)$	138
HAM/3	$n^-(b_{3g})$	$n^+(b_{2u})$	$\pi_2(b_{1g})$	$\pi_1(b_{3u})$	71
CNDO/S	$n^-(b_{3g})$	$\pi_1(b_{3u})$	$\pi_2(b_{1g})$	$n^+(b_{2u})$	134, 141
	$\pi_1(b_{3u})$	$\pi_2(b_{1g})$	$n^-(b_{3g})$	$n^+(b_{2u})$	145
	$n^-(b_{3g})$	$\pi_1(b_{3u})$	$\pi_2(b_{1g})$	$n^+(b_{2u})$	143
Ab initio	$\pi_1(b_{3u})$	$n^-(b_{3g})$	$\pi_2(b_{1g})$	$n^+(b_{2u})$	146
Ab initio	$\pi_1(b_{3u})$	$\pi_2(b_{1g})$	$n^-(b_{3g})$	$n^+(b_{2u})$	147
Ab initio[a]	$^2B_{3g}(n^-)$	$^2B_{2u}(n^+)$	$^2B_{3u}(\pi_1)$	$^2B_{1g}(\pi_2)$	148

* Ascending ionization energies from left to right.
[a] Due to strong mixing of configurations we use state symmetries rather than orbital symmetries.

In Table 4 we present a survey of some of the suggested orbital sequences in PBQ based on different semiempirical and theoretical calculations. As revealed by the table the different approaches used are still in mutual conflict regarding the interpretation of the PES. It is worth mentioning that also for this molecule a consistent prediction of the orbital sequence is dependent on the use of configurational mixing, i.e. the allowance for non-Koopmans states. This was emphasized by Schweig and coworkers[138] in 1975 using their own CI approach[149] based on CNDO wave functions. Very recently their conclusion was confirmed by Ha in *ab initio* calculations[148].

Turning to the *ortho* isomers, the species OQDM has so far resisted isolation, but its PES has recently been recorded by Schweig and coworkers[150] using their variable temperature photoelectron spectroscopy (VTPES) technique[151, 152]. They succeeded in generating and detecting OQDM by choosing a precursor compound different from one previously used[153]. Semiempirical MO calculations including configurational mixing both for the molecular ground state and the singly ionized states have given an ionization spectrum of the species[130]. The predicted assignments of the ionized states are $^2A_2(\pi)$, $^2B_1(\pi)$, $^2A_2(\pi)$, $^2B_1(\pi)$, $^2A_1(\sigma)$ in order of ascending energy.

In these calculations it was found that the first excited ion state, $^2B_1(\pi)$, was strongly mixed with the HOMO–LUMO shake-up configuration[130]. The energy predicted for the first non-Koopmans state was found to depend rather strongly on the particular calculational approach used (8.6 eV by PPP–CI, 10 eV by PERT–CI)[130]. The PES recently recorded[150] has given strong evidence for an ionization process involving low energy shake-up states.

The PES of OBQ has been recorded by Schweig and coworkers[154]. They have also made assignment of the spectrum by applying their perturbation method (PERT–CI) on MNDO and CNDO/S calculations[154]. The ionic state sequence arrived at is $^2A_1(n^+)$, $^2A_2(\pi_1)$, $^2B_2(n^-)$, $^2B_1(\pi_2)$ in order of increasing energy. As expected the energy splitting between the lone-pair states A_1 and B_2 (1.2–1.8 eV)[154] is substantially larger in this molecule than in PBQ (0.3 eV)[137] due to the proximity of the oxygens.

C. UV Spectra, IR Spectra and Structure of Excited States

Derivatives of quinomethanes and quinone imines show strong absorption in the visible part of the spectrum, and constitute an important group of dyes such as fuchsone, Homolka-base, crystal violet, phenolphthalein and others[3, 189]. In our survey we will not pursue this part of quinone chemistry, however important it might be. We will primarily focus on publications concerned with problems associated with the interpretation of the electronic spectrum of PBQ, and with some properties of its lowest electronically excited states. The problems arise mainly from the fact that excitation from the symmetrized lone-pair orbitals in D_{2h} symmetry leads to two nearly degenerate states $B_{1g}(n^- \rightarrow \pi^*)$ and $A_u(n^+ \rightarrow \pi^*)$, the π^* being the LUMO, having b_{2g} symmetry[68, 155]. The energy splitting between these states is a crucial measure of the lone-pair lone-pair interaction. Transitions from the ^1A_g ground states to these states are symmetry forbidden in the electric dipole approximation.

Since the first detailed analysis of the vapour phase absorption spectrum of PBQ in the UV region was made by Hollas and coworkers[156–158], a wealth of theoretical and experimental studies related to the low energy transitions in this molecule have appeared.

In a series of papers spectroscopic measurements of PBQ single crystals and of PBQ in host lattices have been carried through at very low temperatures[159–169]. Spectral studies of PBQ in the vapour phase have also been reported[170–173]. Furthermore several theoretical studies, both semiempirical ones and *ab initio* calculations, describing spectral properties of PBQ and structural features of its lowest electronically excited state have appeared[174–186].

The detailed analysis of the vapour phase absorption spectrum performed by Hollas and coworkers[156–158] led to the conclusion that the majority of observed bands in the singlet system of PBQ could be interpreted in terms of only the $^1A_g \rightarrow {}^1B_{1g}$ transition. The origin of this, electric dipole forbidden, transition was located by means of a vibrational mode of b_{3u} symmetry which is a 'boat' vibration.

An alternative band assignment locating the origin as the magnetic dipole allowed transition $^1A_g \rightarrow {}^1B_{1g}$ was suggested later in a supersonic jet experiment[171]. The origin of this transition was found to be at 20 045 cm^{-1}, and the energy splitting between the states $^1B_{1g}$ and ^1A_u was reported to be only 54 cm^{-1}, the ^1A_u state being the lower one. The same ordering with a splitting of 64 cm^{-1} in the singlet system has been observed[167] in a Ne host at 4.2 K. This value for the energy of the origin requires a lowest frequency vibration in the vapour of only about 87 cm^{-1}, a value which is extremely low, and which deviates appreciably from values obtained by IR measurements in solution[187, 188], viz. 108 cm^{-1}. Furthermore this value appears to be independent on the solvent. A far-IR study of the vapour phase has indeed confirmed the presence of the very low vibrational frequency. The actual values reported were 88.9 cm^{-1} and 87.5 cm^{-1} for PBQ-h_4 and PBQ-d_4 respectively. The nature of this vibration was found to be a b_{3u} mode boat-type distortion[173]. The large frequency shifts observed in going from vapour to solution were interpreted in terms of intermolecular forces[173]. The origin of this $^1A_g \rightarrow {}^1B_{1g}$ transition was located at 20 047 cm^{-1} for both PBQ-h_4 and PBQ-d_4, in agreement with the value obtained in the supersonic jet experiment referred to above[171].

Problems encountered in MO descriptions of the excited states of PBQ have been thoroughly discussed by Martin and coworkers[182,183]. Their main conclusion is that a description in terms of symmetrized (in D_{2h} symmetry), delocalized molecular orbitals leads to a qualitatively incorrect picture. A proper interpretation of these states would be a symmetry-broken structure resulting from a localized excitation. This description is in accordance with the dimer model of the excited states. The dimer model is also invoked in the interpretation of low-temperature measurements of proton ENDOR spectra of substituted PBQ[166]. It has been shown that the C_{2v} symmetry of the unsubstituted half of the molecule is virtually intact[166]. Stark measurements on crystals of toluquinone[169] have confirmed the description of the $n\pi^*$ excited states in terms of local excitations of the C=O groups. Furthermore it has been claimed that in this molecule the excitation to the lowest state resides on the C=O group not adjacent to the methyl group for both the singlet and the triplet system[169].

Regarding the structure of the $^3(n\pi^*)$ state, spectral interpretations have led to conflicting evidence. One model emerges from the assumption that the splitting between ^3A_u and $^3B_{1g}$ is around 300 cm^{-1}, and that the lower state ($^3B_{1g}$) is distorted from D_{2h} symmetry along a mode of b_{1u} symmetry[70]. The barrier between the two equivalent C_{2v} minima generates a pair of inversion doublets split by 10 cm^{-1}. The alternative model is based on the assumption that the triplet–triplet splitting is 10 cm^{-1} and that both states (^3A_u and $^3B_{1g}$) have roughly D_{2h} symmetry[167]. Valence-bond calculations were not conclusive regarding the presence of a global C_{2v} minimum in the $^3B_{1g}$ state[183].

VI. CYCLOADDITION REACTIONS

Chemical reactions of quinones and quinonoid systems constitute a vast and complex field in chemistry. For a broad and thorough treatment of addition and substitution reactions of quinones we refer to the Chapter by Finley in this series[1]. Furthermore, a good introduction is found in the basic textbook by Tedder and Nechvatal[3].

By including a brief section on cycloaddition reactions on quinonoid systems we intend to put emphasis on some of the underlying theoretical models that have been developed and utilized in the interpretation of such processes. Also we wish to focus on cycloaddition reactions, since these have been applied in a number of recent, elegant syntheses of a number of different products. In particular, there has been a major effort in the field of preparing various anthracycline antibiotics which are effective in cancer chemotherapy[190–195].

Although the efforts in these investigations have been directed towards the potential usefulness of the products, the vast amount of information obtained has also been important for understanding the regioselectivities of these reactions.

Theoretical and mechanistic aspects of cycloadditions to PBQ and substituted PBQs have been widely discussed. One point of central importance in this context has been the analysis of the competition between two reactive sites in PBQ, the carbon–carbon double bond and the carbon–oxygen double bond.

A systematic study of this problem has recently been published by Shiraishi and coworkers[196] who carried through both experimental and theoretical studies of the reactions between substituted nitrile oxides and substituted PBQs. This study and a related theoretical one by Houk and coworkers[197] have demonstrated the versatility of some of the simple interaction models for qualitative predictions. But at the same time they have revealed the shortcomings of these models when small energy differences are decisive.

Kelly and coworkers have applied resonance theory[198] to account for the site of attack by nucleophiles on quinones[190–195]. The resonance picture accounts satisfactorily for the impact of donor substituents on remote unsubstituted bonds, and also for the impact of acceptor substituents on neighbouring bonds. For other important cases like the influence

of conjugating substituents, and the acceptor substituent effect on remote bonds the results are less convincing[197].

The Frontier Molecular Orbital (FMO) theory developed by Fukui[199] is a powerful tool for explaining and predicting reactivities and selectivities in organic reactions[200]. In cases where quinones are involved we have commonly addition of nucleophiles to the quinonoid system. Substituent effects on reaction rates and selectivities are in this framework discussed in terms of the perturbation of the substituent on the LUMO of the quinonoid system.

The works by Shiraishi[196] and Houk[197] are based upon STO-3G calculations and HOMO–LUMO energy differences are computed. The type of information to be inferred from these calculations may be exemplified by the work of Shiraishi[196]. In that work, treating reactions of nitrile oxides with substituted PBQs, distinction is made between two main reaction types: C=O addition (leading to spiro(1,4,2)dioxazole) and C=C addition (leading to an isoxazoline). The former route is determined by the HOMO (nitrile oxide) and the LUMO (quinone) energy differences while the latter is determined by the LUMO (nitrile oxide) and HOMO (quinone) energy differences. The borderline energy difference between two interactions was found to be around 4 eV, although exceptions were found. In view of the simplicity of the method and the inherent shortcomings of the basis set, lack of configuration interaction, consideration of lower-lying orbitals and lack of geometry optimizations, the overall results must be regarded as very good.

VII. POLYMERIZATION REACTIONS

Whereas the quinone family of molecules consists of relatively stable members, the isoelectronic QDMs are highly reactive. For instance, PQDM although made and characterized from pyrolysis of *p*-xylene, exists only in the vapour phase and in low temperature solutions[11]. Upon heating, polymerization takes place[123], and Figure 1 shows the multitude of reaction paths that may occur when different reagents are added. Since diradical structures are essential in the polymerization process, the ease of polymerization should parallel the ability to form diradicals. A narrow gap between the lowest singlet and the lowest triplet state is one criterion for biradicaloid structure, and indeed the energy difference between the singlet ground state and the first triplet excited state for PQDM has been calculated by Coulson and coworkers[37] to be 8–9 kcal mol^{-1}. (The similar energy difference for ethylene is reported to be 82 kcal mol^{-1} [201]). This small energy difference is in accordance with the high reactivity of PQDM. Koutecky and Döhnert[89] have pointed out the lack of precision in this criterion, and suggest the use of occupation numbers in natural orbitals as a measure of biradical character. Whenever two non-bonding occupation numbers are different from zero or two, the system exhibits biradical character, and also by using this criterion PQDM belongs to the category of biradicaloids. Similar results have been found by Flynn and Michl[14]. We wish to point out, however, that the most direct experimental technique for investigating quinonoid vs. biradical character is magnetic studies, and already 50 years ago the dominating quinonoid character of PQDM was established by Müller and Müller-Rodloff[202]. Only sterically hindered and twisted Chichibabin hydrocarbons (see below) were found to be paramagnetic[203]. For a further discussion of electronic properties we refer to Section IV.

As early as in 1904 Thiele obtained poly-PQDM in an attempt to obtain the parent monomer[204]. Although the polymer was initially an undesired product, it has received growing attention in recent years because of its use as plastic coating and other industrial uses. We refer to several review papers[205–208] that give account of the development in the field. Here we will focus our attention on some key points rather than give an extensive account of the area.

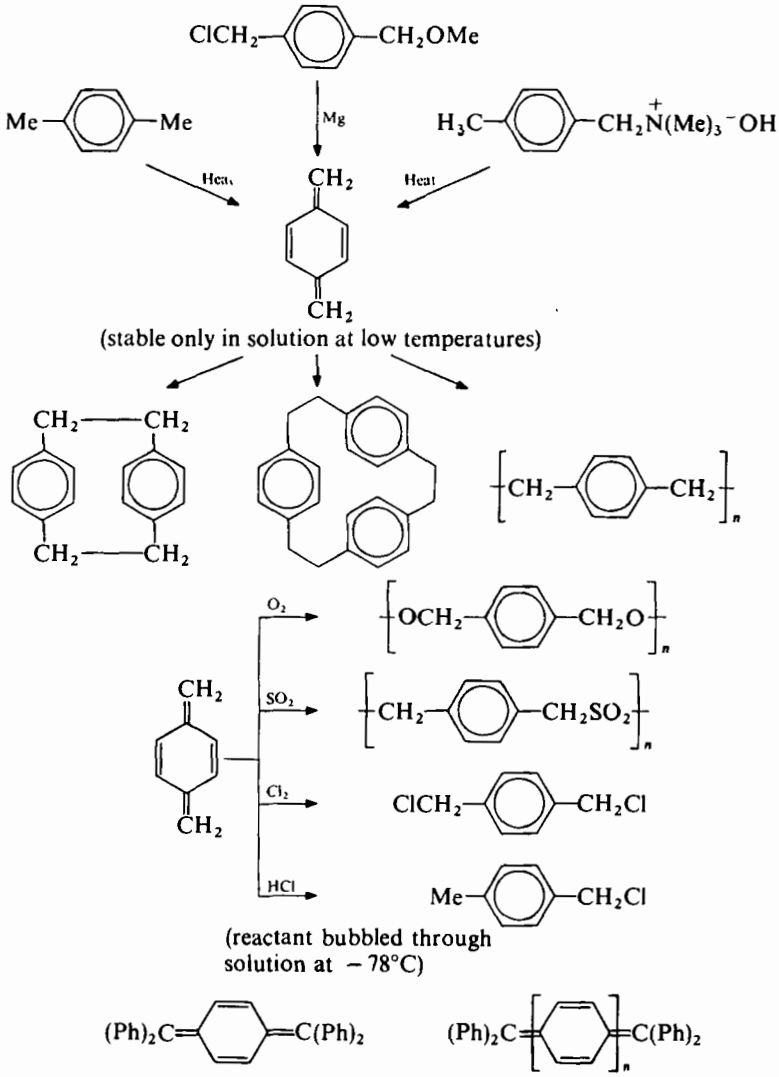
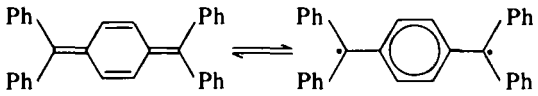


FIGURE 1. Some of the possible reaction paths of PQDM. *Adapted from* Basic Organic Chemistry *by J. M. Tedder and A. Nechvatal, part 2, p. 248 (Ref. 3), published by John Wiley and Sons*

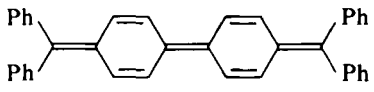
The work by Thiele[204] initiated a series of interesting studies that provided new insight into a variety of fields. For instance, the existence of a diradical was demonstrated in the tetraphenyl derivative of PQDM (usually referred to as Thiele's hydrocarbon, **4**).

Although the equilibrium is strongly shifted to the left (less than 0.2% of diradical form was believed to exist), the possibility of diradicals in reaction mechanisms was established. Furthermore, a number of analogue compounds were found to have a large fraction of

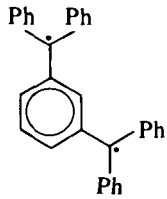


(4)

diradical character in the ground state. Notable examples are the Chichibabin (**5**) and Schlenk (**6**) hydrocarbons, the former of which has been found (on the basis of ESR measurements) to be a paramagnetic species in the dimer form[209]. With an increasing number of rings attached, the fraction of diradical form increases, paralleling the increase in electrode potentials with an increasing number of rings in *p*-quinones (see Section IV). As for the Schlenk hydrocarbons, the stability of free radicals is in accordance with the impossibility of writing classical resonance forms. A modern discussion of the diradical vs. diradicaloid nature of these compounds is given in a review by Platz[210].



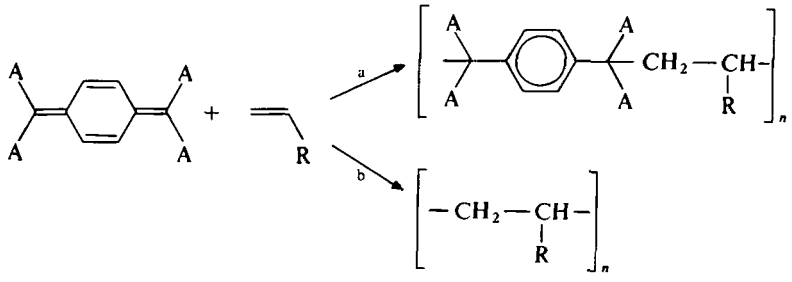
(5)



(6)

Several methods for the preparation of poly-PQDM are now available, and different pyrolytic methods are being used. The review by Iwatsuki[208] gives reaction mechanisms for both isothermal low temperature reactions and a non-isothermal process. Also, the same review mentions a number of different reaction routes giving various yields and qualities of polymers.

An especially pure linear polymer with high molecular weight has been obtained in high yields by Gorham[205] who used a vacuum pyrolysis technique at 600°C. The key intermediate was identified as (2,2)*p*-cyclophane, which was quantitatively cleaved to PQDM which spontaneously polymerized. The method was adapted to a number of substituted poly-PQDMs, many of which have not been prepared by other methods. The products were particularly pure and free of cross-linked and low molecular weight products. A kinetic study has been carried out on the process[211]. The polymers have low permeability to moisture and other corrosive gases, and are useful for the coating of electrical assemblies. The physical and electrical properties of three of these polymers (which are now commercially available) are given in the review by Iwatsuki[208].



Because of the high reactivity of PQDM, copolymerization with vinyl monomers requires a large excess of the latter. If, however, PQDM is substituted with highly electron-withdrawing groups, alternating copolymers (route a) or homo vinyl polymers may be formed (route b)[206].

The propagating species is found to be a diradical formed from the *p*-cyclophane in all cases where the product contains a PQDM unit. Since *p*-cyclophane is a rather strained species, this parallels findings for reactions involving a number of other strained species[212].

For the case of homo vinyl polymerization, a cationic species is believed to be the propagating species[206].

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CHAPTER 2

Physical and chemical analysis of quinones

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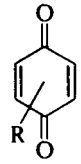
I. INTRODUCTION

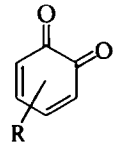
About 22 000 papers dealing with one or more aspects of spectroscopy and/or chemical determination of quinones have appeared since 1973. Most of these, however, just collect singular data on special compounds without presenting any evaluation or processing of these data in analytical or structural respects. Although of high value in a special context, they may be of minor interest in a survey like this. Hence, single compounds are discussed here only

(1) if their analytical features violate the rules derived in our original chapter on the subject[1];
(2) if they are examples of new trends within known methods or even demonstrate the application of methods not yet mentioned in Ref. 1; and
(3) if, in the authors' opinion, they are of high importance for mechanistic, preparative or applied chemistry and/or biochemistry.

We will restrict the matter to be treated in this chapter mainly to the discussion of the monocyclic systems **A** and **B**, showing the typical 1,4-(*para*) or 1,2-(*ortho*)-quinonoid π systems. For an interesting 'chemical definition' of the quinone conception see Ref. 2. Although homo- and hetero-condensed quinones (**C**, **D**) may be of high interest as natural products, they can be discussed only in context with those analytical methods which allow a detection of the typical quinonoid substructure. Thus, for example, ^{1}H NMR data of **C** and **D** mainly characterize the periphery, and are not included in this report.



(A)



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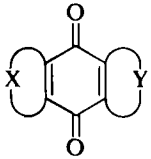
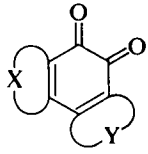


(C)



(D)

X, Y = carbon or heteroatoms or fragments containing them

Moreover, emphasis is laid on methods which allow a qualitative or quantitative analysis of quinones and, eventually, a distinction between the *para*- or *ortho*-type without sophistication.

Thus, each section will take a certain method and describe the parameters underlying the qualitative and quantitative analysis in some detail (especially in dependence of structural and methodological facts), illustrated by some applications of practical interest.

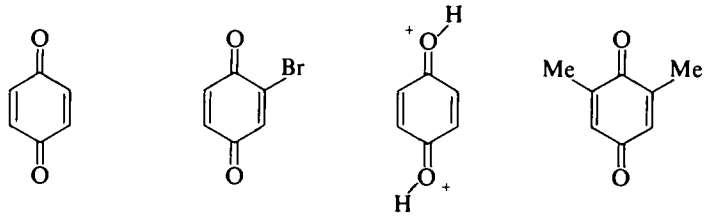
II. NMR SPECTRA OF QUINONES

A. General Remarks

As already pointed out in the original chapter in this series[1], NMR of quinones is in most cases not very specific for the quinonoid state and only in simple monocyclic benzoquinones are typical 'quinonoid' NMR absorptions shown both for ^{1}H- and ^{13}C-NMR. After the first systematic ^{13}C-NMR study on quinones[3] and our compilation[1], there appeared numerous papers dealing with quinonoid systems. Today, one might find assigned ^{13}C-NMR spectra for nearly all reported quinones in the literature.

B. Proton Magnetic Resonance

There have been numerous papers, which report on routine ^{1}H-NMR chemical shifts of the aromatic or side-chain protons of benzo-[4,5], naphtho-[4d,u,5b,6], anthraquinones[6a,g,p,z,7] or anthracyclines[7h,i,m,p,8], and other condensed quinones (including homo[6v,7n,9] or hetero[4a,l,n,5c,k,6e,v,y,z,7h,10] rings), as well as heterocyclic quinones[11]. However, there have been only few fundamentally new additions to the literature dealing with proton NMR of quinones. The H,H couplings in 1,4-benzoquinone (**1**) and 2-bromo-1,4-benzoquinone (**2**) have been remeasured and correlated with results from IR spectroscopy[12]. The stability of benzoquinone in superacid solutions was investigated by proton NMR[13]. Only the diprotonated species **3** was detected with δ-values of 8 ppm for the quinonoid protons and 14.2 ppm for the protons at the oxygen atoms. The solutions were stable at -40°C. A lanthanide-induced shift study revealed that quinones such as 2,6-dimethylbenzoquinone (**4**) bind the lanthanide ion with both carbonyl oxygens[14a]. Lanthanide-induced shift data of 38 naphthoquinones allow the differentiation of the



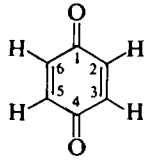
(1) (2) (3) (4)

quinone protons H(2)/H(3) in most cases of unsymmetric substitution of the benzenoid ring[14b].

Porphyrins can be capped with a quinone unit. Up to 4 ppm the quinonoid protons are shielded by the ring current of the porphyrin ring system[15], and the influence of the porphyrin metal ions on the quinone ring was investigated[16] (see also Ref. 17). There have been reports on CIDNP of quinones during photolysis[18-20]. For ^{1}H-NMR spectra of quinone compounds of interest in special fields see the following references: cyclophanes[21], crown ethers[71, 22], triptycenes[23].

C. ^{13}C Magnetic Resonance

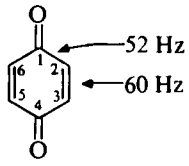
With the development of better assignment techniques in ^{13}C-NMR spectroscopy, it is now possible to assign all carbon atoms even of higher condensed quinones fairly safely. Several groups point out that the use of long range C, H spin–spin coupling constants from gated decoupled spectra is most essential for the correct analysis[24-26]. Some assignment errors in our first compilation[1] had to be corrected on this basis[25, 27]. A full analysis of the C, H spin–spin coupling constants of 1 itself has been published[28].



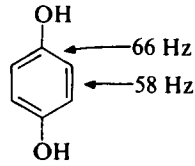
(1)

$^1J_{C(2),H(2)} = 168.4$ Hz
$^3J_{C(1),H(3)} = 10.3$ Hz
$^3J_{C(2),H(6)} = 4.5$ Hz

Very recently a method was published to measure carbon, carbon spin–spin coupling constants in symmetrical molecules[29]. With this method the ^{13}C, ^{13}C spin–spin coupling constants of benzoquinone (1) and hydroquinone (5) were measured[30]. It is interesting though not unexpected that the spin–spin coupling constant of the carbon atoms of the 2–3 bond does not change much from benzoquinone to hydroquinone. Instead, the ^{13}C, ^{13}C spin–spin coupling constant between C(1) and C(2) shows a considerable change. This



(1)

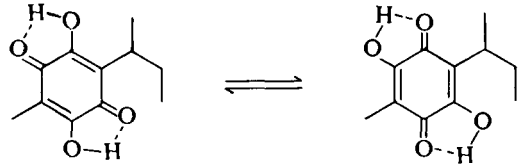


(5)

points to the fact that ^{13}C, ^{13}C spin–spin coupling constants are affected more by local hybridization effects than by delocalization[31].

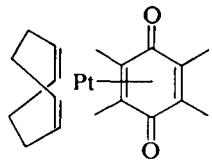
Whereas the main body of the ^{13}C-NMR literature reports the routine data of various quinonoid systems[4d, j, k, o, s, w, 5f, i, j, n–p, t, 6b, c, z, 7h, i, r, 8c, e, 9d, g, 10a, d, j, m, q, 17c, 32–36], some groups have tried to develop increment systems, which allow a fast calculation of expected ^{13}C-NMR chemical shifts for a given quinone[37–40]. However, it has been shown that the quinonoid ring does not resemble a unique entity for ^{13}C-NMR spectroscopy. The substituent-induced chemical shift changes of the olefinic carbon atoms of a quinone correlate well with those in simple olefins and, not unexpectedly, there is virtually no difference between the substituent chemical shifts in the aromatic rings of a condensed quinone and simple aromatic molecules[41]. Furthermore, there is very little 'crosstalk' with respect to the ^{13}C-NMR chemical shifts between the aromatic and quinonoid ring systems in condensed quinones.

Temperature-dependent ^{13}C-NMR spectroscopy was carried out on perezone (**6**) and its derivatives in order to demonstrate the tautomeric equilibrium[39], and to study the hindered rotation of coumarin residues in homologues of juglone[42].



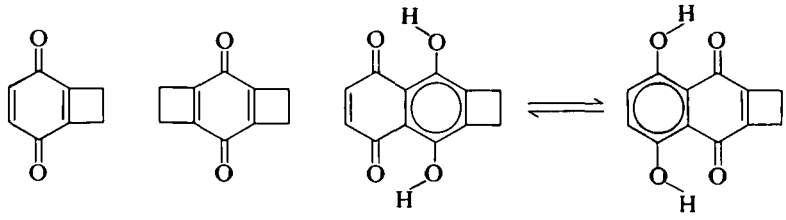
(**6**)

The complexation of quinones with organoplatinum compounds (**7**) was studied[43] and the solution structure of the complexes investigated with low temperature ^{13}C-NMR spectroscopy; however, a clear distinction between η^2 and η^4 structures was not possible.



(**7**)

The effect of strain imposed by mono- or bis-annulation of the cyclobutene ring on 1,4-benzoquinones (**8**, **9**) and on naphthazarin (**10**) was observed by ^{13}C-NMR[44, 45]. Clamping



(**8**) (**9**) (**10**)

in anthraquinonophane causes distinct shifts in the ^{13}C-NMR spectra with respect to the unclamped anthraquinones ($\Delta\delta_{CO}$ up to 3 ppm)[46].

The solid state ^{13}C-NMR spectra of quinones have been measured with the cross-polarization/magic angle spinning (CP/MAS) technique, and the solid state reaction between quinones was followed by this method[47]. The solution and solid state spectra of simple quinones are rather similar.

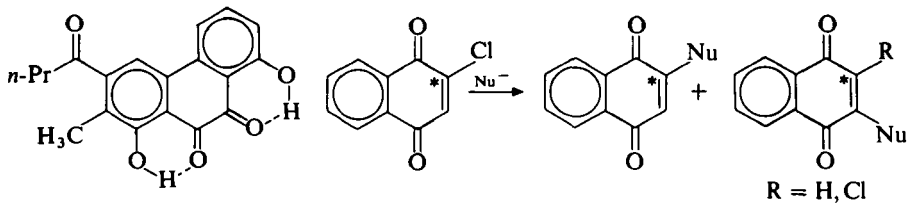
D. ^{17}O Magnetic Resonance

^{17}O-NMR spectroscopy was performed on several simple quinones. The linewidths are acceptable and the chemical shift dispersion is sufficient to be of some diagnostic value[48].

E. Analytical Applications

Quinones may be easily recognized by the carbonyl resonance near 180 ppm if no other carbonyl groups are present in the molecule. However, the distinction between 1,2- and 1,4-quinones is not always straightforward[1] (for a successful case see Ref. 5i).

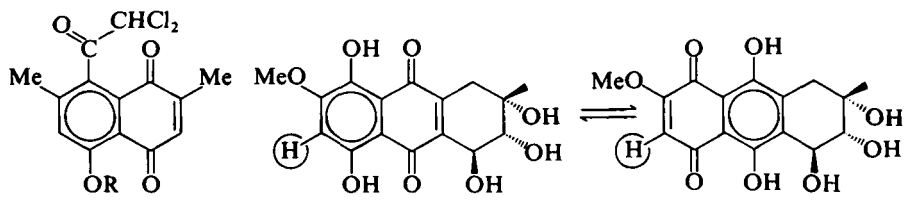
Although, presently, nearly all new quinones are characterized by ^{1}H- and/or ^{13}C-NMR spectroscopy, essential structural assignments or quantitative determinations are rarely based on NMR only. Examples are the application of long-range ^{1}H/^{13}C heteronuclear correlation spectroscopy (LR HET COSY) to the structure elucidation of murayaquinone (**11**)[49a] and cervinomycin[49b] or the investigation of the regiochemistry of nucleophilic



(**11**) (**12**) (**13**) (**14**)

displacements in chloronaphthoquinone (**12**). The ratios of the products, **13** and **14**, were determined by comparison of the ^{13}C-NMR spectra of labelled and unlabelled material, starting with 2-[^{13}C]-2-chloro-1,4-naphthoquinone (**12**)[50].

The biosynthesis of mollisin (**15a**) has been studied, using sodium [1-^{13}C]-, [2-^{13}C]-, and 1,2-[di-^{13}C] acetate[51a]. High levels of acetate incorporation and conversion of mollisin into its acetate (**15b**) allowed the assignment of all ^{13}C-chemical shifts and ^{13}C, ^{13}C coupling constants of the latter compound. Likewise, the biosynthesis of the



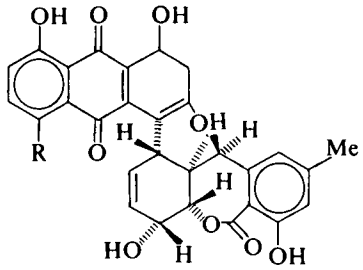
(**15**) (**a**) (**16**) (**b**)

a: R=H
b: R=COMe

kinamycin antibiotics (heterocondensed naphthoquinones) has been investigated by ^{13}C-NMR analysis of the enrichment of carbon atoms after feeding of [1,2-$^{13}C_2$]-acetate to cultures of *Streptomyces murayamaensis*[51b].

^1H-NMR has been used to settle the question of 'naphthazarin tautomerism' in bostrycin (**16**) in favour of structure **16b** by comparing the shift of the circled proton (δ = 6.45, DMSO-d_6) with that of the corresponding proton in model compounds[52a]. For the investigation of a similar tautomerism in 1,4-dihydroxy-9,10-anthraquinon-9-imines by ^1H-NMR see Ref. 52b.

The structures of rubellins A (**17a**) and B (**17b**), two novel anthraquinone metabolites isolated from *Mycosphaerella rubella*, have been assigned, mainly by detailed analysis of



a: R=H **b**: R=OH **(17)**

their ^1H- and ^{13}C-NMR spectra[53a]. Thermochromism of 1,4-benzoquinones substituted with a R–N–CH_2CH_2OH group is caused by equilibration with the corresponding quinone ketals, as shown by ^{13}C-NMR investigation[53b]. Finally, analysis of high-boiling fractions of shale oil, containing quinones, by combined ^1H-NMR and IR spectroscopic methods is also possible[54].

III. IR SPECTRA OF QUINONES

A. General Remarks

Only few new compilations and discussions of IR data of quinones are available[55–57], although complete calculations and analyses of fundamentals of several quinones have been reported since 1973: 1,4-benzoquinone[58], 1,4-naphthoquinone[58a, 59], 9,10-anthraquinone[58a, 59b, c, 60], chloro-1,4-benzoquinones[61] and (in part) their fully deuterated analogues, with some differences in the assignments given by different authors. Vibrational analysis was also suggested for vitamins K_1, K_3, K_4, K_5 involving fundamental and combination tones showing a preponderance of quinonoid structures in all of them[62].

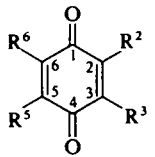
Besides IR, Raman spectroscopy could equally well be used. However, only few investigations are known to us: chlorinated 1,4-benzoquinones[61], naphthoquinone[57a] and anthraquinone[57a].

Before reading the following text or using Tables 1 and 2, the general remarks on pages 186, 187 of Ref. 1 should be considered. Again, the discussion will be restricted to the position of the double-bond vibrations near 6 μm. All new data should be treated with caution, since there is no complete set of $\tilde{\nu}_{C=O}$ measured in the same solvent under identical conditions.

B. Benzoquinones

A wealth of data has appeared[4, 5, 6n, 10f, i, p, 21, 22, 44, 56, 63], single data or series of them, with simple or very complicated, even exotic, substitution patterns. Some examples for 1,4-

TABLE 1. Carbonyl absorption of 1,4-benzoquinones



Compound no.	R^6	R^5	R^3	R^2	$\tilde{\nu}_{C=O}$ (cm^{-1})	$\bar{\tilde{\nu}}_{C=O}$ (cm^{-1})	Solvent	References
(9)	$-CH_2-CH_2-$		$-CH_2-CH_2-$		1670	1670	CCl_4	44
(18a)	*c*-C_3H_5	H	H	*c*-C_3H_5	1654	1654	[b]	63l
(18b)	H	*c*-C_3H_5	H	*c*-C_3H_5	1640	1640	[b]	63l
(19)	$C_{12}H_{25}$	H	H	$C_{12}H_{25}$	1655	1655	CCl_4	4t
(20)	$C_{12}H_{25}$	OH	OH	$C_{12}H_{25}$	1645	1645	CCl_4	4t
(21)	$C_{12}H_{25}$	OMe	OMe	$C_{12}H_{25}$	1670	1670	CCl_4	4t
(22)	Allyl	OH	Me	OH	1610	1610	KBr	10f
(23)	Allyl	OMe	Me	OMe	1650	1650	Neat	10f
(24)	H	H	OMe	OMe	1680, 1670 1635	1662	KBr	63m
(25)	H	OPh	H	OMe	1680, 1613	1646	[b]	4b
(26)	H	OH	H	OH	1604	1604	Paraffin	4c
(27)	$-O-(CO)-O-$		$-O-(CO)-O-$		1685, 1662	1673	THF	63i
(28)	H	H	SMe	SMe	1655	1655	$CHCl_3$	5d
(29)	H	H	H	$N(Me)CH_2R$	1675, 1640	1658	Film	4h
(30)	H	$N(Me)CH_2R$	H	$N(Me)CH_2R$	1630	1630	KBr	4h
(31)	H	NHPh	H	NHPh	1640	1640	Paraffin	4c
(32)	NHAc	H	H	Cl	1684, 1628	1666	Nujol	5a
(33)	$CON(Et)_2$	NH_2	$CON(Et)_2$	NH_2	1605	1605	KBr	5g
(34)	H	H	H	$COCH(Me)_2$	1670	1670	KBr	5h
(35)	H	H	H	COOH	1630	1630	$CHCl_3$	4e
(36)	H	H	OH	COOH	1630	1630	Nujol	4e
(37)	H	COOMe	H	COOMe	1666	1666	KBr	63j
(38)	CN	Cl	Cl	CN	1710, 1680	1695	KBr	5f

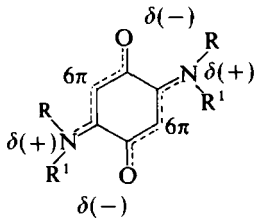
[a] The arithmetical average of the two $\tilde{\nu}_{C=O}$ values given; see Ref. 1.
[b] Solvent not stated.

benzoquinones (to supplement Table 8 of Ref. 1) are given in Table 1, whereas 1,2-benzoquinones (to supplement Table 10 of Ref. 1) may be found in Table 2. By and large, the rules given in Ref. 1 concerning the appearance of the spectra as well as the site and type of substitution are still valid. However, the details presented by different authors do not always harmonize.

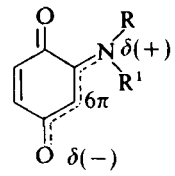
The examination of asymmetrically substituted quinones revealed that the carbonyl frequencies are split for all classes of compounds, representing the vibrations of the two distinct carbonyl groups (LFER equations of $\tilde{\nu}_{C=O}$ being determined)[64]; see, however, doubling by Fermi resonance[1].

If we compare the 1,4-benzoquinones of Table 1 with **1** ($\bar{\nu}_{C=O}$ = 1671 cm^{-1} in solution)[1], we can again conclude that electron-donating groups generally lower $\bar{\nu}_{C=O}$ (consider e.g., the pairs **1/18**, **1/20**, **1/28**, **1/29**, **1/31**), whereas electron-withdrawing groups raise it (e.g. **1/38**). However, it seems that MeO and COOH/COOMe were exceptions. The effect of the methoxy group[1] is still not clear-cut. Comparing **19** with **21**, we would expect a $\Delta\bar{\nu}_{C=O} = +7.5\ cm^{-1}$ for OMe, comparable to that of Cl. The pair **1/24** would also suggest a shift to higher wave numbers by OMe, as long as the two higher absorptions (1680, 1670 cm^{-1}) are used for calculating $\bar{\nu}_{C=O}$. If the third (1635 cm^{-1}) is also considered, a small shift in the opposite direction can be traced. Contrary to this situation, $\Delta\bar{\nu}_{C=O}$ for SMe ($-8\ cm^{-1}$ from **1/28**) and NR_2 ($> -13\ cm^{-1}$; **1/29**; **29/30**, see also Ref. 41) are straightforward. Comparison of **9** and **19** shows that internal strain caused by annelation of a cyclobutene ring increases $\tilde{\nu}_{C=O}$.

Again, the frequency-lowering effect of hydrogen bridging between a hydroxy group in the *ortho* position and the quinone carbonyl group on $\bar{\nu}_{C=O}$ is obvious, e.g. **20/21**, **22/23**, **1/26**, with $\Delta\bar{\nu}_{C=O}$ ranging from 25 to 65 cm^{-1} (part of the shift may be due to differing of solvents). Hydrogen bonding also seems to occur between amino groups and the quinone carbonyl (e.g. in **33**), whereas in **36** the hydroxy group is more likely to prefer bridging with the carboxyl group (**35/36**). The difference in $\bar{\nu}_{C=O}$ of the aminoquinones **29** and **30** can be explained by a suggestion of Dähne and coworkers[4m]. Accordingly, **30** has the structure of



(E)



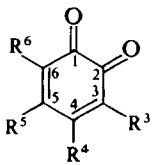
(F)

a coupled 'merocyanine' (**E**), whereas **29** shows one 'merocyanine' and one 'polyene' structural element (**F**). This leads to the polymethine carbonyl absorption at 1630–1640 cm^{-1} for both compounds and to an additional polyene carbonyl absorption at 1675 cm^{-1} for **29**.

An 'intermolecular' hydrogen bridge between a quinone and a hydroquinone being fixed in cyclophanes is nicely demonstrated comparing compounds **39/40** ('parallel' arrangement), whereas in the case of compounds **41/42** ('vertical' arrangement) the effect is much smaller[21b,d,g]. Mono- and polyquinones fixed by crown ether or alkyl bridges seem to show no unusual $\tilde{\nu}_{C=O}$ values[21a,22].

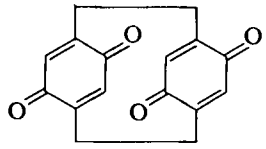
In the case of 1,2-benzoquinones (Table 2) again only few new examples have been reported. Whereas Table 10 of Ref. 1 mainly contains 4,6- and 3,4,6-substituted quinones,

TABLE 2. Carbonyl absorption of 1,2-benzoquinones



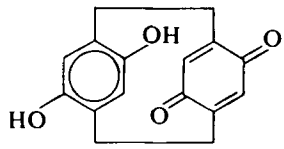
Compound no.	R^6	R^5	R^4	R^3	$\tilde{\nu}_{C=O}$ (cm^{-1})	$\bar{\nu}_{C=O}$[a] (cm^{-1})	Solvent	References
(43)	Me	H	H	Me	1681, 1659[b]	1670	CH_2Cl_2	63 h
(44)	–O–CH_2–O–		H	Me	1620	1620	KBr	4 y
(45)	–O–CH_2–O–		Me	Me	1625	1625	KBr	4 y
(46)	–O–CH_2–O–		*n*-Pr	*n*-Pr	1655	1655	$CHCl_3$	4 y
(47)	–O–CH_2–O–		H	$C(Me)_3$	1668	1668	$CHCl_3$	4 y
(48)	H	–O–C(Me)Et–O–		H	1660	1660	Paraffin	4 x
(49)	H	NHPh	NHPh	H	1615	1615	Paraffin	4 c
(50)	H	H	N(Me)Ph	H	1680[b], 1631 (1616)	1658	KBr	4 m
(51)	Br	Br	OMe	Me	1689	1689	Nujol	4 k

[a] The arithmetical average of the two $\tilde{\nu}_{C=O}$ values given.
[b] Higher intensity.



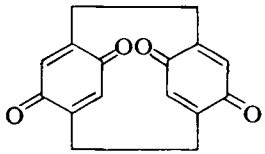
1660 cm^{-1}(KBr)

(39)



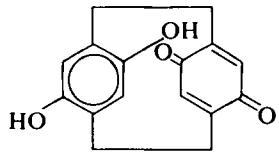
1620 cm^{-1}(KBr)

(40)



1660 cm^{-1}(KBr)

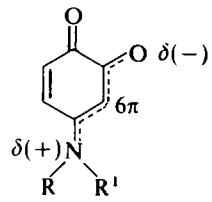
(41)



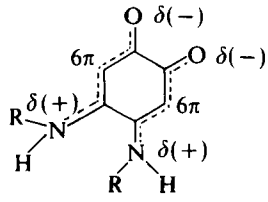
1645 cm^{-1}(KBr)

(42)

Table 2 of the present report also includes other substitution patterns. However, still, too few compounds have been measured to derive substituent shift rules. Whereas **43** corresponds well to 1,2-benzoquinone itself ($\tilde{\nu}_{C=O}$ = 1680, 1658 cm^{-1})[1], it is surprising that the methylenedioxy-substituted derivatives **44–48** show only one carbonyl absorption at relatively low frequencies (1620–1668 cm^{-1}). In the case of **49/50**, Dähne's explanation[4m] again holds: **50** contains one polyene and one merocyanine structure (**G**), **49**



(G)

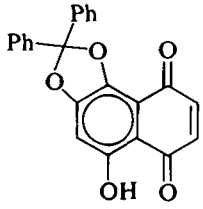


(H)

reveals two coupled merocyanine structural elements (**H**). Hence, two $\tilde{\nu}_{C=O}$ values are observed for **50** (polyene: 1680; polymethine: 1631 and/or 1616? cm^{-1}), and one $\tilde{\nu}_{C=O}$ for **49** (coupled polymethine: 1615 cm^{-1}).

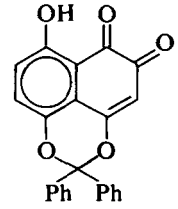
C. Condensed Quinones

A wealth of IR data of homo- and heterocondensed quinones is available, which is far beyond the scope of this article: naphthoquinones[4d, 5b, 6, 7q, 8c, f, g, 9h, 10l, o, 14b, 20e, 52a, 65–72], anthraquinones[5t, 6a, p, 7, 8f, 52a, 65, 72, 73], anthracyclines[7h, i, m, p, r, 8, 74, 75], other homocondensed quinones[6v, 7n, 9, 65, 71, 76, 77] and heterocyclic or heterocondensed quinones[4l, 5c, 6l, v, 10, 11, 32b, 49b, 63g, 66, 70, 78–80]. A collection of the carbonyl absorptions of some parent homocondensed quinones is given in Table 11 of Ref. 1. Homocondensed 1,2-quinones seem to absorb at higher frequencies than 1,4-quinones, however, the



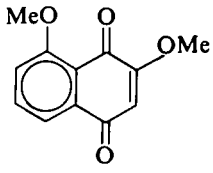
(52)

1670, 1645, 1610 cm^{-1}
(KBr)[52a]



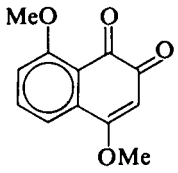
(53)

1670, 1650, 1628 cm^{-1}
(KBr)[52a]



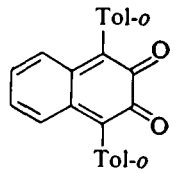
(54)

1670, 1645 cm^{-1}
(KBr)[6h]



(55)

1680, 1640 cm^{-1}
(KBr)[6h]



(56)

1655(m), 1629(s) cm^{-1}
(CH_2Cl_2)[71]

difference may be small, e.g. **52/53** and **54/55**. For comparison, the values for a 2,3-naphthoquinone (**56**) are also given.

A correlation of $\tilde{\nu}_{C=O}$ with the bond order $P_{C=O}$, calculated by the SCF method for 36 parent quinones (mainly condensed quinones), proved to be poor[65].

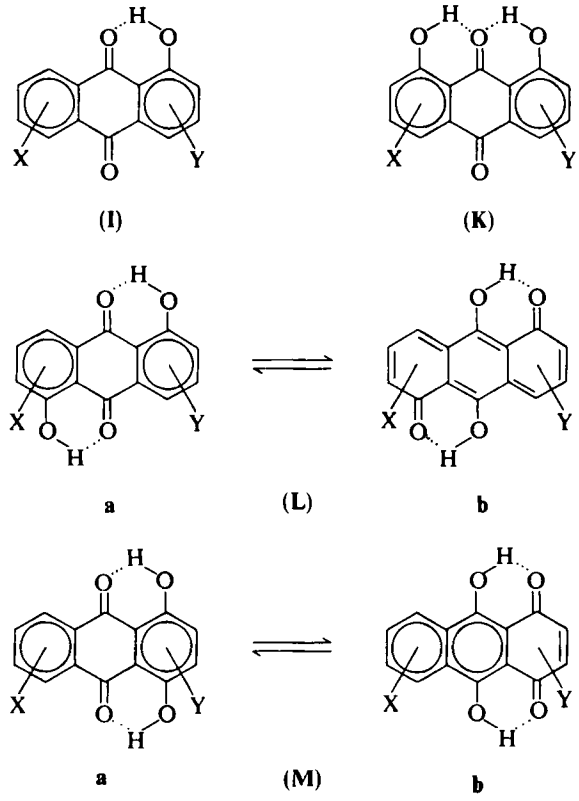
As already demonstrated[1], the influence of substituents (even in the non-quinonoid rings), in general, follows the rules given for benzoquinones, the effect of the methoxy group again being not straightforward. No systematic investigations of the substituent effects are available, and, indeed, they would involve tremendous synthetic efforts. Even in the simplest cases of 1,4- and 1,2-naphthoquinones, the number of positional isomers is very large (Table 3). Some comparable measurements on di- and trisubstituted naphthoquinones (Me, OH, OMe, OAc, F) are available[60, x].

TABLE 3. Positional isomers of naphthoquinones

Substitution type		1,4-Naphthoquinone	1,2-Naphthoquinone
Mono	R	3	6
Di	R, R	9	15
Di	R^1, R^2	15	30
Tri	R, R, R	10	20
Tri	R^1, R^2, R^3	60	120

As regards the other homo- and heterocondensed quinones the reader is referred to the literature quoted above.

For the lowering of $\tilde{\nu}_{C=O}$ due to the 'naphthazarin tautomerism', (see page 155 of Ref. 1 and compounds **10** or **16** in this report), many new examples in the naphthoquinone[6y, 8f, g, 101], anthraquinone[6a, 7d, h–j, m, o, 8f, g], anthracycline[7h, l, m, p, r, 8b, d, f, g, j–m, 74] and naphthacenequinone[9c, d] series have been reported. Anthraquinones/anthracyclines may



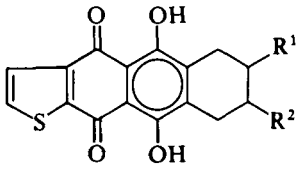
serve as examples. The most interesting combinations of one or two hydroxy groups are (**I**)–(**M**), X and Y being any substituent.

Compounds **I** show a $\tilde{\nu}_{C=O}$ which is ca. 20–30 cm^{-1} lower than in the case of the corresponding methoxy compound, which may be attributed to an intramolecular hydrogen bridge.

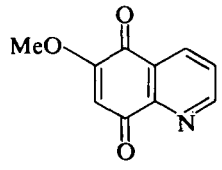
A bifurcated hydrogen bridge as in 1,8-dihydroxyquinones (**K**) does not lower $\tilde{\nu}_{C=O}$ noticeably with respect to **I**. On the other hand, 1,5- and 1,4-dihydroxyquinones **L** and **M**, with a possible bridging of both carbonyl groups, show very low $\tilde{\nu}_{C=O}$ values (1605–1630 cm^{-1} for **L**, 1609–1630 cm^{-1} for **M**, with an accumulation each between 1610 and 1620 cm^{-1}). Therefore, as in naphthazarin[1], a tautomerism involving the structures **a** and **b** might be envisaged in these cases, although the structures **b** are energetically less favourable than the structures **a**, both for **L** and **M**. Whereas **L** and **M** generally show only one carbonyl absorption, there are two in the case of **I** and **K**, one lying around 1655–1680 and the other around 1620–1635 cm^{-1}. Therefore, it has been pointed out[81] that the absorption at lower frequency should be ascribed to the hydrogen-bridged carbonyl

group. Due to the possible occurrence of Fermi resonance[1], this conclusion has to be further confirmed. For the analogous effect in 1,8-dihydroxyphenanthraquinones, such as **11**, and in heterocondensed quinones, such as **57**, see Ref. 49a and Ref. 10h, respectively.

Most heterocondensed or heterocyclic quinones investigated are related to natural products and are derived from indole (e.g. derivatives of mitomycine C)[5c, 10b-g, o, q, 78],



(57)



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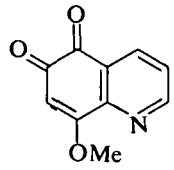


(59)

a: R^1 = Ac, R^2 = H
b: R^1 = H, R^2 = Ac

1590 cm^{-1}(KBr)[10h] 1685, 1670 cm^{-1}(KBr)[63g] 1700, 1642 cm^{-1}(KBr)[63g]

isoindole (38 compounds in $CHCl_3$, $\bar{\nu}_{C=O}$ = 1649–1670 cm^{-1}, correlations of $\bar{\nu}_{C=O}$ with Hammett's σ[57c]), indazole[10d, l], quinoline/isoquinoline[5c, 10f, h, k, n, 63g, 69] (e.g. **58**, **59**[63g]), thiophene[10h, 32b], and carbazole[79, 80].

D. Analytical Applications

The distinction of 1,2- and 1,4-benzoquinones using $\bar{\nu}_{C=O}$ is less straightforward than has been supposed in Ref. 1 since the new data of Table 2 extend the region of $\bar{\nu}_{C=O}$ for 1,2-benzoquinones to lower frequencies (ca. 1620 cm^{-1}). Although IR spectroscopy is an excellent method for the investigation of hydrogen bridging in quinones, it has not acquired any essential importance in their general structural determination in the last decade. A certain lack of clarity of the IR spectra and the complexity of $\bar{\nu}$/structure relations may be some of the reasons.

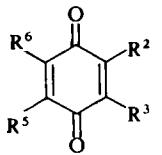
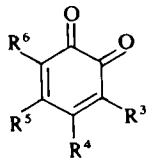
IR spectroscopy combined with other methods, on the other hand, has been used for analytical purposes, e.g. to study high-boiling fractions of shale oil (IR, NMR)[54] and to determine the rate of dehydrogenation of phenol and quinone in soil (IR, voltammetry)[81]. Quantitative determination of quinones applying Lambert–Beer's law to the C=O absorption band are possible, although not in use.

Alternatively, quinones may be characterized indirectly by IR or Raman spectroscopy of their reduction products (semiquinones, dianions)[56, 82].

IV. UV/VIS SPECTRA OF QUINONES

A. General Remarks

UV/vis is the classic spectroscopy in the realm of quinones. It is therefore not surprising that most of the publications in the field since 1973 deal with UV/vis in one way or the other. Reviews[55, 83, 84] as well as an atlas[85], have appeared. In the present authors' opinion, there have been two crucial developments in UV/vis spectroscopy of quinones since 1973: The first of these concerns theoretical calculations of electronic energy levels and of the spectra derived from them, as well as complete analyses of the absorptions in many individual compounds, especially by Nepraš, Fabian and coworkers[86], Kuboyama

TABLE 4. UV spectra of benzoquinones  and 

Compound no.	R^6	R^5	R^4	R^3	R^2	Absorptions λ_{max}(nm) (log ε)	Solvent	Ref.
(61)	H	H	—	–CH=CH–$(CH_2)_4$–		249(4.20), 368(3.25), 439[a](2.34)[b]	Cyclohexane	4g
(62)	H	H	—	–O–$(CH_2CH_2–O)_4$–		253(4.11), 400(3.15) [c]	CH_2Cl_2[d]	22a
(63a)	H	$C(Me)_3$	—	H	$C(Me)_3$	253(4.25), 305(2.47), 458[e] 261(4.18)	*n*-Heptane	87a, 87c
(63b)	H	$C(Me)_3$	—	NH_2	$C(Me)_3$	273(4.13), 465(3.21) [c]	$CHCl_3$	4v
(64)	$NHC(Me)_3$	H	—	H	$C(Me)_3$	278(4.24), 486(3.47) [c]	Ethanol	4v
(65)	H	Cl	—	H	Cl	270(4.42), 325(2.53) [c, f]	*n*-Heptane	87a
(35)	H	H	—	H	COOH	255(3.84), 338(3.38) [c]	MeCOOH	4e
(34)	H	H	—	H	$COCH(Me)_2$	246(4.28), 300(2.66)[a], 450(1.48)	MeCN	5h
						248(4.32), 291(2.75)[a] [c]	CH_2Cl_2	4j
(66)	H	H	—	H	COMe	250(4.26) [c] [c]	CH_2Cl_2	4j
(67)	Me	Me	—	–$(CH_2)_3$–C(O)–		264(4.19), 364(2.95) [c]	CH_2Cl_2	4j
(68)	H	H	—	H	CHO	288(3.59), 355(3.05) [c]	CH_2Cl_2	4j
(69)	CN	CN	—	Cl	Cl	270(4.06), 372(2.94) [c, g] 280(4.01)	MeCN	103a
(48)	H	–O–C(Me)Et–O–		H	—	293(4.23), 395(3.23) [c]	Ethanol	4x
(70)	H	OMe	H	OMe	—	300(3.51), 350(3.77), 490(2.70)	Water	103b

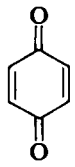
[a] Shoulder.
[b] Shoulders at 460 (2.09) and 492 nm (1.64).
[c] Not stated.
[d] A. Merz, private communication; see also Ref. 22c (MeCN).
[e] Further absorption at 175.5 nm (4.37).
[f] Further absorption at 186.5 nm (4.27).
[g] Further absorptions at 209 (4.20), 216 (4.18), and 226 nm (4.16).

and coworkers[87] and by others[88]. The second area involves investigations of molecular and charge transfer complexes, often in connection with the design of organic conductors, or for biochemical reasons (benzoquinones[63j, 89–94], condensed quinones[94, 95], triptycene[23, 96], cyclophane[21a, d–f, i–k, 63h, 97, 98] and porphyrin[5q, r, 99, 100] quinones).

Neither field can be treated in great detail in this chapter, which is devoted to the analysis of quinones as such. Besides UV/vis, photoelectron spectroscopy[88d, 101] has become a tool for the investigation of quinones, and will be treated below in Section IV. E. Fluorescence, luminescence, and phosphorescence studies can be no more than mentioned[86c, i–m, 88a, 102].

B. Benzoquinones

In spite of the existence of many single UV/vis data of quinones, only very few are suitable to supplement Tables 12 and 13 of Ref. 1. Often, the substituents are rather complicated, only one absorption is given, the intensities are lacking, or the data are hidden in a figure. Data on some new compounds are collected in Table 4. From the three tables mentioned above, the absorption characteristics of 1,2- and 1,4-benzoquinones were computed and arranged in Table 5. In addition to the three absorptions given for each



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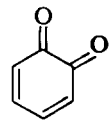


(60)

benzoquinone type, there is a strong $\pi \rightarrow \pi^*$ absorption at shorter wavelengths [(1: 171.5 nm, $\log \varepsilon = 4.19$, 1,1,1,3,3,3-hexafluoroisopropanol (HFP))[87a]; 60: 200 nm[86d], 'strong'[88c], ethanol], which have not been recorded in Tables 4 and 5 since most authors did not take measurements below 220 nm. The $n \rightarrow \pi^*$ band seems to be a superposition of two nearly degenerate transitions[88c].

Several calculations using different quantum mechanical methods, which cannot be discussed here, prove the assignments of Table 5. They are, however, at variance with each other as to the symmetry species[86d, 87a, 88a–f, h, l].

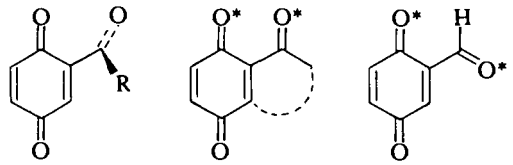
TABLE 5. Absorption characteristics of 1,4- and 1,2-benzoquinones

Type	λ_{max} (nm)	$\log \varepsilon$	Assignment
1,4-	①240–300	3.8–4.5	$\pi \rightarrow \pi^*$
(*para*)	②285–485	2.4–3.5	$\pi \rightarrow \pi^*$
	③420–460	1.2–2.3	$n \rightarrow \pi^*$
1,2-	①250–300	2.6–4.2	$\pi \rightarrow \pi^*$
(*ortho*)	②370–470	2.8–3.5	$\pi \rightarrow \pi^*$
	③500–580	1.4–1.8	$n \rightarrow \pi^*$

Unfortunately, there is no series of substituted benzoquinones measured in the same solvent. Nevertheless, some conclusions may be drawn from Table 4 (in agreement with Ref. 1).

(1) Substitution causes bathochromic shifts of all absorptions (a small hypsochromic shift of the n → π* transition by Me and Cl has been reported, see Ref. 1).
(2) In 1,4-benzoquinones, substitution mainly influences the second π → π* transition. The difference in λ_{max} (Δ nm) between substituent and parent compound is small for *electron-withdrawing substituents* [COOH (**35**): Δ = 50 nm; R–C=O (**34**, **67**, corrected for the two methyl groups): Δ = 5–10 nm] and large for electron-donating (Δ nm see Ref. 1) substituents. As to additivity rules or influence of substitution position, see also Ref. 1, page 197.

The difference in magnitude of Δ nm for H–C=O and R–C=O (**68**, and **34**, **67**) is surprising. It may be due to conformational factors. Thus, the COR group is perpendicular



(N) (O) (P)

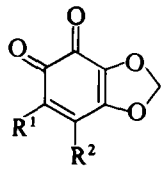
to the ring in **34** (N)[4j] (see also COOR[88m]), planar with a '*syn*' conformation of the two marked carbonyl groups in **67** (O)[4j] (see also Ref. 63e), and with an '*anti*' conformation of those carbonyl groups in **68** (P)[4j].

The absorption areas of Table 5 are supported by many additional compounds not mentioned here (see Refs[4d, g, v–x, 5f, h, k, t, v, 21g, 22, 63b], for solvent effects see Ref. 104).

There are also quinones which do not fit into the absorption domains of Table 5. These are mainly amino and polyalkoxy (polyhydroxy) quinones; for onio-substituted quinones see Ref. 5o. Since the substituents involved cause large Δ nm values (apparently for all three bands), a strong bathochromic shift combined with a change in extinction is not unexpected[4h, m, p, s, 5j, n, u, 10f, 49, 105, 106]. Furthermore, it should be mentioned that the spectra of polyhydroxy quinones are subject to solvent and pH variation[107].

Two types of compounds will be discussed in more detail. Dallacker and coworkers[4y] reported the UV/vis spectra of eight 1,2-benzoquinones **71**, all measured in MeCN. Three absorptions, I–III, are found, which are puzzling, when correlated to the absorption areas of Table 5 or to those of 3- and 4-methoxy-1,2-benzoquinone (Table 13, Ref. 1). However, it would be reasonable to assume that band I corresponds to the high frequency absorption of 1,2-benzoquinone (**60**), being red-shifted by about 10 nm in **71**. Accordingly, II would correspond to ①, and III to ② of Table 5, a correlation which is also suggested by band intensities and by the strong substitution dependence of band III, characteristic of the second π → π* transition (see above). However, a clear-cut substituent/shift relation for **71** cannot be derived at present, and the n → π* absorption may also contribute to band III. The strong bathochromic effect of the methylenedioxy group $-OCH_2O-$ on bands II and III is also evident in 1,4-benzoquinones. Here the following gradation, reflecting a certain ring-strain effect, has been observed[108]: 2,3-dimethoxy < $O-(CH_2)_3-O$ < $O-(CH_2)_2-O$ < $O-CH_2-O$.

A second interesting compound is azidanil (tetraazido-1,4-benzoquinone, **72**)[88k]. Its UV/vis spectrum shows four absorption bands I–IV, the variation widths being due to the



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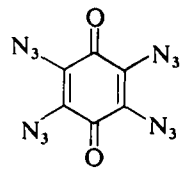
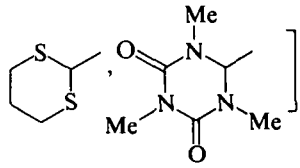


(72)

	λ_{max}(nm)	log ε
I :	208–214	3.47–4.21
II :	232–288 (347)	1.83–4.05
III:	435–580	1.26–3.81

	λ_{max}(nm)	log ε
I :	205–215	4.18–4.47
II :	268–281	4.40–4.55
III:	355–382	4.11–4.26
IV:	540–570	2.39–2.50

R^1 = H, Me, *n*-Pr, *t*-Bu, Br,
R^2 = H, Me, Et, *n*-Pr



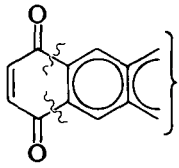
solvents (*n*-hexane, cyclohexane, MeCN, MeOH) used. Again, three $\pi \rightarrow \pi^*$ transitions I, II (corresponding to ① of Table 5), III (corresponding to ②), and one $n \rightarrow \pi^*$ transition IV (corresponding to ③) are observed. Compared to **1**, the azido groups exert their strongest effect on band III, which is expected, as long as only $\pi \rightarrow \pi^*$ transitions are considered. Most surprising here is the strong red shift of the $n \rightarrow \pi^*$ transition of about 110–120 nm. The assignment was achieved by calculations using the PPP–CI method[88k] indicating also that the charge density distribution in **72** is not much different from that of chloranil (tetrachloro-1,4-benzoquinone). Indeed, the bands II and III of **72** correspond nicely to those (i.e. ① and ②) of the perchlorinated quinone (see Ref. 1, Table 12).

C. Condensed Quinones

1. The parent compounds

As already pointed out[1], the spectra of condensed quinones are rather complex. Only the most important homocondensed parent compounds will be discussed here. Many quantum chemical calculations (PPP, PPP/CA, INDO/S–CI) have been made on these systems[86b, c, e–h, m, 87a, b, 88b, c]. Although, in principle, the π system is delocalized, PPP calculations with configuration analysis (CA) have revealed that (especially in higher annelated quinones) the electronic transitions may be treated as local transitions in 'fragments'[86h]. One possible way of dividing a quinone into fragments is shown in **Q**, which allows local transitions in the enedione fragment, in the acene fragment, and charge transfer (CT) transitions *between* these two fragments[86h]. According to this procedure, it is generally possible to identify 'benzenoid' transitions with the dominant character of L_b or L_a transitions of acenes (plus some CT character), 'quinonoid' transitions with a localization in the benzoquinone (endione) part, and CT transitions[86g, h].

In the case of 1,4-naphthoquinone (**73**), the assignment given in Table 14 of Ref. 1 has been completely confirmed as regards the $\pi \rightarrow \pi^*$-, $n \rightarrow \pi^*$- and the benzenoid/quinonoid



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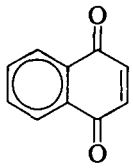
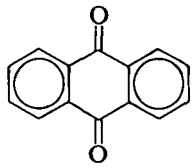


(73)



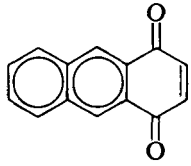
(74)

band notation[86b, g, 87a, 88b, c]. In addition, a fifth (high-frequency) $\pi \rightarrow \pi^*$ transition, which had been predicted on the basis of calculations, was also observed experimentally at 193.5 nm ($\log \varepsilon = 4.58$) in *n*-heptane[87a].

9,10-Anthraquinone (**74**), the parent compound of many synthetic and natural dyes, has been extensively studied since 1973[86b, f, 87a, 88c, 109]. A comprehensive literature review is presented in Ref. 86f; some features will be summarized in the following.

The assignments of the five absorptions given in Table 14 of Ref. 1 in terms of $\pi \rightarrow \pi^*$-, $n \rightarrow \pi^*$- and benzenoid/quinonoid band classification have been confirmed[86b, f, 87a, 88c], although the benzenoid band at 250 nm is of more complex origin, involving also benzene-to-carbonyl charge transfer[86f]. Interestingly, the second quinonoid $\pi \rightarrow \pi^*$ transition at about 340 nm, which can usually be found only in substituted anthraquinones, has now been detected in *n*-heptane solution ($\lambda_{max} = 319.5$ nm, $\log \varepsilon = 3.68$)[87a]. In addition, two high-frequency $\pi \rightarrow \pi^*$ transitions were found at 204 nm ($\log \varepsilon = 4.57$) and 181 nm ($\log \varepsilon = 4.61$)[87a].

In contrast to **74**, the lowest frequency $\pi \rightarrow \pi^*$ transition of 1,4-anthraquinone (**75**) is located at much longer wavelengths (ca. 400 nm), therefore, the $n \rightarrow \pi^*$ transition is only observed as a shoulder on the long-wavelength tail of the $\pi \rightarrow \pi^*$ band. For the other bands see Refs[86b, 88c].



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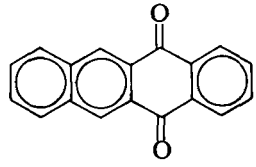

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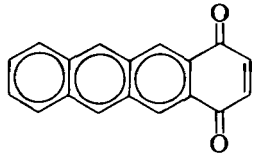

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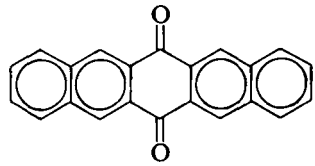


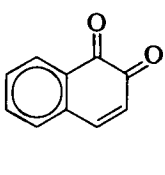
(78)

Higher-condensed 1,4-quinones have also been investigated, experimentally and theoretically: 5,12-tetracenequinone (**76**)[86b, 109b], 1,4-tetracenequinone (**77**)[9f, 86m], 6,13-pentacenequinone (**78**)[86b, 109b], other linear condensed *p*-quinones[9f, g] and some angular condensed *p*-quinones[9h, 86c, 88c]. CNDO/S–CI calculations[109b] show that $n \rightarrow \pi^*$ transitions are practically independent of the extension of the ring system.

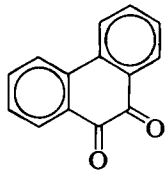
$\pi \rightarrow \pi^*$ Transitions, on the other hand, experience a bathochromic shift, which may reverse the usual order of $n \rightarrow \pi^*/\pi \rightarrow \pi^*$ transitions.

The UV/vis spectra of singly and doubly protonated species derived from **73–78** can be interpreted on the basis of the PPP method[86a, n].

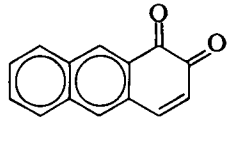
Investigations on homocondensed 1,2-quinones are much more scarce. The assignments given in Table 15 of Ref. 1 have been confirmed for 1,2-naphthoquinone (**79**)[87b, 88b, c], as



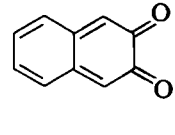
(**79**)



(**80**)



(**81**)



(**82**)

regards the $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ categories. Two further high frequency $\pi \rightarrow \pi^*$ absorptions were calculated and observed in 1,1,1,3,3,3-hexafluoro-2-propanol (HFP) (196 nm, log ε = 4.39; ~ 170 nm, log ε = 4.35)[87b]. Since no configurational analysis[86] has been performed, the assignment of 'benzenoid' and 'quinonoid' bands given in Table 15 of Ref. 1 should still be regarded as tentative.

For 9,10-phenanthraquinone (**80**) the former and the new[87d, e] data are collected in Table 6. The remarkable changes of λ_{max} in the low-frequency $\pi \rightarrow \pi^*$ bands in moving from heptane to HFP solutions are attributed to a strong hydrogen-bond formation between **80** and HFP, a strong proton donor[87d]. Calculations (PPP) of the absorptions of **80**[87d, 88c] do not always satisfactorily fit with the experimental data[87d]. For diazaphenanthrenequinone (phenanthrolinequinone) see Ref. 110.

PPP calculations are also available for the $\pi \rightarrow \pi^*$ transitions of 1,2-anthraquinone (**81**)[88c] and INDO/S–CI calculations for the $\pi \rightarrow \pi^*$ transitions in 2,3-naphthoquinone (**82**)[88b].

2. *Substituent effects*

Substituents render the spectra of condensed quinones even more complex, whereby type, number and position play an important role. Polarity of the solvent used, hydrogen bridging, special steric interactions or charge transfer from substituents to the carbonyl groups are further causes. Absorptions may overlap, accidentally coincide or overtake each other as a result of hypso- or bathochromic substituent shifts. Moreover, the bands may not only be perturbed, but new bands may arise.

Since systematic investigations on mono- and/or disubstitution are lacking (and also would involve too great expense, cf. Table 3), no general rules can be derived. Even semiempirical calculations often do not allow unequivocal assignments of *all* absorptions of a compound in question: for special information, the reader is referred to pages 201, 204 of Ref. 1 and to the literature compiled in the following: 1,4-naphthoquinones[6a, c, i, m, o, t, w, y, z, 8f, g, 51, 52, 87a, 88i, 111, 113, 114]; 1,2-naphthoquinones[6b, o, t, y, 52, 68c, 87b, 112, 116]; 9,10-anthraquinones[6a, 7h, m–o, q, 8f, g, 46, 52, 86f, i–l, 113, 115]; anthracyclines[8f, g, i, k, l, 74]; phenanthraquinones[87d]; other homocondensed quinones[6v, 9]; heterocondensed quinones[4p, 6c, v, 10b–d, f, h, j, p, 49b, 79, 102a, 111, 117–122].

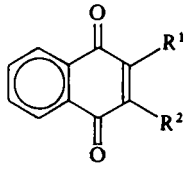
Alkoxy, hydroxy, alkylamino and amino groups, in the case of polysubstitution, cause bathochromic shifts of all, or, at least, of the lowest frequency $\pi \rightarrow \pi^*$ transition (hereafter abbreviated as LFPT)[6a, c, i, o, w, 8f, g, 10p, 53, 74, 86f, i–l, 113, 114, 117].

TABLE 6. UV/vis spectra of 9,10-phenanthraquinone (**80**)

Absorptions									Solvent	References
λ_{max}(nm)/(log ε)										
178	209.5	256	263		314	~ 332	398	~ 500[a]	*n*-Heptane	87d, e
	210	256	264.5		321		414.5		Ethanol	87d
		256	265		322		410		Methanol	1
		(4.46)	(4.49)		(3.62)		(3.13)			
182	210	253.5	261	~ 275	333.5		442	sh 490[a]	HFP	87d
(4.50)	(4.57)	(4.50)	(4.50)	(4.13)	(3.78)		(3.14)			

[a] $n \rightarrow \pi^*$, all others $\pi \rightarrow \pi^*$ transitions.

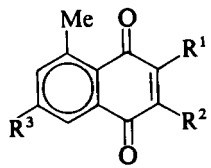
TABLE 7. LFPT[a] of 2,3-disubstituted 1,4-naphthoquinones



Compound no.	R^1	R^2	Ethanol λ_{max}(nm)	Cyclohexane λ_{max}(nm)/(log ε)
(73)	H	H	ca. 330	
(83a)	OMe	H	333	328 (3.53)
(83b)	OMe	OMe	335	329 (3.46)
(83c)	OMe	Cl	338	334 (3.49)
(83d)	NHMe	H	452	423 (3.45)
(83e)	$N(Me)_2$	H	471	444 (3.53)
(83f)	NHMe	Cl	477	454 (3.04)
(83g)	NHMe	OMe	492	484 (3.45)
(83h)	NHMe	NHMe	544	525 (3.34)

[a] Lowest-frequency $\pi \rightarrow \pi^*$ transition.

In 1,4-naphthoquinones, methoxy groups in position 2 and/or 3 have practically no influence on the 'quinonoid' LFPT (**73** → **83a** → **83b** → **83c**, Table 7), which is hidden in **73** itself below the 'benzenoid' band at 335 nm[114]. This is further demonstrated by tri- and tetrasubstituted 1,4-naphthoquinones of type **84**[60], if we assume the (337–408 nm) absorption to be the LFPT. Moreover, the absorption pattern as a whole is relatively constant in methanol.



(**84**)

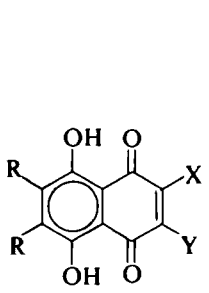
	R^1	R^2	R^3
a	OMe	H	OMe
b	H	OMe	OMe
c	OMe	OMe	OMe
d	H	OMe	OH
e	H	OH	OMe
f	H	OH	OH

262–266 nm (log ε = 4.25–4.39)
290–298 nm (log ε = 4.09–4.17)
337–348 nm (log ε = 3.36–3.62)
400–408 nm (log ε = 3.10–3.25)

Alkylamino groups in position 2 (**83d, e**) seem to shift LFPT to 420–470 nm[6c, 114], which appears to be reasonable in the light of PPP SCF-MO calculations[114]. Moreover, the extinction would be too high for the $n \rightarrow \pi^*$ transition, usually found in this range.

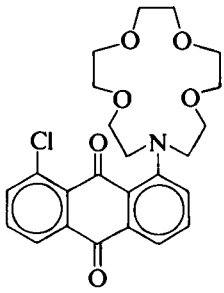
Remarkable is the further shift of LFPT up to 550 nm in the case of 2,3-disubstitution with strong donors (e.g. **83g, h**), in agreement with a high CT character of this absorption[61, 114] (*vide supra*).

It may be of interest that naphthazarin-type (see Section III.C) quinones (**85**) also reveal strong absorptions in the visible area (520–550 nm), even if only one donor substituent X is present[6w].

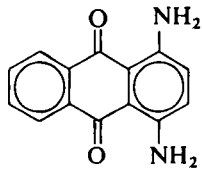


(85)

R = H, Cl
X = *O*-Alkyl, *N*-Alkyl
Y = H, Cl



(86)



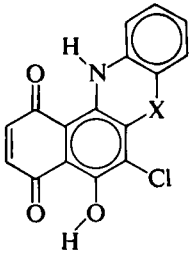
(87)

Even more work has been carried out with donor-substituted 1,4-anthraquinones, which are important as dyes. Spectra of 1- and 2-aminoanthraquinones and the whole series of diaminoanthraquinones have been measured and calculated (PPP, PPP-CA)[86i-l, 123, 124] (for a short summary see Ref. 86i). Again, the LFPT band apparently involves strong CT character[86i, 123, 124] and therefore is shifted bathochromically (410–470 nm for 1-, 2-aminoanthraquinones[86i], 493 nm for 1-dialkylamino-anthraquinone **86** of the crown ether type[113]). Compound **86** shows hypso- or bathochromic shifts in the light absorption upon addition of salts, which has been discussed in view of the crown ether complexation in the donor or acceptor part of the molecule[113].

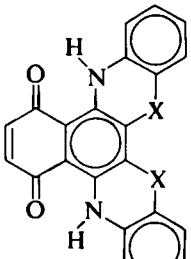
Strong red shifts are calculated (PPP-CA) and observed for diamino-substitution[86j-l]. It may be of interest that 1,4-diaminoanthraquinone (**87**) with a naphthazarin-type system exerts the strongest red shift of the LFPT band of all diaminoanthraquinones.

In principle, the same gradation is observed with dihydroxyanthraquinones: 1,4-dihydroxyanthraquinones (including the 'naphthazarin system') of the general formula **Ma** (Section III.C) show LFPT bands at 520 nm and beyond[8g, 53], whereas 1,5-dihydroxyanthraquinones (**La**) and 1,8-dihydroxyanthraquinones (**K**) reveal these bands at 440–460 nm[6a, 8f, 53, 74]. This is in contrast to the effect on the carbonyl absorption $\bar{\nu}_{C=O}$ in the IR region (Section III.C), where **M** and **L**, but not **K**, give rise to a remarkable frequency lowering.

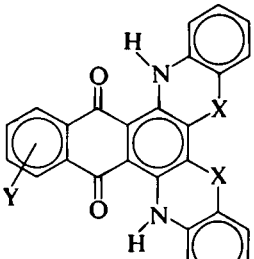
This unique effect of the 'naphthazarin unit' is further demonstrated for heterocondensed 1,4-quinones[10h, 117]. Systems like **88–90** (X = S or Se; Y = H or F_4), so called IR dyes



(88)



(89)



(90)

for optical recording media, reveal two strong absorptions in the visible region: 616–725 nm ($\log\varepsilon = 3.83$–4.25) and 642–780 nm ($\log\varepsilon = 3.66$–4.19) in $CHCl_3$[117a]. We suppose that at least one or both of these bands are due to charge transfer from the S,Se rings to the carbonyl groups (see also Ref. 117b). For related compounds see Ref. 117b–e.

In the series of condensed 1,2-quinones, 1,8-dihydroxyphenanthraquinone would correspond to 1,4-dihydroxyanthraquinone, and, indeed, the derivative **11** shows an absorption of $\lambda_{max} = 524$ nm ($\log\varepsilon = 3.65$) in methanol[49a], which might be ascribed to the red-shifted LFPT.

D. Charge Transfer Spectra

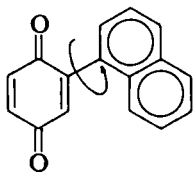
In sections IV.B, C we have already mentioned that the LFPT band of a quinone may show charge transfer (CT) character, if an intramolecular CT transition is defined as 'an electronic transition from an occupied molecular orbital localized in one part of a conjugated system to an unoccupied molecular orbital localized in the other part of the same conjugated system'[89c]. Charge transfer electron donor–acceptor complexes in a more concise sense, however, possess *insulated* donor and acceptor groups or areas in two different molecules (intermolecular CT) or within the same molecule (intramolecular CT). They give rise to a new band in the visible spectrum, which is usually broad and featureless, and not always well separated from the quinone spectrum.

The following compounds were mainly used as donors for *intermolecular* quinone CT complexes: aromatic hydrocarbons[4j, 63j, 90b, e, 91, 92, 95], amines[63j, 90c, i–k, q, 93, 96a], amino acids and proteins[90d, p], nitrones[90f, 92d], *N*-heterocycles[63e, j, 90h, l, m, q–s], phenols (quinhydrone)[90l], sulphides[90a], tetrathiofulvalene[63j, 90n], hexamethylenetetratellurafulvalene[90o] and ferrocene[21k, 90g]. The acceptor quinones were preferentially halogenated and cyano-substituted 1,4- and 1,2-benzoquinones, as well as the parent quinone **1**, but such complicated systems as 'poly' triptycene quinones[96a] have also been used.

Among others, the frequency ν_{CT} of the CT band is determined by the ionization potential I^D of the donor and the electron affinity E^A of the acceptor. Series of relative electron affinities of quinones and other acceptors are available[125, 126]. These are given detailed treatment in Ref. 127; for special information see the references collected in Section IV.A.

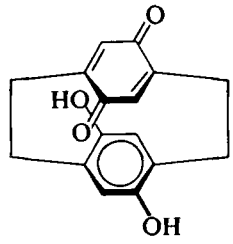
In the case of intramolecular CT transition, there is continuous change from planar conjugated π systems (like condensed quinones, see section IV. C) via conformational nonrigid or twisted π systems, like **91**[89c], to insulated π systems, as the cyclophanes **40**, **42**[21d] and **92**[21l] or the triptycene **93**[23] and finally to spacer-separated π systems, as in porphyrin-linked quinones[99, 100].

Considerable effort has been involved in synthesizing cyclophane quinones[21, 97, 98]. The compounds **40** and **42**, as examples, reveal drastic differences in their CT bands: the absorption intensity of **40** is about ten times higher than that of **42**, with the absorption maximum being blue-shifted by only 20 nm. Since **40** and **42** have the same E^A of the acceptor and the same I^P of the donor, this observation clearly demonstrates the orientational dependence of the CT absorption (**40**: pseudogeminal; **42**: pseudo-*ortho*)[21d]. This was satisfactorily explained by simple HMO theory and using π-electronic methods explicitly allowing for electron interaction[98b]. The differences in ν_{CT} and extinction are due to the lower transannular interaction between the frontier orbitals (relevant for the CT band) of donor and acceptor in **42** with respect to **40**. On the other hand, a through-bond homoconjugative interaction between the donor and acceptor rings has been proposed for CT in the triptycene quinone **93**[23].



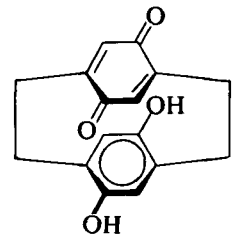
(91)

λ_{CT} = 431 nm (CH_2Cl_2)
505 nm (CF_3COOH)



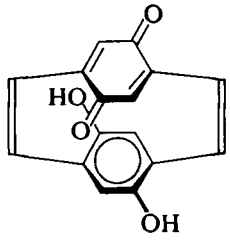
(42)

λ_{CT} = 515 nm (MeOH)



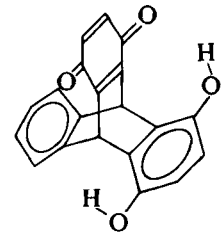
(40)

λ_{CT} = 495 nm (MeOH)



(92)

λ_{CT} = 517 nm (EtOH)



(93)

λ_{CT} = 430 nm (Me_2SO)

E. Photoelectron Spectra

The He(I) photoelectron spectra (UPS) of **1**[88d,101a-c] and **60**[101d,e] are easily distinguishable in the region of lowest ionization potentials (9–13 eV), as may be seen from the stick spectrum in Figure 1[101f]. The molecular orbitals from which ionization occurs (given in Figure 1) have been assigned on the basis of MO calculations (MINDO/3) and

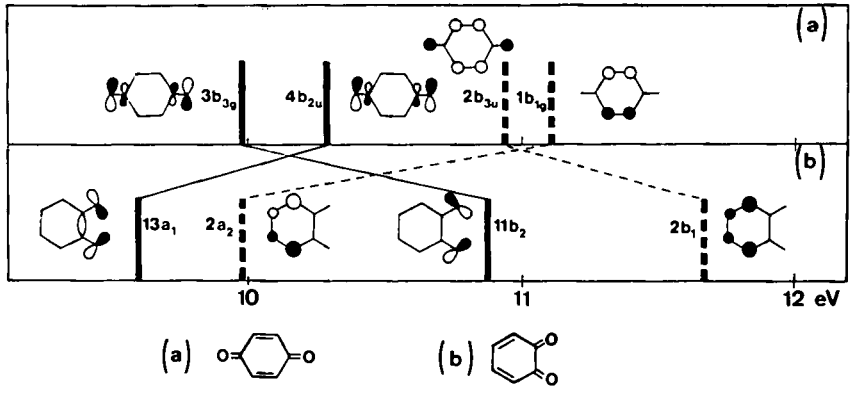


FIGURE 1. He(I) photoelectron stick spectra (UPS) according to Ref. 101f (a) of **1**, (b) of **60**

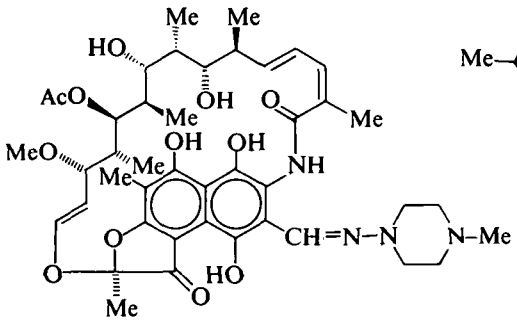
qualitative bandshape criteria (for **60**)[101d] and empirically (vibronic structure of UPS bands and substitution effects, for **1**)[101c]. The latter assignment is still a matter of controversy[88d, e, 101a, b, g-k]. The influence of substituents (alkyl[101c, d, e, l, q], halogen[101c, g, m] and of condensation (naphthoquinones[101h, n, p]) has also been investigated. For X-ray emission spectra (XPS) of **1** and condensed quinones see Refs 101o, p; for electron transmission spectroscopy (ETS) see Ref. 101q.

F. Analytical Applications

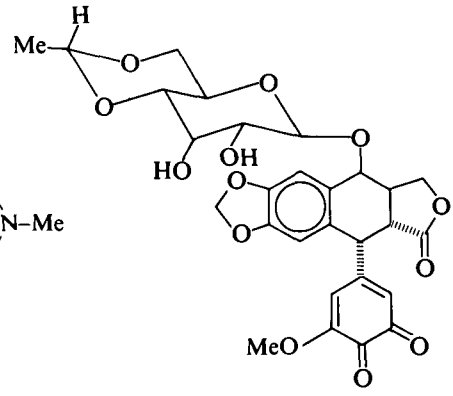
UV/vis spectroscopy is easily performed with μg samples. In particular, the rather unique absorptions in the near UV/vis region may be of diagnostic value. Even a distinction between 1,2- and 1,4-benzoquinones is possible, since the *o*-quinones usually show their LFPT and the $n \rightarrow \pi^*$ transition at lower frequencies. In every case, the effect of substituents, especially of OR and NHR/NR_2 groups, should be carefully analysed. The quantitative determination of quinones via application of the Lambert–Beer law on their characteristic absorption maxima is a standard method.

Examples of the analytical use of UV/vis spectroscopy have already been mentioned throughout this section. Further examples are the application of isoprenoid quinone analysis for bacterial classification and identification[128], the spectrophotometric determination of **1** and **60** in mixtures with their dihydroxy compounds[129], the characterization of the quinonoid oxidation products of hydrocarbons in the presence of antioxidants[130] and the identification of natural quinones[131]. The long-wavelength absorption (and CD bands) or rifampicin (**94**) and rifampicin quinone (**95**) were used to monitor the effects of *Escherichia coli* RNA polymerase binding of DNA, dinucleotides and nucleoside triphosphates[132].

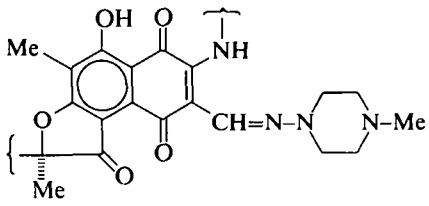
New developments include the combination of UV/vis spectroscopy with electrochemical methods (spectroelectrochemistry) for the investigation of electrode processes, e.g. occurring in the diffusion layer in a DMSO solution of **1**[133] and for monitoring



(94)



(96)



(95)

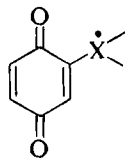
the formation of electrochemically generated products, e.g. in the oxidation of the antineoplastic agent etoposide to its 1,2-quinone (**96**)[134]. The application of HPLC with UV/vis detection has become a powerful analytical tool for quinones and will be discussed in Section VII.A.

Furthermore, CT absorption may be used for the determination of quinones[135], as well as of the donors, e.g. amines[136]. The structure of polymer film coatings obtained by electropolymerizing of naphthol derivatives (containing quinonoid units) has been elucidated by XPS[137]. Finally, quinones may be analysed by the UV/vis spectra of their corresponding semiquinones obtained by reduction[138].

V. ESR/ENDOR SPECTRA OF QUINONE ION RADICALS

A. General Remarks

As pointed out earlier[1], ESR investigation of quinones is only feasible when the diamagnetic parent compounds are converted to paramagnetic species. This transformation can be done by oxidation of the quinone to the corresponding radical cation[139]; by reduction of the quinone to radical anions (semiquinones)[1]; by photoexcitation of the quinone and quenching of the resulting triplet state[140b]; or by combination of the parent compound with a paramagnetic molecule[138d] (**R**). We will restrict the discussion to the first



(**R**)

two methods. The main spectroscopic methods pertinent to the spin density distribution in free radicals are ESR, ENDOR and CIDEP.

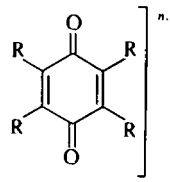
There have been a few reports on CIDEP of quinones during photolysis[140, 141]; the method, however, is too complicated to serve as a standard analytical technique. ESR and ENDOR, on the other hand, are now standardized, and numerous reports on hyperfine splitting (HFS) constants a and g factors of radicals derived from quinones have appeared since 1973[142]. These spectra may therefore be used to identify the corresponding quinones.

B. Cation Radicals

Only two papers deal with ESR investigations of quinone cation radicals[139, 141a]. Photooxidation of **1** at room temperature as well as electrochemical oxidation of tetrakis-(dimethylamino)-1,4-benzoquinone (**97**) produced the corresponding cations (**1a**, **97a**).

The g values and coupling constants of these one-electron oxidation products are collected in Table 8 together with the data of the semiquinones (**1b**, **97b**) obtained by one-electron reduction of the same quinones. The ESR spectrum of **97b** was poorly resolved since the small proton HFS and the line width were of comparable magnitude. The a_H value was determined from an ENDOR experiment; coupling with N could not be observed at all. These findings are in accordance with McLachlan calculations[139], which predict a very small spin density at the N atoms in the anion (1/14 of that of the corresponding cation) due to the different localizations and symmetries of the singly

TABLE 8. ESR spectra of 1,4-quinone cation (a) and anion (b) radicals



Compound no.	R	*a* (Gauss)	Charge *n*	*g* Value	Solvent	References
(1a)	H	2.99 (4H)	+1	2.0038	CF_3COOH	141a
(1b)		2.37 (4H)	−1	2.0047	EtOH	1
(97a)	$N(Me)_2$	3.32 (24H) 3.32 (4N)	+1	2.0032	DMF	139
(97b)		0.112 (24H) 0.0 (N)	−1	2.0046	DMF	139

occupied molecular orbitals in **97a** and **97b**[139] (for the oxidation of a quinone closely related to **97**, leading to a diamagnetic dication, see Ref. 143).

Obviously, the spin density distribution as well as the *g* value depend heavily on the oxidation state of the paramagnetic species. However, not enough data are available to derive rules for the variation of these properties.

Oxidation of 1,4-dihydroxybenzenes in H_2SO_4 also yielded cation radicals[149]. These species are, however, not oxidation products of quinones and may rather be classified as diprotonated semiquinone anions, i.e. phenol cation radicals. Nevertheless, it is of interest that the *g* values are smaller than 2.004 and therefore comparable to those observed in the cations obtained by quinone oxidation. Moreover, they can be linearly related to the π-electron spin density at the O atoms.

C. Anion Radicals

Various reducing agents (Na, K, amines, H_2/Pt, $Na_2S_2O_3$ or amalgams)[1,150] and electrolytic reduction were used to prepare semiquinones from the corresponding quinones. The most universal method, however, proved to be the autoxidation of alkaline solutions of hydroquinones[151].

1. g Values

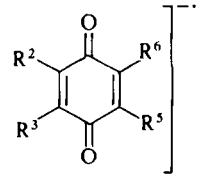
In semiquinone radicals, the spin density on the oxygen atoms particularly contributes to the *g* values. On the other hand, the oxygen atoms are the basic sites of the radicals and are therefore prone to interact with solvent and/or counter-ions. For this reason, solvent polarity as well as temperature and counter-ion concentration influence the magnitude of the *g* values[152,153]. The addition of crown ethers with strong affinity to metal ions leads to complexed ion pairs which show alkali metal HFS even at room temperature[146]. These observations point to fast temperature-dependent equilibria between free radicals and those forming hydrogen bonds to the solvent or building ion pairs with the counter-ions. Therefore, the data derived are time-averaged values of these different states. Consequently, the identification of semiquinones using *g* values only is unreliable.

An exception was observed for tetrahalogenated semiquinone anions where a substantial contribution to *g* originates in the spin-orbit interaction of the halogens[154]. The values increase significantly with an increasing atomic number of the halogen and may be used to identify these species.

2. *Hyperfine structure constants*

In Tables 9 and 11 the HFS coupling constants a are collected for some of the new semiquinones in order to supplement Tables 17 and 18 of Ref. 1. Data derived from semiquinones with larger substituents as in L-adrenalinesemiquinones[155] or heterocyclic compounds such as triazolo-[144], quinoline-[156], isoquinoline-[156], quinoxalinesemiquinones[156] and diaziquone[157], were not included.

TABLE 9. ESR spectra of 1,4-semibenzoquinones

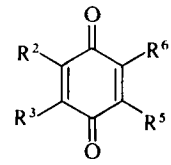


No.	R^2	R^3 a (Gauss)	R^5	R^6	Solvent	References
(98b)	NH_2 1.85(N) 0.75(2H)	H 0.18	Me 4.65	H 0.75	DMF/H_2O	144
(99b)	NH_2 2.5(N) 0.90(2H)	H 0.7	NH_2 2.5(N) 0.90(2H)	H 0.7	DMF/H_2O	144
(24b)	OMe 0.0	OMe 0.0	H 2.65	H 2.65	H_2O	145
(100b)	NH_2 0.6(N) 0.0(H)	NH_2 0.6(N) 0.0(H)	H 3.0	H 3.0	EtOH	146
(101b)	$-O-CH_2-O-$ 0.18		H 2.63	H 2.63	H_2O	145
(102b)	OMe 0.0	OMe 0.0	Me 2.45	H 1.98	H_2O	145
(103b)	OMe 0.0	OMe 0.0	Me 2.15	Me 2.15	H_2O	145
(104b)	NH_2 1.75(N) 0.90(2H)	H 0.2	H 4.9	H 1.52	EtOH	146
(105b)	NH_2 1.0(N) 0.25(2H)	H 1.3	H 1.3	NH_2 1.0(N) 0.25(2H)	EtOH	146
(106b)	CN 0.61(N)	CN 0.61(N)	H 1.05	H 1.05	DME*	147
(66b)	COMe 0.25(3H)	H 3.89	H 1.25	H 2.49	EtOH	142

* DME, dimethoxyethane.

A serious problem arising in the characterization of quinones from their corresponding anion radicals is the dependence of a on the polarity of the solvent, the temperature and the counter-ion. A detailed investigation on a series of various substituted 1,2- and 1,4-semibenzoquinones in solvents with decreasing solvation capability (H_2O, EtOH, DMSO, DMF and HMPA) revealed that the changes of a are at a maximum for all radicals when the data determined in H_2O and HMPA were compared[148] (Table 10). This is due to the fact that aprotic solvents (like HMPA) solvate the ions only weakly, whereas protic

TABLE 10. Solvent effect on a of 1,4-semibenzoquinones[148]



Compound no.	R^2	R^3 a (Gauss)	R^5	R^6	Solvent
(107b)	$C(Me)_3$	H	H	$C(Me)_3$	
	0.0	1.31	1.31	0.0	H_2O
	0.0	2.25	2.25	0.0	HMPA
(4b)	Me	H	H	Me	
	2.1	1.87	1.87	2.1	H_2O
	1.85	2.22	2.22	1.85	HMPA
(108b)	OMe	H	H	OMe	
	0.80	1.47	1.47	0.80	H_2O
	0.50	1.92	1.92	0.50	HMPA

solvents form hydrogen bonds to the basic sites (O atoms). In the latter case, the electron distribution is perturbed, which is manifested as changes in a with the solvent. As a general trend of the solvent effect we may notice that protic solvents decrease the spin density at positions 2, 3, 5 and 6 in 1,4-semibenzoquinones and at positions 3 and 6 in 1,2-semibenzoquinones; the opposite effect was observed at positions 4 and 5 of the latter.

The applicability of ESR spectroscopy to the analysis of quinones requires well resolved spectra, which can be interpreted with limited expense. This feature is often met with symmetrically substituted species, where only one or two different nuclei contribute to the splitting pattern. However, the effect of solvent variation on the spin density distribution is of the same magnitude as the substituent effect. Therefore, data determined in different solvents must be examined critically.

From a comparison of the compounds of Tables 9 and 10 we may derive general trends for the variation of the proton HFS caused by different substituents.

(1) In 2,3-disubstituted 1,4-semibenzoquinones, electron donating substituents such as NH_2 (**100b**), or OMe (**24b**), increase a_H at positions 5/6 compared to **1b**; CN (**106b**) has the opposite effect.

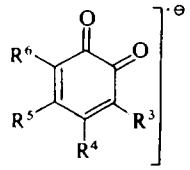
(2) In 2,6-disubstituted 1,4-semibenzoquinones (**105b, 4b, 107b** and **108b**), these effects are reversed; the more electron releasing the substituent the smaller a_H at positions 3/5 becomes.

(3) In 2-substituted 1,4-semibenzoquinones (**66b, 104b**), substituents of opposite electronic properties (COMe and NH_2) also cause opposite shifts of the three non-equivalent a_Hs at positions 3, 5 and 6: NH_2 increases a_{H5} and decreases a_{H3} and a_{H6} compared to a_H in **1b**, for COMe the reverse behaviour is noticed.

Steric effects may also play an important role in perturbing the spin density distribution. In the case of vicinal OMe groups, this has been observed by Gascoyne and Szent-Györgyi[158]. Whereas the HFS of the two OMe groups in **108b** is well resolved, semiquinones with two *vicinal* methoxy groups in no case revealed HFS of the OMe protons. The authors attributed this surprising effect to the steric hindrance, breaking the hyperconjugation between the quinone ring and the methyl moiety of the methoxy groups. Vicinal amino groups (**100b**) also suffer a significant decrease in spin density compared to

2,6-di- or 2-monosubstituted species (**105b**, **104b**). These effects may also be observed in 1,2-semibenzoquinones (Table 11); however, the spin density of the unsubstituted species is five times larger at positions 4/5 than at 3/6. HFS of OMe groups at positions 3 or 6 therefore could not be observed (HFS of NH_2 decreased significantly), when other substituents were vicinal. Substituents at positions 4/5 also suffer a significant decrease in *a* when the vicinal positions 3/6 were additionally substituted.

TABLE 11. ESR spectra of 1,2-semibenzoquinones



Compound no.	R^3	R^4 *a* (Gauss)	R^5	R^6	Solvent	References
(**109b**)	NH_2	H	H	H	EtOH	150
	1.65(N)	0.0	5.1	0.85		
	0.70(2H)					
(**110b**)	H	NH_2	H	H	EtOH	150
	1.90	2.10(N)	3.10	0.85		
		3.95 (2H)				
(**111b**)	NH_2	NH_2	H	H	EtOH	150
	1.15(N)	1.60(N)	3.20	0.89		
	0.0 (H)	0.95(2H)				
(**112b**)	H	NH_2	NH_2	H	EtOH	150
	0.2	2.25(N)	2.25(N)	0.2		
		0.90(2H)	0.90(2H)			
(**113b**)	OMe	OMe	H	H	H_2O	145
	0.0	0.44	3.92	1.70		
(**114b**)	OMe	OMe	H	Me	H_2O	145
	0.0	0.53	2.95	1.85		
(**115b**)	OMe	Me	H	OMe	H_2O	145
	0.0	5.61	1.70	0.61		
(**116b**)	H	OMe	OMe	H	H_2O	145
	0.32	1.10	1.10	0.32		
(**117b**)	H	$-O-CH_2-O-$		H	H_2O	145
	0.33	4.22		0.33		
(**118b**)	OMe	OMe	OMe	H	H_2O	145
	0.0	0.10	1.20	0.60		
(**119b**)	OMe	OMe	H	OMe	H_2O	145
	0.0	0.90	1.10	0.68		
(**70b**)	OMe	H	OMe	H	H_2O	145
	0.75	1.70	1.00	0.95		
(**120b**)	$C(Me)_3$	H	H	$C(Me)_3$	EtOH	142
	—	3.3	3.3	—		
(**121b**)	COOEt	H	H	H	EtOH	142
	0.092	1.445	2.537	3.727		

Several authors[159-162] designed additivity rules and increment systems to compute the proton coupling constants of various substituted 1,4-[160,161] and 1,2-semibenzoquinones[159], or semianthraquinones[162]. The correlation of experimental data and theoretical results obtained from the derived models is good. The range of substituents

under consideration is not complete, however, and therefore the applicability of these systems is limited.

3. Secondary products

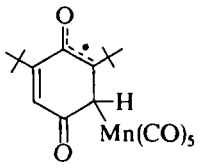
A problem arises in the preparation of semiquinones in alkaline media because of the formation of secondary products. Quinones having free positions on the quinonoid ring react with hydroxide ions[163] or alkali hydroxides in alcohols[164] to give the hydroxy- or alkoxy-substituted semiquinones. The formation rate of these products increases with increasing alkali concentration of the solvent. When OH^- is the attacking species, the products of 1,2- and 1,4-quinones are identical and reveal the 2-hydroxy-1,4-semiquinone structure[163]. The spectra obtained from these product mixtures are unsymmetrical and dependent on time due to the different g values and the reaction kinetics of the (at least) two species.

4. Metal complexes

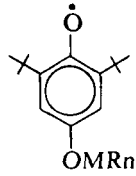
A large group of researchers used various metals salts, organometallic reagents or transition metal complexes to stabilize semiquinones by complexation with the metal[165, 166].

The addition of diorganothallium hydroxide to solutions of catechols yielded persistent 1,2-semiquinones; in ion pairs consisting of radical anions and organothallium counter-ions, the metal HFS could be observed[159, 167]. When group IIIa elements (Al, In, Ga) or Sn were reacted with 3,6-di-*t*-butyl-1,2-benzoquinone, hexacoordinated triradical complexes were formed[168]. The variety of semiquinone complexes was much larger when transition metal salts or complexes were used. Hexacoordinated structures in different oxidation states with three 1,2-semiquinone ligands as well as complexes with mixed ligands were observed[169]. The g values of these complexed species differed significantly from those of the free semiquinone radicals; often a strong coupling with the metal ions was found[169, 170].

1,4-Semiquinones react with metals and metal complexes in a less defined manner. Decacarbonyldimanganese and 2,6-di-*t*-butyl-1,4-benzoquinone (**107**) thus give an 'α-keto'-type spin adduct (**S**)[171a]. The spin density distribution is comparable to that observed



(S)



(T)

M = Si R = Me[172]

M = Ge, Sn, Pb R = Me[171a]

M = Ge R = Et[171b]

in the 2-cyclohexanoyl radical and therefore not of the 1,4-semiquinone type. The quinone **107** was also used as spin trap for various organometallic radicals[172] to give the 4-substituted phenoxy radicals (**T**).

D. Analytical Applications

ESR spectroscopy is a useful tool in the analysis of many naturally occurring semiquinones. Pedersen was able to identify quinones and quinols in plant extracts by their

HFS and g values, and quantitative analysis was performed by comparing the ESR signal intensity with standard curves[142, 173]. A review, collecting the various applications of ESR in medicine, reports (among others) on semiquinone studies[174].

Chemical reaction pathways may also be investigated by ESR spectroscopy, as shown by Bubnov and coworkers[175] for the photoreduction of the sterically hindered 3,6-di-*t*-butyl-1,2- and 2,6-di-*t*-butyl-1,4-benzoquinone (**120**, **107**).

Determination of biochemical pathways and the verification of reaction models may be facilitated using the sensitive ESR technique. Semiquinones were detected in fulvic and humic acids; from the change of the spin concentration by electrolysing the samples, it was concluded that they are at least partially responsible for the reducing capability of these materials[176].

The primary step of photosynthesis consists of a photochemical one-electron transfer to an electron acceptor (often a quinone). Many authors have investigated the photochemically induced generation of semiquinone radicals in biological materials and model systems by ESR[177].

VI. ELECTROCHEMICAL METHODS

A. General Remarks

Electrochemistry is another discipline usually thought to be predestined for the analysis of quinones, since a typical feature of the latter is their cathodic reduction proceeding as a single two-electron or as two separated one-electron transfers, depending on the conditions, and often being 'quasi-reversible'. For the reasons given below, and since the electrochemistry of quinones is treated in detail in another chapter of this book, neither a detailed discussion of the principles underlying the applied methods, nor a collection of data is presented in this section.

B. Voltammetric Methods

Mainly, linear sweep voltammetry (LSV)[178], especially in the form of polarography (i.e. LSV at the dropping mercury electrode[178-180]) or cyclic voltammetry (CV)[178, 181, 182] were used for the investigation of quinones. The applied potential is altered linearly (LSV, polarography) or triangularly (CV) with time, and the resulting current is recorded. A more expensive, newer polarographic method also used in quinone analysis is pulse polarography (PP), above all in the form of differential pulse polarography (DPP)[178-180]. In principle, a rectangular voltage pulse is applied to the mercury-drop electrode within a short time interval at the end of the lifetime of the drop (PP). In the case of DPP, the current is measured a few ms before applying the pulse to the mercury drop, stored, and then subtracted from the value measured in the second half of the pulse period. In this way, concentrations of 10^{-8} M may be detected in comparison with 10^{-7} M in PP.

The resulting experimental data are half-wave potentials $E_{1/2}$ (polarography) or peak potentials E_p (LSV, CV and DPP), and the current values at these potentials. In the case of reversible redox processes, $E_{1/2}$ of LSV and E_p of CV are simply related to each other and to the formal potential E° (equation 1).

$$E^\circ = E_{1/2} = 1/2 \cdot (E_p^{ox} + E_p^{red}) \tag{1}$$

The value of the potentials depends on the reference electrode and may be influenced by electrode materials, supporting electrolytes, and diffusion potentials (connection to the reference electrode).

$E_{1/2}$ and E_p are characteristically different for 1,2- and 1,4-quinones. Moreover, the peak and half-wave (or wave) heights as current quantities are proportional to the concentration

of the electroactive quinones, and allow their quantitative determination. It should be clearly stated, however, that many other compounds are also electroactive in the potential area in question, a fact which may hamper quinone analysis involving $E_{1/2}$ and E_p values only.

Investigation of electrode kinetics, the genuine domain of LSV and CV and highly interesting for reaction mechanisms, is of no practical importance for diagnostic purposes, since the relevant data (e.g. k values) are not easily accessible.

For compilations of potential data of quinones and for discussions see the following references: LSV[1, 6b, 57c, 77, 110, 158, 183, 184], CV[7a, 1, 9a, 22b, 46, 184h, v, 185].

Besides the usual metal electrodes, thin-layer electrodes[186a] have been used. Several papers deal with chemically modified electrodes, either using quinones as substrates to modify electrodes[187] or investigating the behaviour of quinones on modified electrodes[188]. These are interesting new developments, but not yet suitable for a general, easy analytical approach.

Thin-layer voltammetry of quinones[186b] subjects a very thin layer (δ = 10–50 μm) of solution to electrolysis in order to eliminate diffusion effects (restricted diffusion).

C. Coulometry

Coulometric techniques determine the quantity of material electrolysed from the amount of charge passed through the electrochemical cell, on the basis of Faraday's law (equation 2):

$$N = Q/n \cdot F = (1/n.F) \cdot \int_0^t i \cdot dt \qquad (2)$$

where N = number of moles of the substance being electrolysed; n = number of electrons transferred per molecule; Q = total charge passed (Coulombs); i = current (Amperes); t = time (s); F = Faraday's constant (96.485 Cb mol^{-1}).

In controlled-potential coulometry (CPC), a constant potential is applied to the working electrode in order to electrolyse the substrate completely. The current is integrated to give the charge needed for an exhaustive electrolysis. In constant-current coulometry (CCC)[189], the experimental parameters are now current i (set constant) and time t, i.e. $Q = i \cdot t$. For quinone analysis, mainly CCC was used, especially in the form of secondary coulometric titration[189], i.e. the quinone is not reduced directly at the electrode but rather by an electrogenerated reagent.

D. Other Methods

Besides the hitherto mentioned 'dynamic' methods ($i \neq 0$), potentiometry as a 'static' method ($i = 0$) has also been applied to quinones in the form of the well-known potentiometric titration.

Electrochemical detection (ELD)[190] has been used in the chromatography of quinones (see Section VII). The underlying electrochemical principle is direct-current amperometry (the measurement of electrochemical current in response to a fixed electrode potential) in a special form of chrono-amperometry (measuring the current as a function of time). Since the mobile phase must be able to carry an ionic current, only reversed phase (RP) chromatography with aqueous solutions (with or without methanol, acetonitrile, or tetrahydrofuran) can be used. Of course, ELD *per se* cannot discriminate quinones from other substances (see Section IV.B).

Finally, it should be stated that electrochemical methods can be combined with other spectroscopic methods in a static or hydrodynamic way to determine quinones. ESR

spectroscopy is mostly used for this purpose (see Section V for examples, Ref. 191a for a general discussion), but UV/vis is also a candidate (see Section IV.F) and ^{1}H-NMR has been chosen to determine the electron exchange rate between **1** and **1b** or ubiquinone and its semiquinone[191b].

E. Analytical Applications

Electrochemical methods have been mainly applied to the analysis of natural quinones or the investigation of quinonoid compounds as models for biochemical reactions. Besides the literature already mentioned in Section VI. A–D, a few more examples are given below, starting with voltammetry.

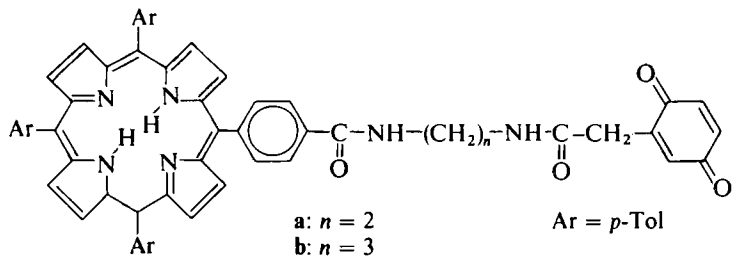
1,2-, 1,4- and 2,3-Quinones and hydroquinones may be discriminated using CV in the presence of sodium borate in an alkaline medium[192]. The borate interacts with 1,2-dihydroxybenzenes and the resulting complex can be oxidized at more positive potentials than the free form. An example of the application of CV to mechanistic problems is the redox system etoposide/etoposide quinone (**96**), with an extensive investigation of the pH influence[134].

Quinones formed during oxidation of phenols in waste water may be determined polarographically in the presence of excess phenols making use of a change of $E_{1/2}$ values with the quinone concentration in relation to the pH[193].

The cathodic reduction of anthracyclines (especially of daunomycin), potential antitumour antibiotics, has attracted much interest[194]. It has turned out that glycoside elimination occurs only after a two-electron reduction[194d]. Possible relations between redox potentials and cytotoxic[195] as well as antineoplastic[196] activity of simpler quinones have been investigated. In the case of 1,4-benzo- and naphthoquinones the compounds of the lower (i.e. more negative) redox potentials generally possess the most potent antitumour properties towards a Sarcoma 180 test system. Benzoquinones with a less negative redox potential than naphthoquinones were in general inactive against Sarcoma 180[196]. The reaction of phenanthraquinone (**80**) with Ehrlich ascites tumour cells of mice[197a] and the electrochemical reductive activation of mitomycin C[197b] have been further targets of voltammetry.

Another item investigated was the electron transport in model compounds for biological systems: hydroxyquinones[198], ubiquinones[199], or linked porphyrin quinones (PQ)[200]. Thus, the energies of the charge separated $P^{+\cdot}Q^{-\cdot}$ states of the amide-linked ('spacered') PQ molecules **122** and **123** in CH_2Cl_2 amount to 1.37 ± 0.02 eV, taken as the difference in redox potentials for the formation of $P^{+\cdot}Q$ and $PQ^{-\cdot}$[200].

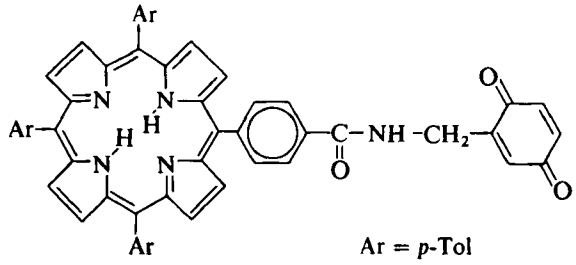
Besides CV, differential pulse voltammetry (DPV) with alternating current was used for these investigations. Examples for the application of differential pulse polarography (DPP) are the determination of quinonoid and other functional groups of enomelanin from *Vitis vinifera*[201], the analysis of non-volatile water pollutants, as quinones, without



a: $n = 2$
b: $n = 3$
c: $n = 4$

Ar = *p*-Tol

(**122**)



(123)

separation[202], or the indirect microdetermination of quinone 1[203]. For this purpose, 1 was reduced by I^- in the presence of acid. The liberated I_2 was then extracted into $CHCl_3$ and reduced to I^- with $NaHSO_3$. The iodide was afterwards oxidized with Br_2/H_2O to IO_3^-, which was determined by DPP, the detection limit being 1.2×10^{-6} M quinone.

Finally, reports on voltammetric analysis of pharmacologically active[204] and clinically relevant[205] quinones are also available.

Direct coulometric investigations (reductions) have been performed on simply substituted 1,4-benzoquinones (CPC)[184c, h, 206], tetrahydroxy-1,4-benzoquinone[198], ubiquinones (CPC)[184r], and condensed quinones (CPC)[184e]. Indirect coulometric titrations used electrogenerated Cu^+ from a copper electrode[207a], Fe^{2+} (CCC)[207b], Ti^{3+} [208], and Ce^{4+} [209] for the quantitative determination of quinones and for drug control[210].

Examples of potentiometric titrations (end point detection) of quinones are the direct reaction of quinones with Ti^{3+} [211], Fe^{2+} [212], or V^{2+} [213], or the indirect titration of a mediator which reacts with the quinone[214].

VII. CHROMATOGRAPHY OF QUINONES

A. General Remarks

As other organic molecules, quinones may be purified, detected and determined by chromatographic methods. Gas chromatography (GC), liquid chromatography (LC), high-performance liquid chromatography (HPLC) with normal or reversed phase (NP or RP), thin-layer chromatography (TLC), or paper chromatography (PC) have been used. Since quinones are coloured, they may be easily detected in LC, TLC, or PC even by the naked eye; and for GC the usual detectors are suitable.

As a rule, however, special detection techniques were used together with LC, HPLC, or TLC, the three chromatographic methods chiefly applied to quinones. In the case of HPLC and LC, all physical methods discussed in this chapter, i.e. ^{1}H-NMR, ^{13}C-NMR, IR, Raman, UV/vis spectroscopy (and luminescence[215]), ESR spectroscopy, as well as electrochemistry (ELD), are suitable, although UV detection was the method of choice.

Supercritical fluid chromatography/Fourier-transform-IR spectrometry with an automatic diffusive reflectance interphase ensures high sensitivity; it was applied to acenaphthenequinone[216a].

HPLC/ESR needs paramagnetic species and has been used by Creber and Wan[216b] to isolate and characterize rhenium carbonyl quinone complexes.

Few HPLC/ELD investigations on quinones are known, since substituted quinones will not always dissolve in the polar mobile phase used for reversed phase (RP) chromatography and necessary for ELD (see Section VI.D). Hg-film[217] and glassy carbon[218] electrodes have been tested. The observed oxygen overpotential on glassy carbon proved

to be more negative (relative to Hg/Au), thus allowing the determination of quinones (2.5 pmol) via reduction in the presence of dissolved O_2.

In TLC the suppression of fluorescence of added special indicators is familiar, but spray reagents (see Table 12) or vapour development (e.g. with OsO_4[219]) have also been used.

Retention times (GC, LC, HPLC) or R_F values (TLC) are characteristic and identify the quinone. Intuition and empiricism are still requested in this field, and a collection of chromatographic data is not provided here. Peak areas of recorded or computer-processed chromatograms (GC, LC, HPLC) allow an easy quantitative determination, whereas the densitometric[220] evaluation of TLC spots provides some problems.

The present authors recommend TLC as an inexpensive, simple, fast and effective method for a qualitative characterization of quinones. It should be stated, however, that some quinones are highly unstable in the adsorbed state, especially when exposed to light, hence there may be 'tailing' due to the formation of hydroquinones which, in turn, are prone to be partially air-oxidized, when subjected to TLC.

Reviews on chromatography treating also quinones (e.g. LC[221]) or specialized on certain classes of quinones (e.g. anthraquinones[222]) are available.

B. Coupling with Spectroscopic Methods

After a chromatographic purification, the products are usually further characterized or structurally investigated by spectroscopic methods. An advantage over this procedure would be attained by an immediate spectroscopic investigation of the compounds as they are eluted, either in a direct or by-pass flow system or by a type of stop-flow procedure.

In contrast to the detection methods mentioned in Section VII.A which just monitor the elution profile at a singular point of the spectral domain (e.g. at a singular wavelength in UV), complete spectra of the eluted (and separated) compound would be available before isolating the sample. The most effective coupled system, gas chromatography–mass spectroscopy (GC–MS) has, indeed, proved to be of high value also for quinones[223], and even TLC–MS may be of advantage in special cases[224]. Other combinations (such as HPLC coupled to UV or NMR spectroscopy or to CV, installed in an electrochemical detector) seem not to have been met with interest in quinone chromatography, so far. Only a type of LC–voltammetry has been investigated for the quinone-like 6-methyldihydropterins[225].

C. Analytical Applications

A selection of applications of chromatographic methods to quinones is presented in Table 12, and a few special aspects of natural quinones are enumerated below. Further literature may be found in the references quoted in Table 12.

Naphtho- and anthraquinones of the bark of *Rhamnus fallax*[241] (HPLC, TLC), α-tocopheryl quinone in blood[242] (HPLC–UV) and prenyl quinones (0.1 nmol) from spinach leaves[243] (RP–HPLC–ELD, MeOH/EtOH/0.05 M $NaClO_4$) have been determined. The investigation of metabolization of aromatics was another item: 1,4-naphthoquinone from 1-naphthol by liver microsomes (RP–HPLC–ELD, MeOH/EtOH/0.05 M $NaClO_4$)[244]; benzo[*a*]pyrene quinones from the corresponding hydrocarbons also by liver chromosomes (HPLC–TLC) or human lymphocytes (HPLC)[245].

Isoprenoid quinones in bacteria[128a, 246] or in marine diatoms[247] may also be chromatographically isolated and identified (NP and RP TLC, HPLC, UV, MS).

TLC is also a versatile method for checking the purity of drugs. Thus, rifampicin quinone (**95**) can be detected in the antibiotic rifampicin **94** and quantitatively determined with UV/vis after extraction of the TLC zones[248].

TABLE 12. Chromatographic analysis of quinones

Method (adsorbent)	Detection[a]	Type of quinone	Remarks	References
HPLC (silica gel, LiChrosorb ® -Si60, -diol, -RP8 ® ; Permaphase ODS ®)	UV	**1**, **73**, **74**, toluquinone, prenylquinones		226, 227
(HP) LC (silica gel/octadecyl)	UV	**73**, **79**, naphthoquinones	Polarity effect of mobile phase	228
HPLC (silica gel, μBondapak CN ®)	UV	Hydroxy-, methylnaphthoquinones		229
HPLC (silica gel/RHg^+)	UV	Miscellaneous quinones	Selectivity for S, O, N donor ligands	230
LC (cyclodextrin)	UV	**1**, **73**, **74**, **79**, 2,5-dimethyl-**1**		231
HPLC (RP/ion-pair chromatography)	UV	Pyrroloquinoline quinones	(From enzymes)	232
TLC (silica gel)	Spray reagents: RB, 4-A, DBDC, P, I_2, 1 N NaOH	**1**	(0.2–10 μg)	233

TLC (silica gel, cellulose)	FQ, (spray) reagents: RB, 4-A, P, DBDC 1N NaOH, H_2SO_4, UV light	**1, 73, 74**, naphthoquinones		234, 235
TLC (silica gel)	FQ	3,4-Benzpyrene quinones		236
TLC (silica gel/$AgNO_3$)	Spray reagents: RB, anilino-naphthalene sulphonic acid, long-wavelength UV	Prenylquinones		237
GC (silicone oil or grease, OV 17, DC 550)	FID	**1**, methyl-, methoxy-1,4-benzoquinones	(< 0.1 μg/μl)	223a
GC (Chromosorb WAW DMCS ® coated with apiezon L ® or diethylene glycol succinate polyester/H_3PO_4	ECD, FID	**65**, chlorinated benzoquinones		238
Paper chromatography	Spray reagents: Na nitroprusside/NH_4OH, Na vanadate, NH_3-vapour, 1% NaOH/methanol	Miscellaneous hydroxyquinones	(10–25 μg) (≥ 5 μg)	239 240

[a] Abbreviations: RB = rhodamine B; 4-A = 4-aminoantipyrine; DBDC = 2,6-dibromoquinonechloroimide; P = phosphomolybdic acid; FQ = fluorescence quenching; FID = flame ionization detector; ECD = electron-capture detector.

Finally, it has been demonstrated by HPLC and GC–MS that **74** and 1-chloroanthraquinone (among about 200 other organic compounds) are formed by incineration of municipal waste[249] and by means of gel chromatography that **73** and **80** are present in weathered Ecofisk crude oil[250]. Application of HPLC (silica gel) and TLC [polyamide or $Mg(OH)_2$] combined with UV/vis fluorescence spectroscopy and MS to air pollution analysis[251] revealed the presence of **74**, 3 benzo[*a*]pyrene quinones, and of dibenzo[*b,def*]chrysene-7,14-quinone.

VIII. CHEMICAL METHODS

A. General Remarks

In principle, all chemical reactions of quinones described in this book may be used for a qualitative and, in some cases, quantitative analysis of quinones, as well as of the reactants. Originally, colour reactions and spot tests[1] were of main importance in qualitative analysis. They are still in use, although mainly in combination with chromatographic separation techniques (especially TLC) and spectroscopic methods (preferentially UV/vis). Some colour reactions will be discussed in more detail in Section VIII.B.

UV/vis spectroscopy of coloured and uncoloured reaction products also allows a quantitative determination (photometry). Certain reactions of quinones give rise to luminescence[102a,215], or fluorescence[252,253] which allow a quantitative analysis of quinones. Quinones are easily reduced to semiquinones or dihydroxybenzenes (or the corresponding anions), which may be determined by ESR (see Section V) or UV spectroscopy[254]. Finally, redox titration[212,213,255] is also widely used, with a variety of end-point detectors: colour indicators, coulometry (see above), and potentiometry (see above).

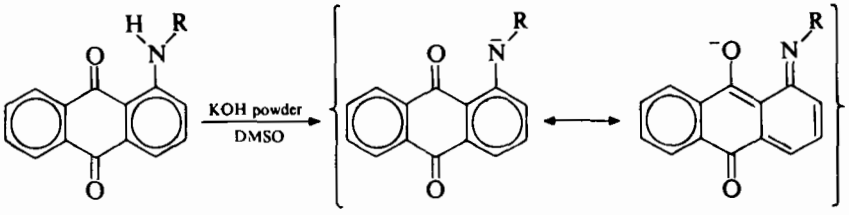
B. Colour Reactions

1. *Introduction*

The term colour reaction is used in this section to mean reactions in which the colour changes (to another colour or to colourless). The different types of colour reactions of quinones and the various tests based on them have been already classified in Table 20 of Ref. 1. Meanwhile, a lot of new colour reactions have been reported, which may be divided into reactions of quinones with bases (anion formation[71]), with free or incipient carbanions[256,257], with amines and their derivatives[4c,5u,258], *N*-heterocycles[259] and sulphinic acids[260]. Some are described below in greater detail.

2. *Anion formation*

Anion formation from hydroxyquinones as a colouring principle has been demonstrated earlier[1]. The analogous reaction occurs also with aminoanthraquinones[7e]. Thus, for example, 1-amino-9,10-anthraquinones (**124**) produce green amides (**125**) (λ_{max} = 695 nm) with KOH/DMSO in air. The formation of amide anions is demonstrated: (1) by recovering **124** after quenching with water, (2) by the formation of *N*-alkylated products at room temperature after the addition of alkyl halides, (3) by the absence of a typical colour change, when 1-dimethylamino-9,10-anthraquinone (**127**, see below) is treated with KOH/DMSO. Under an atmosphere of nitrogen, the anions **125** are further reduced via a one-electron transfer from OH^- to give the corresponding dianion radicals (λ_{max} = 560–570 nm; ESR signal).

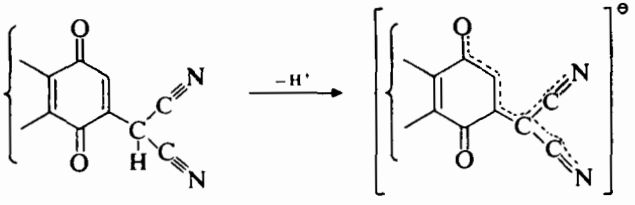


(124) (125)

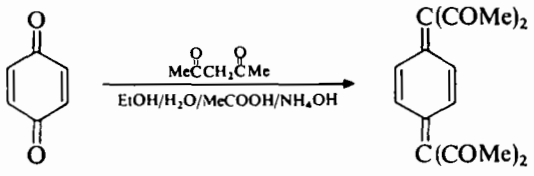
a: R = H
b: R = Me

3. *Reactions with carbanions*

Quinones are able to add carbanions formed from CH-acids (like acetoacetic ester, malononitrile or nitromethane) and a base (like ammonia in ethanol) via their α,β-unsaturated carbonyl systems. The substitution products, resulting after subsequent reoxidation, e.g. U, are even stronger CH-acids and dissociate into their blue-green or



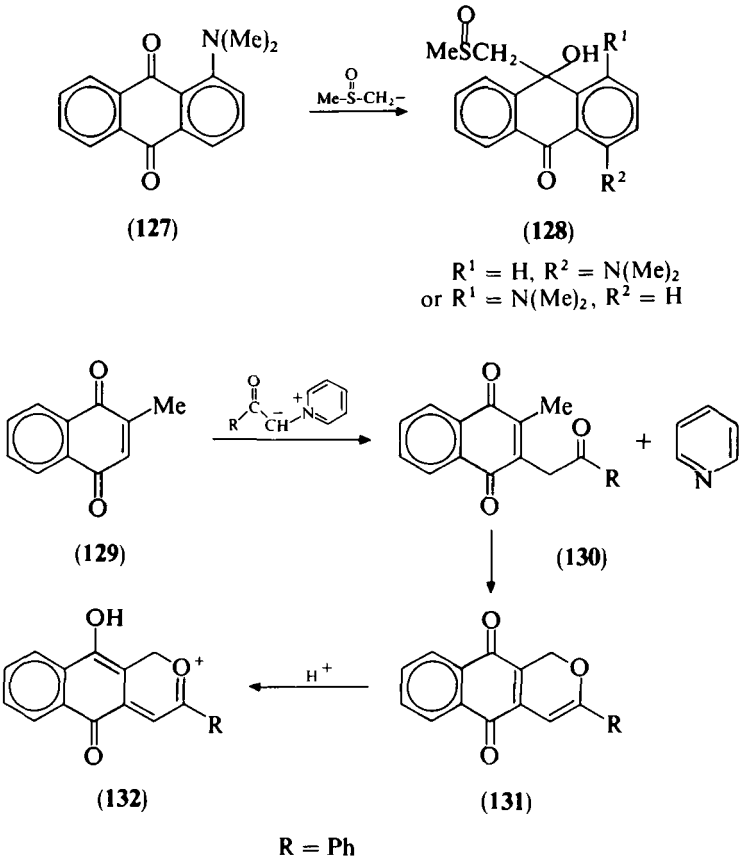
(U) (V)



(1) (126)

violet-blue anions, e.g. V. This is the typical feature of the Kesting–Craven test[1]. For a new application to 2-methyl-1,4-naphthoquinone see Ref. 256. Recently it has been shown that addition to the carbonyl group of quinones is also possible under the reaction conditions[257a]. The resulting quinodimethane **126** can be used for a spectrophotometric determination of 1 in water[257a]. If there is no quinonoid position free, the Kesting–Craven test does not work, since adducts like U cannot be formed, and addition to the carbonyl group seems to occur[7e]. The resulting quinol derivative **128** gives rise to a hypsochromic shift (510 → 420 nm).

Another interesting reaction involves the addition of pyridinium ylides to quinones[68b], e.g. to **129**. The Kesting–Craven adduct **130** may be transformed via bromination and dehydrobromination to **131**, containing the basic skeleton of fungal and aphid pigments.



(127) (128)

$R^1 = H$, $R^2 = N(Me)_2$
or $R^1 = N(Me)_2$, $R^2 = H$

(129) (130)

(132) (131)

R = Ph

In trifluoroacetic acid, **131** is instantly protonated to give a brilliant purple solution slowly changing to inky blue-black. The purple cation, assumed to be **132**, has λ_{max} = 310 and 529 nm (log ε = 4.31, 3.29) and may be considered as the cationic counterpart of **125**.

Closely related to the addition of carbanions is the reaction of **1** and **73** with the nucleophilic carbon of the isocyano group in organic isonitriles; however, the primary adduct adds a second isonitrile molecule to give dark blue 4,7-isoindolediones. In the case of **1**, the same reaction sequence may occur twice, ending up in the formation of 1,5- and 1,7-bis(arylamino)benzodipyrrolediones. For more details see Ref. 257b.

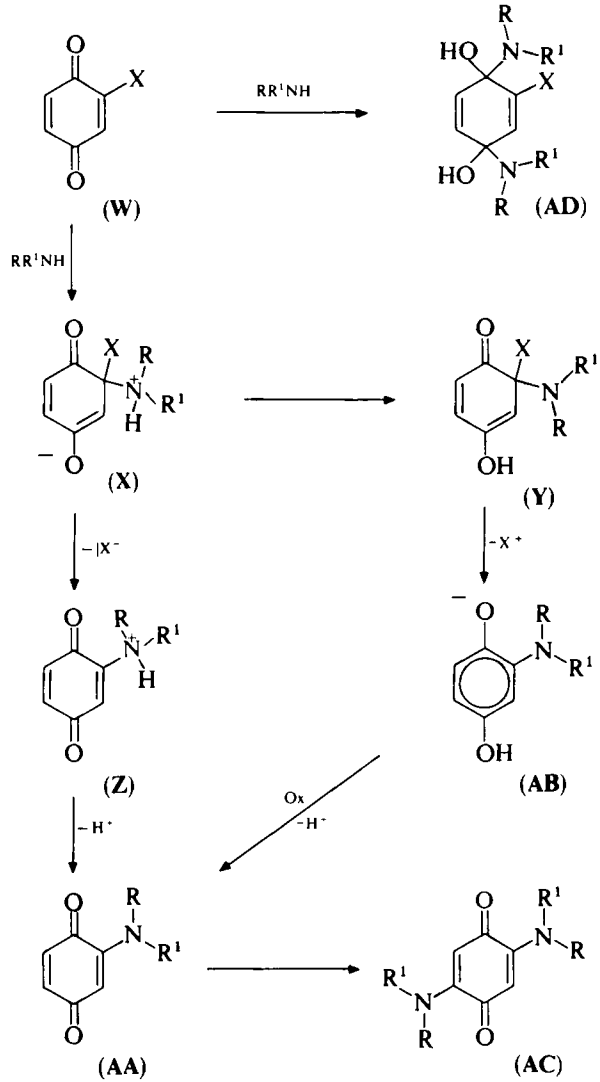
4. Reactions with amines

The vast majority of colour reactions of quinones involves amines and their derivatives. In principle, the primary reactions may be: complex and charge transfer complex formations; electron transfers; and addition/elimination or addition/oxidation reactions involving C=C or C=O bonds. Some readers may have missed categories like 'oxidation' or 'substitution' in the above enumeration. However, the oxidation of amines by quinones is no simple and uniform process, it may start with electron transfer or with addition. A detailed discussion of this problem, relying on redox potentials, is provided for 1,2-

phenanthrolinequinones by Eckert and Bruice[110]. Finally, substitution at the quinonoid system is mostly a sequence of addition and elimination reactions.

A profound knowledge of quinone–amine colour reactions has been accumulated by Kallmayer and his coworkers and by other authors[4c, 5u, 258]. Their investigations often originate in pharmaceutical interests and necessities. However, a complete elucidation of the mechanisms or even of the structure of the coloured reaction products is not always essential for a quantitative (photometric) determination.

We will now concentrate on additions; charge transfer complexes have already been mentioned in Section IV. Consider the reaction of an amine with the α,β-unsaturated quinonoid system (**W**). 1,4-Addition will first lead to the adduct (**X**) or (after proton



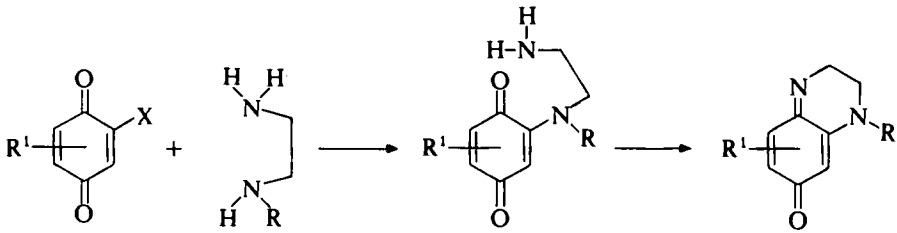
transfer) to the equivalent **Y**. If X is prone to leave as an anion, we arrive directly at the quinone **Z** or (after deprotonation) the quinone **AA**. The result is a formal *substitution* of X via an addition–elimination mechanism. The aminoquinone **AA** absorbs at longer wavelengths than the quinone **W** (see Section IV) and may be used for an indirect photometric determination of **W** and/or the amine, provided the reaction proceeds quantitatively.

Chlorine and SO_3H (or the salts $SO_3^-M^+$) seem to be suitable leaving groups X in the sense of the outlined scheme. This is demonstrated by the reaction of 2,3,5,6-tetrachloro-1,4-benzoquinone (chloranil) with primary, secondary and tertiary aliphatic and aromatic amines[258a] or of sodium rifamycin-3-sulphonate with aromatic and aliphatic secondary amines (with primary aliphatic amines, the $SO_3^-Na^+$ group is not substituted, but the *ansa* ring of rifamycin is cleaved instead)[61].

The reaction **W** → **AA** may alternatively proceed via **Y** and leaving of X as X^+ to give the anion **AB** of a hydroquinone, which would be deprotonated (by the amine) and oxidized (e.g. by **W**) to the quinone **AA**. Quinol halides as **Y** are indeed known to act as 'positive halogen' donors[261]. Moreover, a primary single electron transfer from the amine to the quinone and the subsequent recombination of the semiquinone and aminium radical ions is a reasonable third alternative.

For X = H, the reaction presumably takes the course **W** → **Y** → **AB** → **AA**, since hydrogen usually leaves as H^+, especially in the presence of a base. Examples are the reactions of **1** with a large series of primary and secondary amines[4c, h, 258j, 262], or of alkylated 1,4-benzo- and naphthoquinones with secondary amines[5u, 258i]. In the latter case, additional substitution of a hydrogen atom of a quinone ring methyl group by the amine, or photochemical dealkylation of the amino function to give the monoalkylamino quinone have been observed[5u, 258i] (see also Kallmayer and Tappe[6y]). It should be mentioned that the reaction sequence **W** → **AA** may occur a second time, starting with **AA** as substrate, to produce the bis-adduct **AC**[4c]. However, a 1,2-bisaddition product of type **AD** (addition to the carbonyl groups) has also been obtained with an excess of the amine, starting with the dihydroxyquinone **26**, which dehydrates to **AC** in boiling aniline[4c].

In the case of a bisamine like ethylene diamine, the primarily formed substitution product **AE** (equivalent to **AA**) reacts further via 1,2 addition of the second amino function

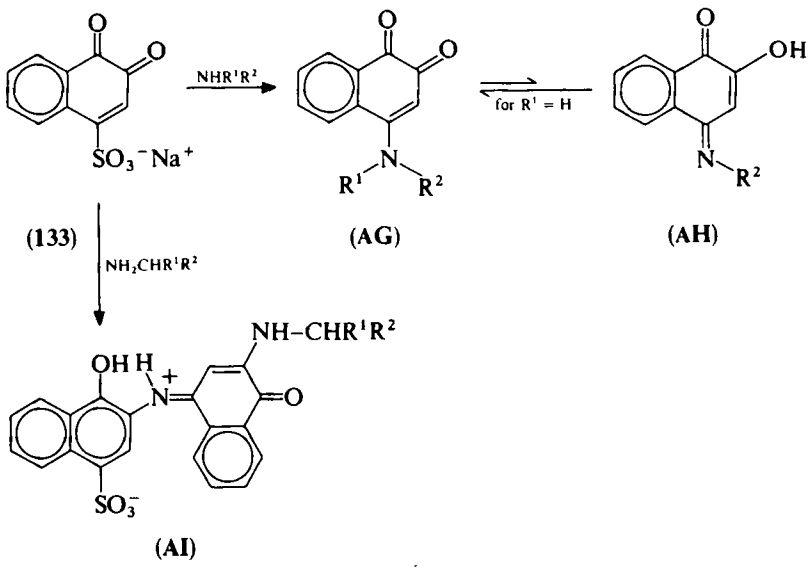


to the adjacent carbonyl group and subsequent dehydration. The final reaction product has the quinoxalinone structure **AF**[6s, 258b–f, k]. Due to a retro-Mannich reaction, 2,3-dimethyl-1,4-naphthoquinone undergoes dealkylation to 2-methyl-1,4-naphthoquinone under the reaction conditions[258k]. For the corresponding (naphtho)thiazinones from naphthoquinones and cysteamine see Ref. 258g.

Quinoxalines themselves are suitable to characterize 1,2-quinones[1, 6b, 258h]. Most of the other quinone–amine reactions discussed here for 1,4-quinones are also observed with 1,2-

quinones. For the sake of brevity, the reader is referred to the relevant literature: 1,2-benzoquinone (**60**)[4c]; 1,2-naphthoquinone-4-sulphonates (like **133**)[6b, 68a]. Reactions of 1,2-quinones (**60**, **133**) with amino acids seem to be of the same category[258l, m].

It is interesting to note that **133** reacts with secondary aliphatic as well as with primary and secondary aromatic amines to yield directly the yellow substitution product **AG**, which might exist in a tautomeric form **AH** in the case of primary amines. With primary aliphatic amines possessing at least one hydrogen at the α-C atom, however, complex violet mixtures are formed, containing **AI** and other products besides **AG**[68a, 258n]. In spite of this, the reaction could be standardized to an effective procedure for determining primary aliphatic amines in the presence of secondary aliphatic amines, which is of importance for pharmaceutical preparations (e.g. noradrenaline in adrenaline)[258o].



For a quantitative photometric determination by means of colour reactions involving so many different pathways and reaction products, it is essential to make effective use of calibration.

5. Other reactions

Reactions of quinones with pyrrol[6b], 1,2,4-triazole[6b], methimazole[259a], thiamine[259b], 8-hydroxyquinoline[259c], 3-phenylthiazolidine-2,4-dione[259d] and benzenesulphinic acid[260] have been investigated. The reactions of *N*-heterocycles with quinones resemble those of amines discussed above; however, some heterocycles (pyrrol) may attack the quinone via a carbon instead of a nitrogen atom.

C. Analytical Applications

Chemical reactions of quinones are easily performed, proceed quickly and do not need special equipment. As already mentioned, they may be used for the determination of the quinones as well as of the substrates. Most investigations have been done to determine the

reaction partners and not the quinones. Examples, especially in the field of pharmaceutical preparations and in biological materials, have already been mentioned in Section B and may be found additionally in the references presented there. For a review on the detection and determination of psychopharmaceuticals of the desipramine type by quinone–amine reactions see Ref. 263. Some of the applications to quinones are reported below.

Menadione (2-methyl-1,4-naphthoquinone, **129**) was detected by TLC in the presence of other 1,4-naphthoquinones (even of 2-ethyl-1,4-naphthoquinone) after reaction with 4-aminophenol[264]. The colour reaction with thiosemicarbazide[265], 8-hydroxyquinoline[259c], 3-phenylthiazoline-2,4-dione[259d] or benzenesulphinic acid[260] allows a detection of quinones (5–80 μg). The thiosemicarbazide reaction is specific in the presence of aliphatic and aromatic aldehydes, aliphatic ketones, phenols, 1,3-dihydroxy- and 1,3,5-trihydroxybenzenes. However, 1,2-dihydroxy- and 1,2,3-trihydroxybenzenes also produce colours[265]. 8-Hydroxyquinoline can also be applied to a detection of quinones on paper and TLC chromatograms[259c]. A characteristic fluorescence occurs in the reaction of 3-aminothiocarbostyril with the 1,4-quinones **1** and **73**, which allows a distinction from the corresponding 1,2-quinones **60** and **79**, not producing such fluorescence[253]. Reviews are available for the analysis of isoprenoid quinones[266] and anthraquinone drugs[267].

IX. CONCLUSIONS

This survey has reviewed several new results relevant to the physical and chemical analysis of quinones. Nevertheless, the conclusions and suggestions for a qualitative and quantitative determination given in Ref. 1, especially with respect to the distinction between 1,4- and 1,2-quinones, are still valid in the main. The emphasis has clearly shifted in favour of the physical methods. This is further demonstrated in some recent reviews on the analysis of isoprenoid quinones[266] and anthraquinones[268, 269]. However, the full potential of these methods for quinone analysis is still far from having been exhausted. Many authors were satisfied to present the results of one or two methods, although combinations were also used, e.g. (UV, IR, MS, ^{1}H-NMR)[128b], (UV, MS, ^{13}C-NMR)[33b], (LSV, IR, UV, ^{1}H-NMR, ^{13}C-NMR)[4j], to give just a few examples. UV/vis spectroscopy as a versatile method is still very popular, although its disadvantages become especially evident with condensed quinones. It is astonishing to observe that hardly any systematic investigations into the effects of substituents or other structural parameters on spectroscopic data have been undertaken in recent years. This may reflect the general tendency in chemistry to investigate applications in technology or biology rather than to do basic research.

Due to the pitfalls of every method we suggest that all methods available should be applied, if the structure of a quinone is to be determined; even a crystal structure determination may be necessary. To our knowledge, about 100 crystal structures of quinones have been solved since 1973, comprising simple systems like **60**[270], as well as complicated natural quinones. If, on the other hand, a known quinone is simply to be detected, e.g. as impurity in a preparation, a simple chemical colour test may still be the method of choice.

X. ACKNOWLEDGEMENTS

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CHAPTER 3

Mass spectra of quinones

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I. INTRODUCTION

A detailed description of the positive-ion electron impact mass spectra of quinones was given in this series several years ago[1]. In the meantime mass spectral data of quinones have been reported in a large number of papers for the sake of characterization of synthetic or naturally occurring quinones. Concerning the basic behaviour of quinones under electron impact, relatively little new information can be extracted from these publications.

The nature of the $C_4(Ph)_4^+$ ions formed by consecutive loss of two CO molecules from tetraphenyl-1,4-benzoquinone is still a matter of interest and has been reinvestigated by more advanced mass spectrometric techniques.

The importance of mass spectrometry for structure elucidation and identification of naturally occurring quinones is illustrated in this chapter by recent examples. Bowie and coworkers demonstrated that negative-ion mass spectra of substituted quinones, not dealt with in the earlier review, yield valuable structural information. This technique is treated in some detail in Section III.

Throughout this chapter, fragmentations substantiated by a metastable transition in the second field-free region or by the metastable defocusing technique in the first field-free region are indicated by an asterisk.

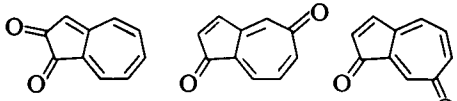
II. POSITIVE-ION MASS SPECTRA

The positive-ion electron impact spectra of quinones exhibit two characteristic features[1], namely (1) the stepwise loss of two molecules of carbon monoxide, and (2) the formation of peaks two mass units higher than the molecular mass due to partial reduction before the ionization step. The latter is particularly pronounced in the case of *ortho*-quinones but also in *para*-quinones having high redox potentials.

A. Electron Impact Induced Decarbonylation

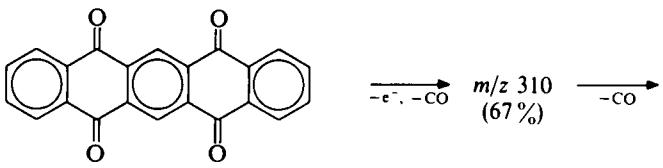
For anthraquinone it could be shown that the second elimination of CO (*m/z* 180 → *m/z* 152) in the second field-free region is not a truly unimolecular process but caused by collisional activation due to sample leakage or residual background gas[2]. This follows from the pressure dependence of the second process. Probably, this finding is of general implication for consecutive metastable reactions.

The stepwise loss of two molecules of carbon monoxide is also found in the non-benzenoid quinones **1**[3], **2**[4] and **3**[4] related to azulene. In the mass spectra of these molecules



(**1**) (**2**) (**3**)

the $[M-2CO]^{+\cdot}$ ions give rise to the most intensive peaks. In accordance with the high tendency for loss of carbon monoxide the mass spectra of pentacene-5,7,12,14-diquinone (**4**) and its derivatives are dominated by four decarbonylation steps[5]. Some years ago the

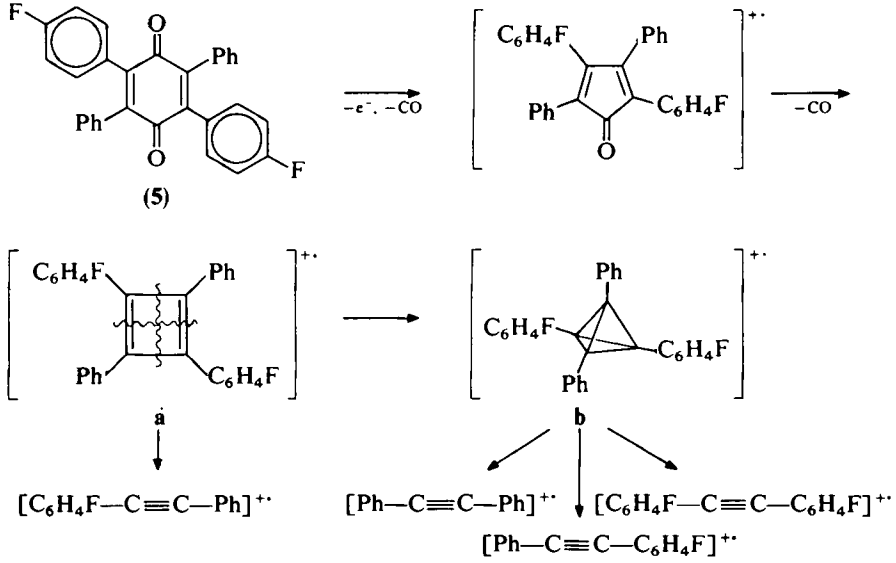


(**4**, *m/z* 338) (100%)

m/z 282 (61%) $\xrightarrow{-CO}$ *m/z* 254 (66%) $\xrightarrow{-CO}$ *m/z* 226 (71%)

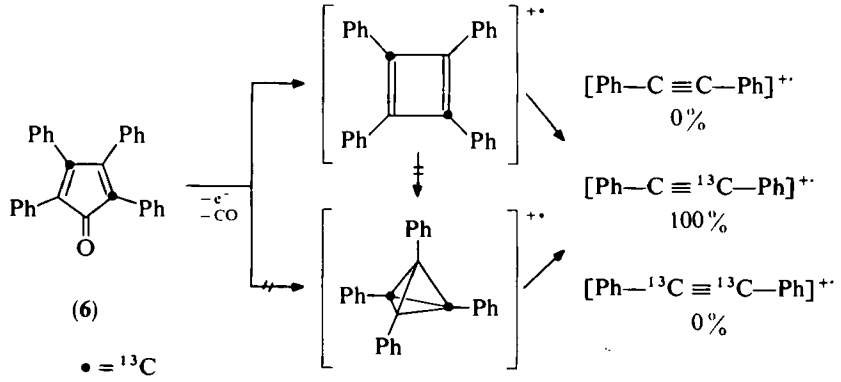
structure of the $[M-2CO]^{+\cdot}$ ion of tetraphenyl-1,4-benzoquinone was investigated by labelling of the aromatic rings with the *para*-fluoro substituent[6]. The key compound in this study was the unsymmetrically substituted 2,5-diphenyl-3,6-bis(4-fluorophenyl)-1,4-benzoquinone (**5**). It was reported that the $[M-2CO]^{+\cdot}$ ion of **5** yields on further decomposition $C_{14}H_{10}^{+\cdot}$, $C_{14}H_9F^{+\cdot}$ and $C_{14}H_8F_2^{+\cdot}$ ions.

A cyclobutadiene structure **a** would only predict monofluoro-labelled product ions. Therefore, Bursey and coworkers[6] concluded that the $[M-2CO]^{+\cdot}$ ions either decompose as a tetrahedrane-like structure **b** or the decomposing species consist of isomeric substituted tetraphenylcyclobutadiene cation radicals undergoing interconversions via **b**. If the tetrahedrane intermediates (or transition states) are undistorted, the intensity ratio of unlabelled, singly labelled, and doubly labelled product ions should be 1:4:1. The experimental ratio obtained by measurement of conventional metastable ion intensities in the spectrum of **5** generated by a single focusing magnetic deflection instrument was



1:4.8:0.84. The divergence between the experimental and the theoretically predicted ratio was rationalized by a distorted tetrahedrane structure. Very similar results were obtained from fluoro-substituted $C_4Ar_4^{+\cdot}$ ions produced from tetracyclone derivatives and other suitably fluoro-labelled precursors.

The tetrahedrane problem was again studied by Schwarz and coworkers[7] using [2,4-$^{13}C_2$]tetraphenylcyclopentadienone (**6**). In contrast to the earlier results, the collision-induced fragmentation of the $[M-CO]^{+\cdot}$ ion of **6**, mass-selected in a triple quadrupole instrument operated under MS/MS conditions, indicated that only one product, the singly labelled ion $^{12}C_{13}{}^{13}CH_{10}{}^{+\cdot}$ was formed. This finding excludes an intermediate tetrahedrane ion.



These contradictory results stimulated a reinvestigation of the F-labelled compounds on a reversed Nier-Johnson geometry mass spectrometer[8]. In Figure 1 the unimolecular MIKE spectrum and the collisionally activated decomposition of the *m/z* 392 ion

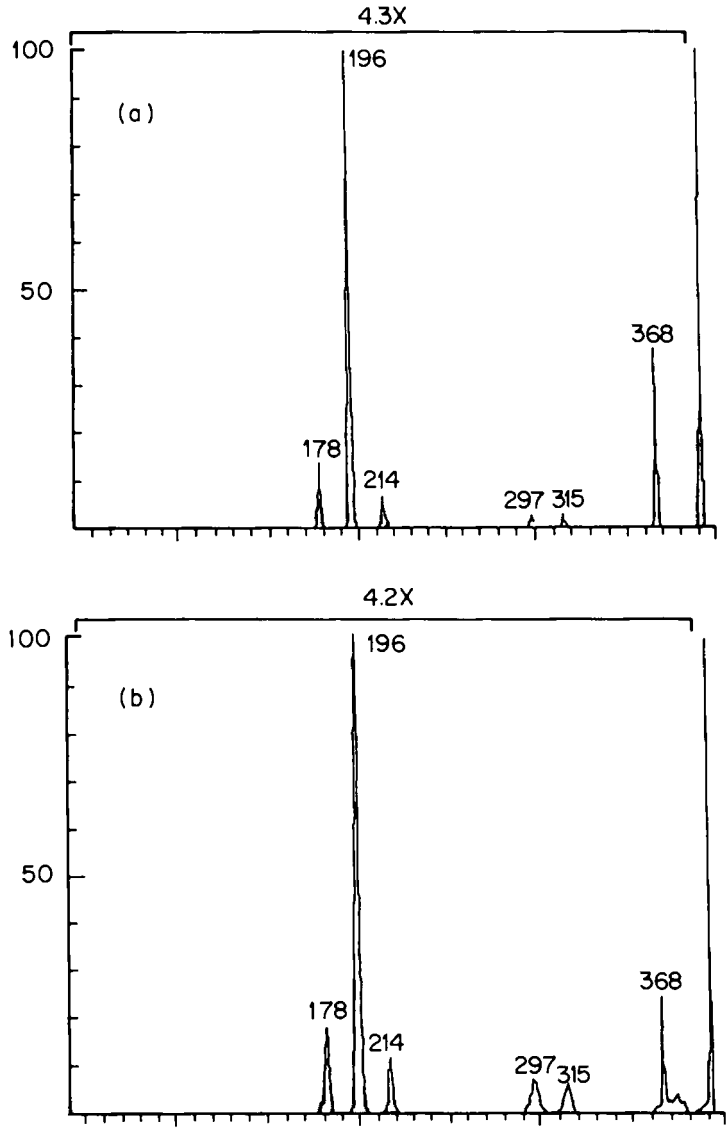


FIGURE 1. Unimolecular MIKE spectrum (a) and collisionally activated decomposition (b) of the *m/z* 392 ion from 2,5-diphenyl-3,6-bis(4-fluorophenyl)-1,4-benzoquinone (**5**). Reproduced from Ref. 8

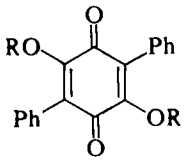
produced by loss of 2 CO from the molecular ion of **5** are given. Both contain peaks at *m/z* 178, 196 and 214. Thus, they confirm the previous results based on assignments of metastable peaks. However, the intensities of peaks diagnostic for the tetrahedral form **b** are lower than found originally. It should be remembered that the previous measurements on metastable peaks correspond to a shorter time-scale. This points to the possibility that

the part of fragmenting ions passing through a tetrahedral form **b** depends on the lifetime (and therefore internal energy) of the observed ions[8]. In this context it is of interest that the conflicting ^{13}C-labelling results were obtained on a quadrupole instrument with a longer time-scale.

Alternatively, an influence of the *para*-fluoro substituent on the population of excited levels has been discussed[8] to account for the presence of peaks diagnostic for the tetrahedral intermediate in the fragmentation of the $[M-2CO]^{+\cdot}$ ion of **5**, whereas corresponding peaks are absent in the decomposition pattern of the $[M-CO]^{+\cdot}$ ion of the ^{13}C-labelled compound **6**.

B. Chemical Changes prior to Ionization

The formation of $[M+2]^{+\cdot}$ peaks often obscures mass spectrometric investigation of quinones[1]. An interesting example has been reported for derivatives of polyporic acid **7a**[9]. The diacetate **7b** and the dimethoxy compound **7c** give *m/z* values corresponding to the molecular masses but ions two mass units larger than these, often of greater intensities, are also observed. The abundance of such ions depends on the sample temperature, the ion source pressure, and the partial pressure of water in the instrument. In addition, ions at *m/z* 420 and 462 are found in the spectrum of **7b** which are parents of the $[M+2]^{+\cdot}$ ions at *m/z* 378. Similarly, $[M+17]^{+}$ and $[M+32]^{+\cdot}$ ions are observed in the spectrum of the dimethoxy derivative **7c**. In view of the low pressure applied it seems unlikely that the reactions observed are bimolecular. The participation of water in the reaction suggests that it occurs on the metallic surfaces of the source, where water is known to be adsorbed. The transfer of acetyl and methyl groups, respectively, may occur at the same site but may also be the result of a solid state reaction or even reaction in the gas phase after vaporization of quinhydrone dimers. Although the exact origin of these peaks is not known, any explanation of the phenomena requires the reduction of the benzoquinone moiety for the formation of tri- and tetraacetates. These findings are of relevance for the establishment of the presence of 2,5-dihydroxy-1,4-benzoquinones in plant extracts.



(**7a**: R = H)

(**7b**: R = COMe)

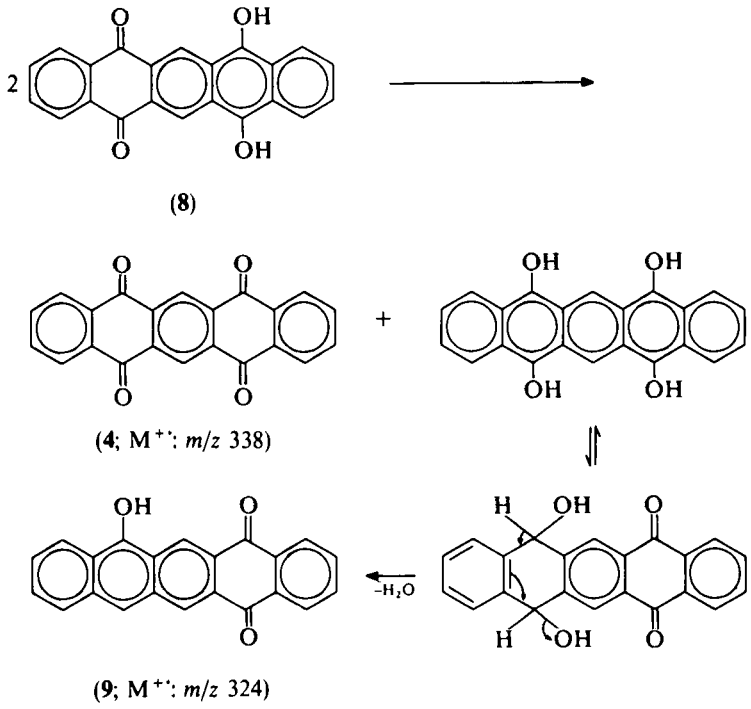
(**7c**: R = Me)

(**7**)

A phenomenon reminiscent of the appearance of $[M+2]^{+\cdot}$ peaks in the mass spectra of certain quinones[1] has been reported for 5,14-dihydroxypentacene-7,12-quinone (**8**)[5]. The 40 eV-EI spectrum of **8** shows no molecular ion peak. However, typical peaks for the dehydroproduct **4** ($M^{+\cdot}$, *m/z* 338) and 5-hydroxypentacene-7,12-quinone (**9**, $M^{+\cdot}$, *m/z* 324) are found. Whereas the formation of $[M+2]^{+\cdot}$ peaks of other quinones results from reduction prior to ionization by residual water, a disproportionation process must be operative to produce **4** and **9**.

C. Structure Determination of Naturally Occurring Quinones

Mass spectrometry proved to be a powerful tool in the structural elucidation of quinones originating from natural sources[1,10,11]. In the following, some selected examples are given.

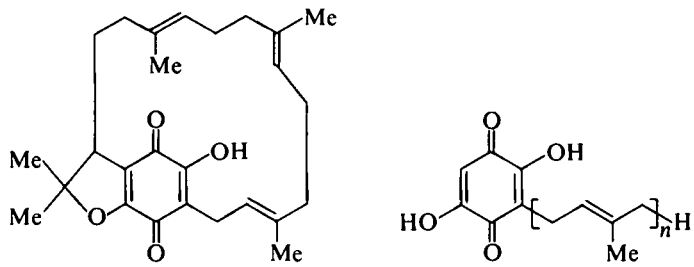


(8)

(4; $M^{+\cdot}$: *m/z* 338)

(9; $M^{+\cdot}$: *m/z* 324)

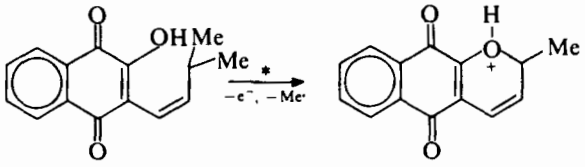
In contrast to the biogenetically related boviquinones (**11**) the mass spectra of tridentoquinone (**10**) and its derivatives isolated as pigments from *Suillus tridentinus* yield intensive molecular ion peaks[12]. This has been rationalized by a pronounced electron impact induced degradation of the isoprenoid side chain in **11**, whereas similar fragmentations are less likely in the molecular ion of the *ansa*-1,4-benzoquinone (**10**).



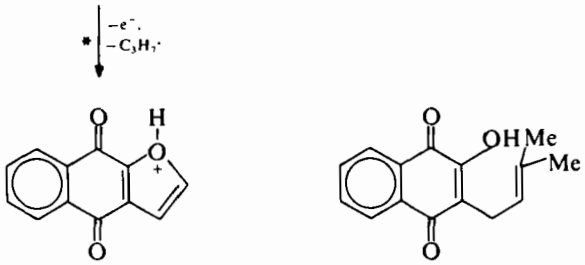
(**10**) (**11**; $n = 3, 4$)

The mass spectrum of isolapachol (**12**) is dominated by fragmentations involving the side chain[13]. The same fragments are formed from the molecular ion of lapachol (**13**), indicating isomerization to a common structure prior to fragmentation.

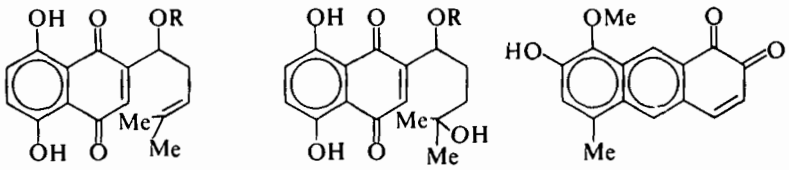
Mass spectrometry has been involved in the structure elucidation of 5,8-dihydroxy-1,4-naphthoquinones of the general type **14**[14,15] and **15**[15] isolated from *Macrotomia euchroma* and *Arnebia nobilis*.



(12; $M^{+\cdot}$: m/z 242) m/z 227



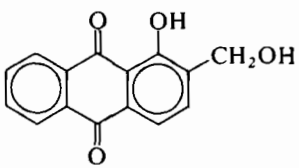
m/z 199 (13)



(14) (15) (16)

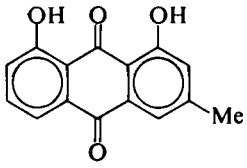
Similarly, the mass spectra of 5-hydroxy-1,4-naphthoquinones found in sea urchins have been investigated[16]. The mass spectrum of the red pigment hallachrome (**16**) obtained by extraction of the seaworm *Halla parthenopeia* with chloroform played an important role in recognizing the *ortho*-quinonoid structure[17]. As expected for an *ortho*-quinone, the molecular ion and the $[M-Me]^+$ ion suffer from pronounced decarbonylations and a prominent $[M+2]^{+\cdot}$ peak is formed.

Naturally occurring anthraquinones are the active principles of many plant drugs. Amongst other recent examples, mass spectrometry assisted the structure determination of the antitumour agent morindaparvin B (**17**)[18] from *Morinda parvifolia*.

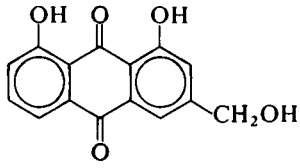


(17)

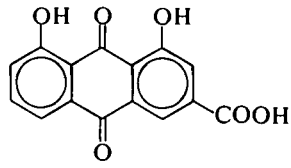
The electron impact mass spectra of the natural 1,8-anthraquinones chysophanol (**18**), aloe-emodin (**19**), rhein (**20**), emodin (**21**) and catenarin (**22**) show intensive molecular ions and a fragmentation behaviour as expected for hydroxylated anthraquinones[19].



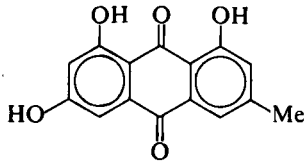
(**18**)

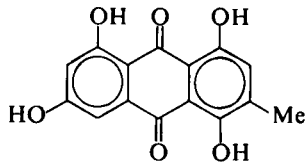


(**19**)

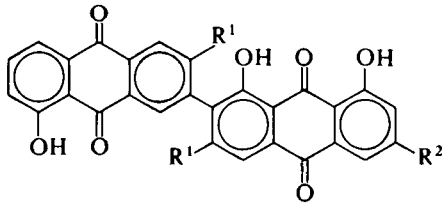


(**20**)





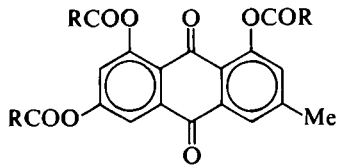
(**21**) (**22**)



(**23a**; R^1 = Me, R^2 = OH)
(**23b**; R^1 = Me, R^2 = H)

Certain *Cassia* species produce dianthraquinones in addition to the monomeric compounds. As shown for cassiamin A (**23a**) and cassiamin C (**23b**) the EI spectra of these dimers are characterized by intensive molecular ion peaks enabling ready distinction from their monomeric counterparts[19]. This is of considerable utility since ^{1}H-NMR spectra often fail in this context. Furthermore fragments are found corresponding to cleavage into the monomers. This feature is particularly useful when the dimer is of the mixed type as cassiamin A.

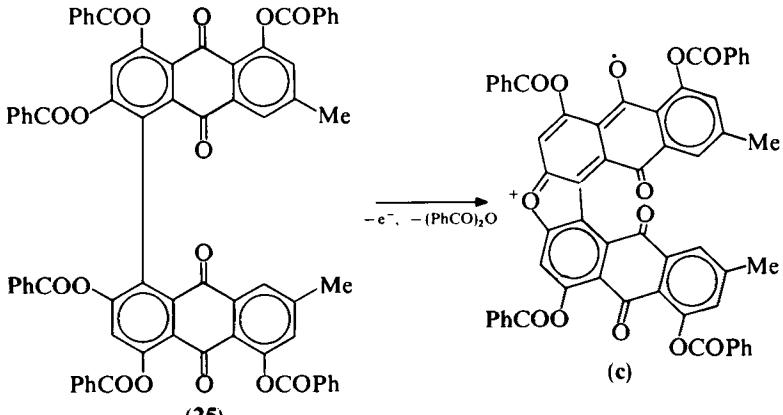
Anthraquinones bearing phenolic hydroxy groups are often acylated prior to spectroscopic and analytical characterizations. The positive-ion EI mass spectra of *O*-acylated



(**24a**: R = Me)
(**24b**: R = Ph)

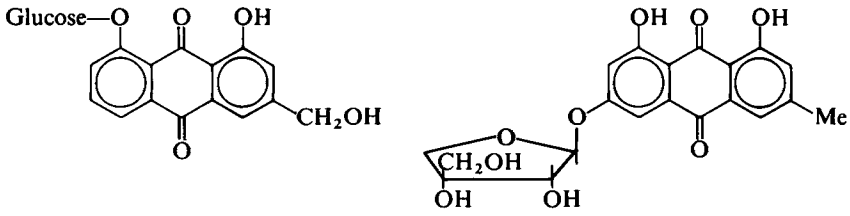
hydroxyanthraquinones exhibit marked differences depending on the nature of the acyl groups. This has been exemplified with the emodin derivatives **24**[20]. Whereas the triacetyl compound **24a** gives three consecutive electron impact induced ketene eliminations, the tribenzoyl derivative **24b** produces an intensive peak at *m/z* 105 for the benzoyl ion and no further fragment ions are detected in the region between *m/z* 105 and the molecular ion.

In contrast, in the mass spectrum of the structurally related hexabenzoyl derivative of skyrin (**25**) (from *Hypericum perforatum* L.) an additional peak at $[M-226]^{+\cdot}$ appears, corresponding to a formal loss of benzoic acid anhydride[20]. Studies with model compounds confirmed that a proximity effect leading to the resonance stabilized fragment ion **c** is responsible for this behaviour.



(25)

Glycosides of polyhydroxyanthraquinones are considered as the pharmacologically active constituents of many crude plant drugs. Their EI mass spectra do not exhibit molecular ion peaks; the base peaks usually correspond to the respective aglycones. Ammonia chemical ionization mass spectrometry has been used as a complementary technique for the identification of these glycosides[19]. However, in the case of aloe-emodin-8-glucoside (**26**) no molecular or quasi-molecular ion could be detected. The chemical ionization spectrum is dominated by an ion which may arise by attachment of ammonia to the glycosidic portion with transfer of a proton onto the aglycone. In addition, an abundant ion for the protonated aglycone is present.



(26) (27)

In contrast, the field desorption mass spectrum of **26** yields a molecular ion and a peak of the composition $[M + Na]^+$ as quasi-molecular ion originating from the attachment of sodium present as traces in the sample[19]. Similar results have been obtained with rhein-8-glucoside.

The structure of 6-*O*-(D-apiofuranosyl)-emodin (frangulin B, **27**) isolated from *Rhamnus frangula* L. has been elucidated by combined electron impact and field desorption mass spectrometry[21]. The field desorption mass spectrum of the pentaacetate shows a quasi-molecular ion peak at *m/z* 614 ($[M+2]^{+\cdot}$) and the sugar part obtained by hydrolysis has been recognized by field desorption and electron impact mass spectrometry of the trimethyl derivative as apiose.

D. Analysis of Quinones by Combined Chromatography/MS Methods

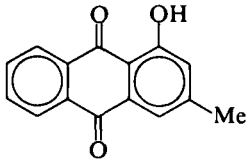
Combined chromatography/mass spectrometry techniques have found wide applications in biochemistry, natural product, environmental, agricultural and technical chemistry to identify and analyse quinones. The well documented fragmentation pattern of quinones[1] facilitates the assignment of chromatographic peaks when the mass spectrometer is used as a specific detector.

Combined gas-liquid chromatography/mass spectrometry has been used to identify the defence secretion components from members of the diplopod order Julia (Anthropoda)[22]. *Julus nitidus* produces a defensive secretion that consists exclusively of 2-methyl-3-methoxy-1,4-benzoquinone. The expelled defensive secretions of *Unciger foetidus*, *Cyclindroiulus coeruleocinctus*, *C. punctatus*, *C. luridus* and *Phyiulus psilosus* consist of mixtures of methyl-1,4-benzoquinone and 2-methyl-3-methoxy-1,4-benzoquinone. Similarly, it has been shown that the secrets of the pygidial glands of staphylinids of the genus *Bledius mandibularis* and *B. spectabilis* contain methyl-1,4-benzoquinone in addition to terpenes, undecene and γ-dodecalactone[23].

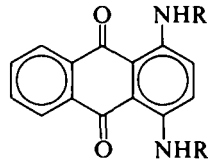
An analytical method for identification of minute amounts of hexahydroubiquinones in lipid extracts with the aid of gas-liquid chromatography/mass spectrometry has been developed[24].

The separation and identification of 37 naturally occurring hydroxyanthraquinones as the corresponding trimethylsilyl derivatives by capillary gas chromatography/mass spectrometry has been described[25].

An interesting application has been reported for the diagnosis of gangrene in potato tubers. The causal organism of this plant disease, *Phoma exigua* var. *foeata*, contains pachybasin (**28**) as anthraquinone pigment. The detection of specific ions from **28** by pyrolysis mass spectrometry, direct probe mass spectrometry and gas chromatography/mass spectrometry as diagnostic approaches offer advantages over other methods[26]. In particular, the GC/MS method has been suggested as a promising technique because of its high specificity, sensitivity, suitability for automation and reduction of total expertise time.



(**28**)



(**29**; R = H—$C_{18}H_{37}$)

Quinones derived from polycyclic aromatic hydrocarbons have been identified by glass capillary gas chromatography/mass spectrometry in diesel exhaust particulate matter[27,28].

Amongst other dyes, 1,4-dialkylaminoanthraquinones (**29**) are added to gasoline to identify manufacture and to trace petroleum contamination in soil, groundwater,

wastewater, etc. Several mass spectrometric and chromatographic techniques have been suggested for this purpose[29]. Due to the low volatility of the anthraquinone dyes (**29**), mass spectrometry as a specific and sensitive detection technique should be combined with high-performance liquid chromatography as the separation method. This has been successfully demonstrated[30] using the thermospray HPLC/MS interface. This device is able to handle high quantities of aqueous solvents and the ionization process is 'soft', resulting in abundant $[M+H]^+$ ion formation. By this method it has been shown that the commercial blue dye is composed of the various alkyl-substituted aminoanthraquinones (**29**) with R ranging from H to $C_{18}H_{37}$. Furthermore, the thermospray HPLC/MS method has been demonstrated to detect dyes in water, soil and gasoline at the low parts-per-million levels.

Recently, a new thin-layer chromatogram scanner/mass spectrometer system has been introduced using 1,4-benzoquinone, 1,4-naphthoquinone and anthraquinone as testing materials[31]. The scanner moves the TLC plates past a pulsed CO_2 laser as a source of desorption energy. The chemical ionization reagent gas sweeps the material desorbed from the TLC spots into the ion source of the mass spectrometer. Reasonable chromatographic peaks have been produced by monitoring mass chromatograms ($[M+H]^+$) from TLC plates spotted with 10 μg of samples of benzoquinone, naphthoquinone and anthraquinone.

III. NEGATIVE-ION MASS SPECTRA

In an electron impact source negative ions can be produced by three main processes[32, 33].

(1) resonant electron capture of secondary (thermal) electrons:

$$AB + e^- \rightarrow AB^{-\cdot}$$

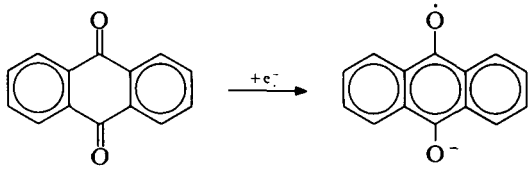
(2) dissociative attachment:

$$AB + e^- \rightarrow [AB^{-\cdot}]^* \rightarrow A + B^{-\cdot}$$

(3) ion-pair production:

$$AB + e^- \rightarrow A^+ + B^- + e^-$$

In general, in an electron impact source operated at 70 eV little or no molecular anions are generated, and fragment ions may be produced by different processes. The problems inherent in negative-ion mass spectrometry may be overcome by using a structural moiety which is able to produce stabilized molecular anions without utilization of non- or antibonding molecular orbitals. The quinone and in particular the anthraquinone system



(d)

yields such stabilized molecular anions of the semiquinone type **d**. The stable unsubstituted semiquinone system **d** shows no decomposition; however, attached substituents may cause unimolecular fragmentations[34].

The molecular anions of 2-alkoxycarbonylanthraquinones (**30**) eliminate alkyl radicals from the ester group[34]. This process increases with the size of R and when a secondary

TABLE 1. Relative intensities of the molecular anion and of the fragment ions at *m/z* 251 and 207 in the negative-ion spectra of 2-alkoxycarbonylanthraquinones (**30**)

30	R	$M^{-\cdot}$	$[M-R]^-$ *m/z* 251	$[M-R-CO_2]^-$ *m/z* 207
a	Me	100	5	7
b	Et	100	7	12
c	*n*-Pr	100	10	16
d	*i*-Pr	100	22	25
e	*n*-Bu	100	12	18
f	*n*-Hex	100	16	20

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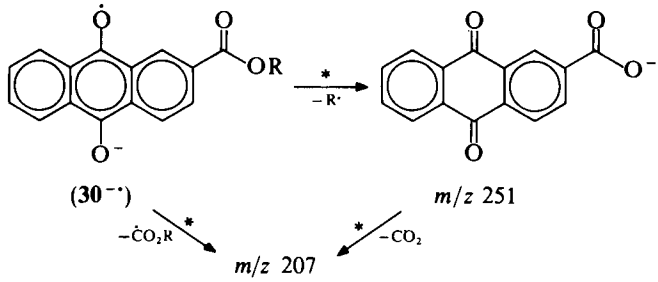
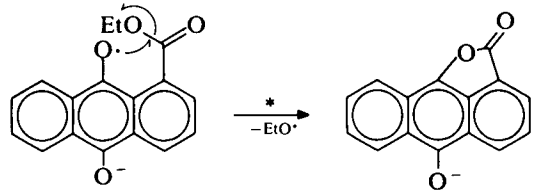
radical is eliminated. The elimination of an alkyl radical is followed by loss of carbon dioxide (Table 1). Figure 2(a) illustrates this sequence for 2-ethoxycarbonylanthraquinone (**30b**). This fragmentation pattern, which has no counterpart in the positive-ion spectra, is substantiated by appropriate metastable peaks and the metastable defocusing technique. As indicated in the scheme by an asterisk a metastable transition is also observed for the loss of the alkoxycarbonyl group.



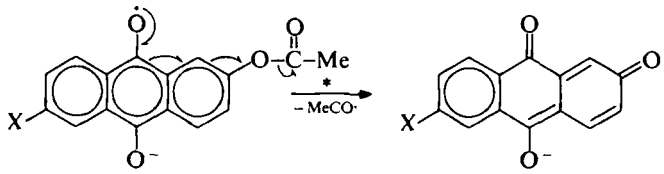
In addition to similar cleavages, the spectrum of 1-ethoxycarbonylanthraquinone (**31**) contains a $[M-EtO]^-$ ion (Figure 2(b)). This is probably the result of a proximity effect which cannot be operative in the 2-substituted isomer.



(**31**$^{-\cdot}$; *m/z* 280) *m/z* 235

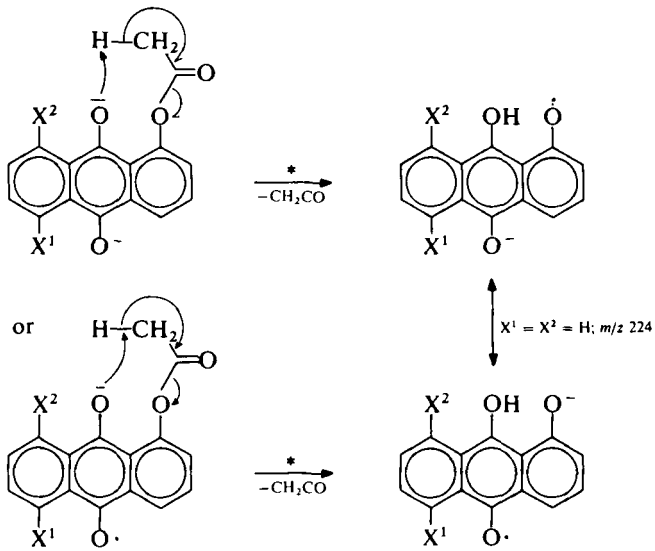
The negative-ion spectra of 1- and 2-acetoxy-substituted anthraquinones are also quite different (Table 2)[34]. The spectrum of the 2-isomer (**32**) is dominated by the loss of an acetyl radical from the molecular anion. On the other hand, the molecular anion of the

1-isomer **33** eliminates ketene, which demonstrates the occurrence of a proximity effect. The hydrogen rearrangement can either proceed to a radical or to an anionic centre.



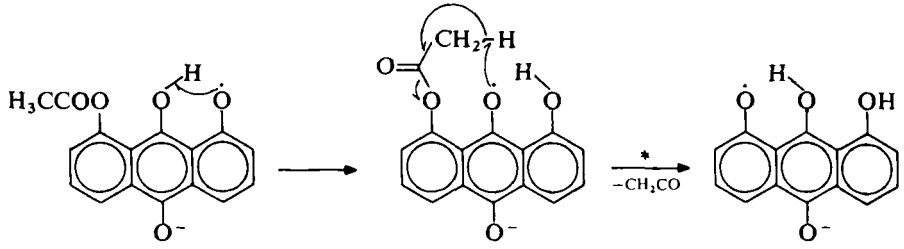
(**32**$^{-\cdot}$; X = H)
(**37**$^{-\cdot}$; X = OCOMe)

X = H; *m/z* 223
X = OCOMe; *m/z* 281



(**33**$^{-\cdot}$; $X^1 = X^2 = H$)
(**34**$^{-\cdot}$; X^1 = OCOMe, X^2 = H)
(**35**$^{-\cdot}$; X^1 = H, X^2 = OCOMe)

In the negative-ion spectra of the disubstituted compounds **34** and **35** the stepwise elimination of two molecules of ketene is observed. In the case of compound **34** the second loss of ketene requires a prior hydrogen transfer if the above mechanism is applicable.



m/z 282 *m/z* 282 *m/z* 240

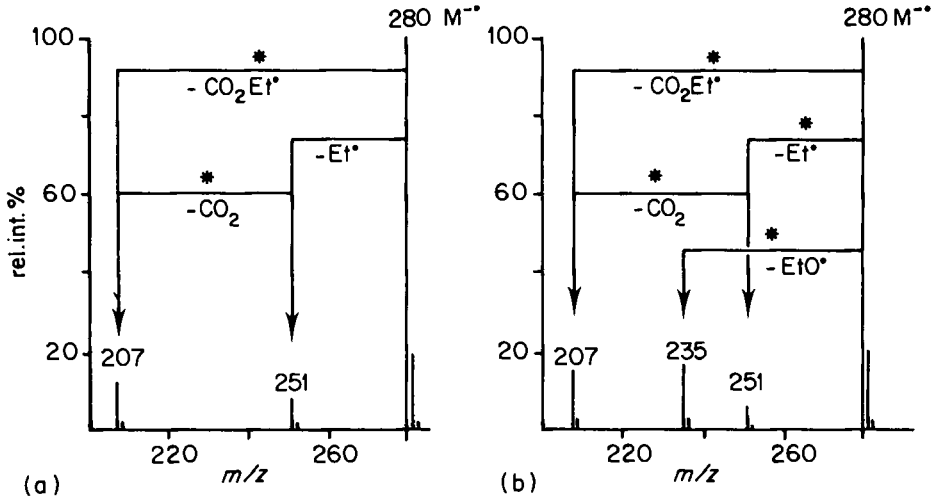


FIGURE 2. Negative-ion electron impact mass spectra of 2-alkoxycarbonylanthraquinone (**30b**) (a) and 1-ethoxycarbonylanthraquinone (**31**) (b). *Reproduced from Ref.* 34, *by permission of the Royal Society of Chemistry*

TABLE 2. Relative intensities of molecular and fragment ions in the negative-ion spectra of mono- and diacetoxyanthraquinones

Compound	$M^{-\cdot}$	$[M-CH_2CO]^{-\cdot}$	$[M-MeCO]^-$	$[M-2CH_2CO]^{-\cdot}$	$M-CH_2CO-MeCO]^-$
32	40	0	100	–	–
33	18	100	9	–	–
34	20	58	15	100	6
35	39	100	4	43	14
36	30	100	10	30	14
37	60	0	100	0	15

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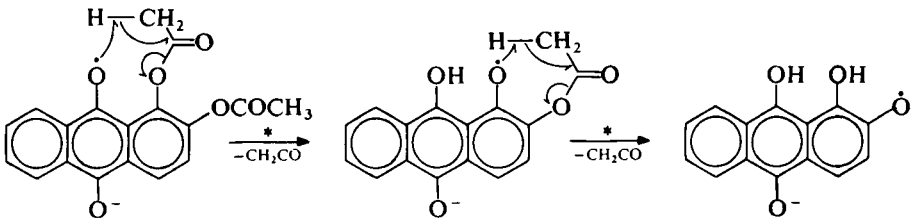
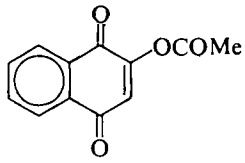
The negative-ion spectrum of 1,2-diacetoxyanthraquinone (**36**) discloses two fragmentation pathways. The major process involves two proximity effects which result in the elimination of two ketene molecules. As demonstrated by appropriate deuterium labelling the first ketene elimination takes place from the 1-position. Additionally a sequence $M^{-\cdot}$–CH_2CO–$MeCO^{\cdot}$ is observed.



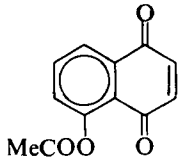
The semiquinone radical anion formed from 2,6-diacetoxyanthraquinone (**37**) contains no phenoxide radical (or anion) centre adjacent to an acetoxy group. Consequently, no elimination involving a hydrogen transfer is possible and the only process observed is loss of an acetyl radical. The fragment formed is an anion with an even number of electrons. Therefore, the loss of a second acetyl radical is impossible if the fragmentation is triggered by the radical site. However, ketene as a neutral molecule can be eliminated leading to a further even-electron ion at *m/z* 239.

The different behaviour of α- and β-acetoxy groups bound to anthraquinones can be applied in the analysis of positional isomers. This information is not forthcoming from positive-ion spectra, as all arylacetate molecular cations eliminate ketene.

Similar rearrangement processes including elimination of ketene are found in the negative-ion spectra of the naphthoquinones **38** and **39**[34].

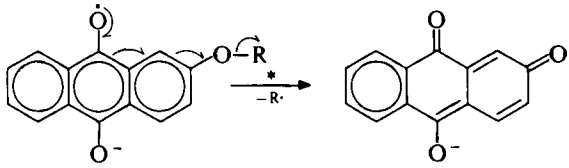


(**38**)



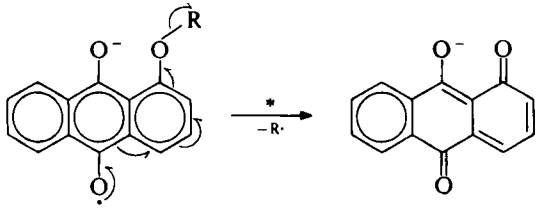
(**39**)

The basic fragmentation of the molecular anions of alkoxy-substituted anthraquinones **40** and **41** involves loss of an alkyl radical to produce resonance-stabilized fragments (Table 3)[35]. Proximity effects which should produce $[M-alkene]^{-\cdot}$ ions from α-substituted compounds **41** (R ⩾ Et) are not observed.



(**40a**$^{-\cdot}$; R = Me)
(**40b**$^{-\cdot}$; R = *n*-Bu)

(**e**)



(**41**$^{-\cdot}$; R = Me)

(**f**)

The stability of the $[M-R]^-$ ions of type **e** and **f** prevents further elimination of alkyl radicals in the case of polyalkoxyanthraquinones. A minor process is the formation of $[M-OR]^-$ ions.

TABLE 3. Relative intensities of molecular anions and fragment ions in the negative-ion spectra of alkoxy-substituted anthraquinones

Compound	$M^{-\cdot}$	$[M-R]^-$	$[M-OR]^-$
40a	100	20	1
40b	38	100	3
41	100	21	1

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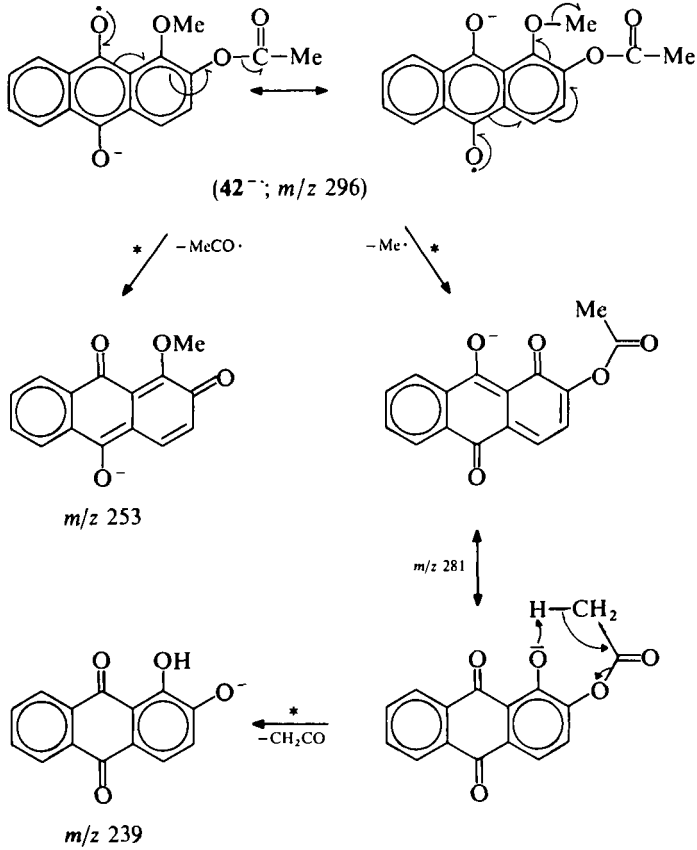
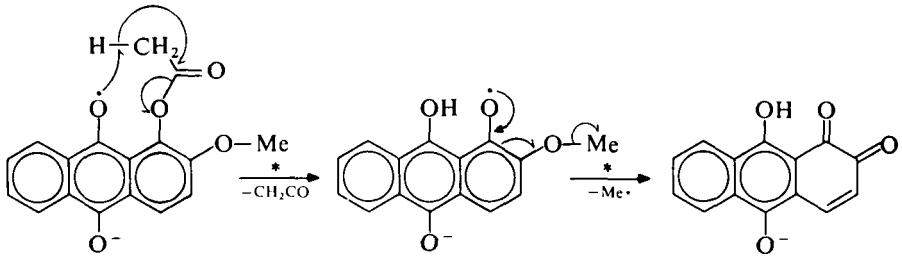
Many naturally occurring anthraquinones contain both methoxy and hydroxy groups. By converting the latter into acetate functions a differentiation between positional isomers is possible. The spectra of **42** and **43** illustrate this point (Figure 3(a), (b))[35]. From the known behaviour of alkoxy and acetoxy groups in the negative-ion spectra of anthraquinones the following sequences are expected; (**42**): $M^{-\cdot}$–Me·–CH_2CO and/or $M^{-\cdot}$–MeCO·, (**43**): $M^{-\cdot}$–Me·–CH_2CO and/or $M^{-\cdot}$–CH_2CO–Me·.

Both fragmentations are expected to occur for **42**. Competitive studies with the derivative monodeuteriated at the acetoxy group yields a primary deuterium isotope effect



k_H/k_D of 2.1 in the ion source and 2.4 in the first field-free region[36]. The close similarity of both values is in accordance with the fact that molecular anions in contrast to molecular cations have uniformly low internal energies since they are formed by secondary (thermal) electron capture.

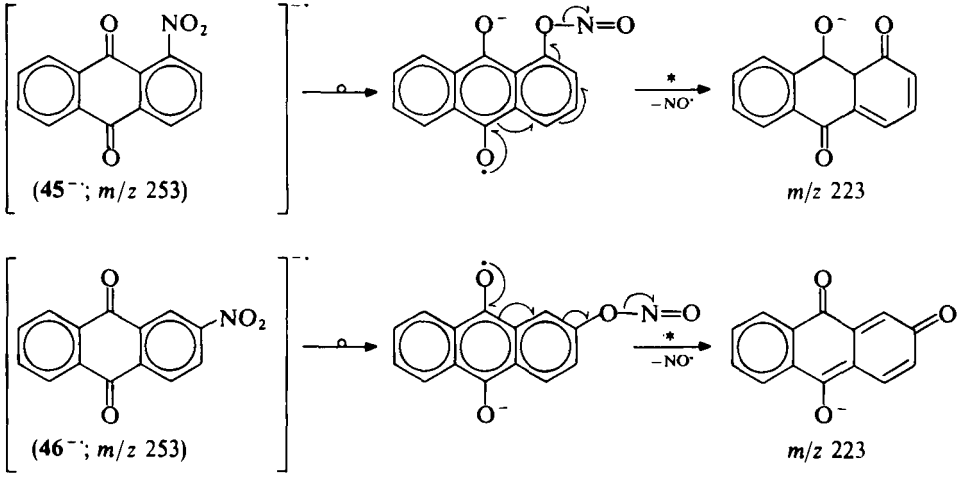
In the case of **43** the fragmentation almost exclusively occurs by initial elimination of ketene (which is not possible with the molecular anion of **42**) and subsequent loss of a methyl radical.



(**43**$^{-\cdot}$; *m/z* 296) *m/z* 254 *m/z* 239

The positive-ion spectra cannot afford such ready differentiation between two anthraquinone isomers. The spectrum of 1,8-diacetoxy-3-methyl-6-methoxyanthraquinone (**44**) (Figure 3(c)) is more complex. However, it clearly indicates the presence of one methoxy group together with either two *peri*-acetoxy (1,4; 1,5; 1,8) or two vicinal acetoxy (1,2) functions.

The molecular anions of 1- (**45**) and 2-nitroanthraquinone (**46**) represent the base peaks in the negative-ion mass spectra[37]. To some extent these species decompose by elimination of NO· to produce fragments with an even number of electrons. Their relative intensities are 5 and 3 %, respectively. These skeletal rearrangements are accompanied by flat-topped metastable peaks.



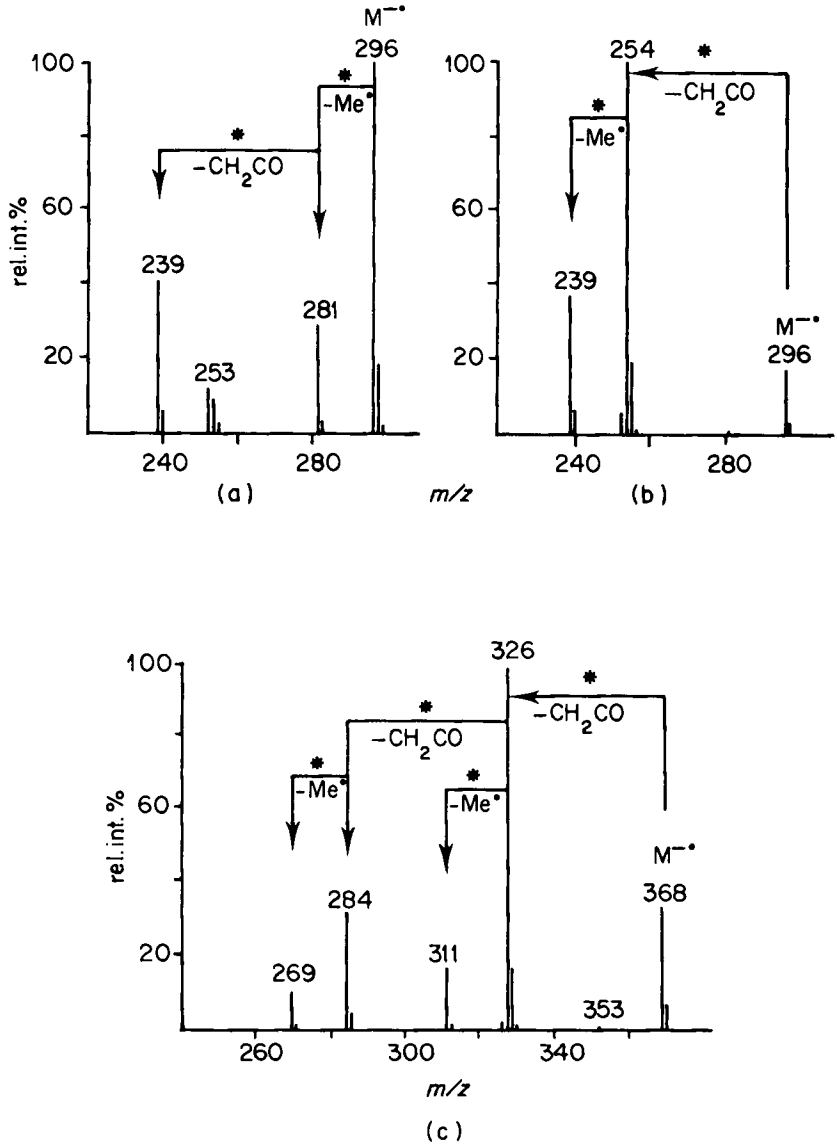
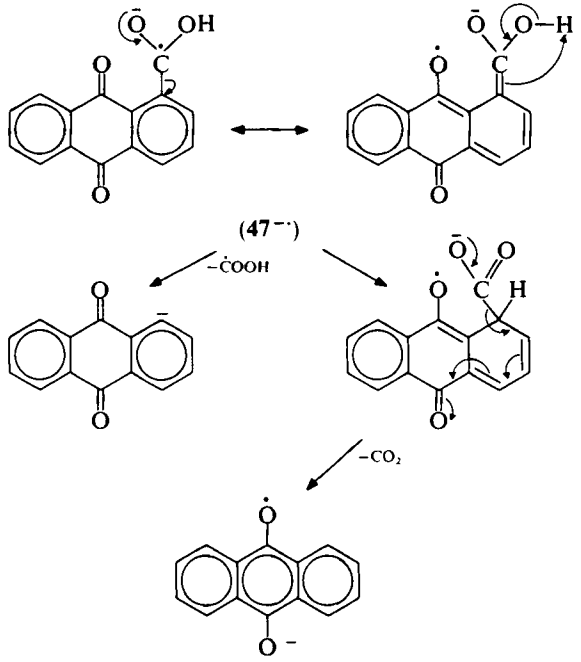


FIGURE 3. Negative-ion mass spectra of 2-acetoxy-1-methoxyanthraquinone (**42**) (a), 1-acetoxy-2-methoxyanthraquinone (**43**) (b) and 1,8-diacetoxy-3-methyl-6-methoxyanthraquinone (**44**) (c). *Reproduced from Ref.* 35, *by permission of the Commonwealth Scientific and Industrial Research Organization, Australia*

Unsubstituted quinones exhibit no fragmentation in the negative mode due to the high stability of the semiquinone radical anions. However, collisional activation with an inert gas in the field-free regions of the mass spectrometer imparts further internal energy to the

molecular anion. These ions then undergo collision-induced decompositions which may be detected in either of the field-free regions, applying techniques originally developed to investigate the collision-induced dissociation of positively charged ions. The collision gas should not yield negative ions and should not react with negative ions to produce ion–molecule product ions. Krypton, nitrogen, benzene and toluene have successfully been applied at pressures of ca. 3×10^{-5} torr. Under these conditions the naphthoquinone molecular anions give pronounced collision-induced peaks in both field-free regions originating from the unusual decompositions $M^{-\cdot}$–CHO· and $M^{-\cdot}$–(CHO· + CO)[38].

The negative-ion spectra of anthraquinone 1- (**47**) and 2-carboxylic acid (**48**) show only molecular anions when measured under normal conditions (70 eV, source pressure ca. 10^{-6} torr)[39]. The collision-induced fragmentation with toluene as collision gas (3×10^{-5} torr) has been detected in the second field-free region by standard magnetic scan and in the first field-free region by the metastable defocusing technique. The molecular anions of both isomers yield identical collisional activation spectra with no proximity effect allowing differentiation between **47** and **48**. The main fragmentations are $M^{-\cdot}$–·COOH and $M^{-\cdot} - CO_2$. The former represents α-cleavage to the charged carboxy group. Driving force for the elimination of CO_2 is the generation of the very stable semiquinone radical



anion. A third peak observed corresponds to the process $M^{-\cdot}$–C_2HO_3·. This process must consist of the consecutive loss of CO_2 and CHO· involving one of the carbonyl centres of the quinone moiety.

Plots of the ionization efficiencies of the molecular anion and the collision-induced $[M-CO_2]^{-\cdot}$ and $[M-CO_2H]^-$ ions of anthraquinone 2-carboxylic acid (**48**) against the nominal electron beam energy are shown in Figure 4[39]. From the ionization efficiency curve of the molecular anion it follows that this ion may be produced in two ways: (1) capture of low energy primary electrons at nominal 5–10 eV and (2) capture of

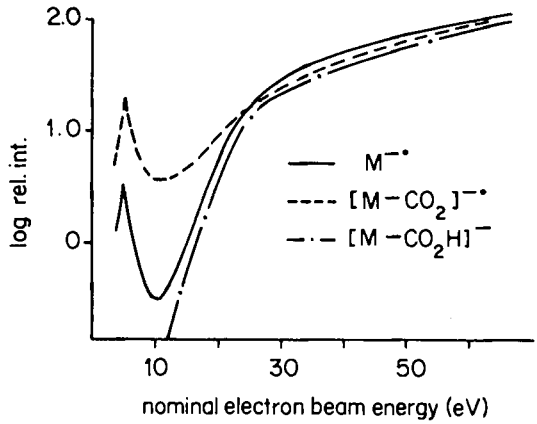


FIGURE 4. Ionization efficiency curves of $M^{-\cdot}$, $[M-CO_2]^{-\cdot}$ and $[M-CO_2H]^-$ from anthraquinone 2-carboxylic acid (**48**). The relative intensity of each ion is arbitrarily taken as 100 % at 70 eV. *Reproduced from Ref.* 39

secondary (thermal) electrons when the nominal beam energy is greater than 15 eV. Obviously, the collision-induced loss of CO_2 is possible from molecular anions produced by either process. In contrast, elimination of $^{\cdot}CO_2H$ occurs only by collisional activation of molecular anions formed by secondary electron capture.

It has been demonstrated by Bowie and Blumenthal[40] that non-decomposing molecular anions can undergo charge inversion by high-energy ion molecule reactions in the analyser regions of the mass spectrometer. This process is accompanied by efficient conversion of translational energy to internal energy leading to subsequent decomposition. Thus, spectra of positive ions are produced from molecular anions.

$$M^{-\cdot} + N \rightarrow [M^{+\cdot}]^* + N + 2e^-$$
$$\downarrow$$
fragments

The spectra obtained are named $+E$ spectra because the electric sector in a double focusing instrument is operated at the reverse potential to that ($-E$) used to measure conventional negative-ion spectra. $+E$ spectra may be determined for dissociations in either field-free region of the mass spectrometer. Decompositions in the first field-free region are detected by the ion kinetic energy technique and in the second field-free region by carrying out a magnetic scan with the electric sector at $-E$ and the magnet set to transmit positive ions. The target gas may be some species which does not produce negative ions in the source (e.g. He, N_2, C_6H_6), or the sample itself may be used as the target gas (pressure in the collision region ca. $3–5 \times 10^{-5}$ torr).

A number of benzoquinones, naphthoquinones, and higher quinones have been investigated by this technique[40,41]. The $+E$ mass spectrum from the naphthoquinone molecular anion is given in Figure 5(a)[40]. It yields very similar information as the conventional positive-ion spectrum (Figure 5(b))[1,42]. In the latter spectrum the peaks are produced by a series of consecutive and competitive unimolecular decompositions; in the $+E$ spectrum the same peaks are obtained via collision-induced dissociations. Differences are seen concerning the abundances of fragments; e.g. in the normal positive-ion spectrum the rearrangement ion $[M-CO_2]^{+\cdot}$ at m/z 114 is of low relative intensity[42], whereas in the

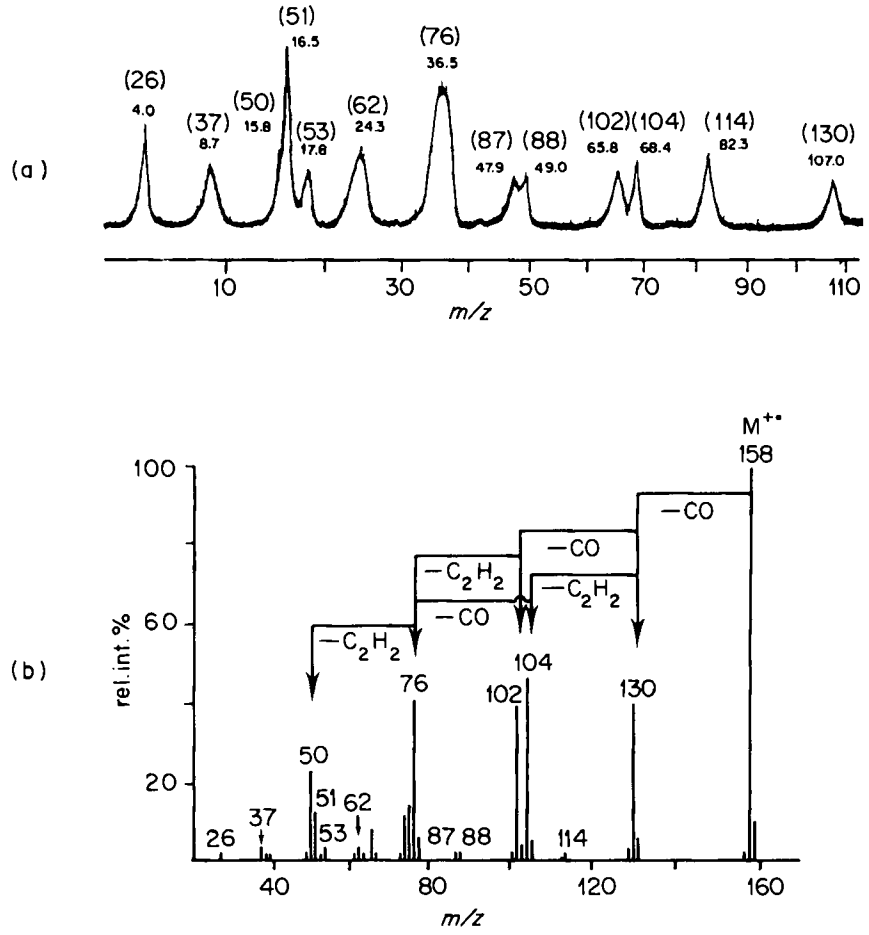
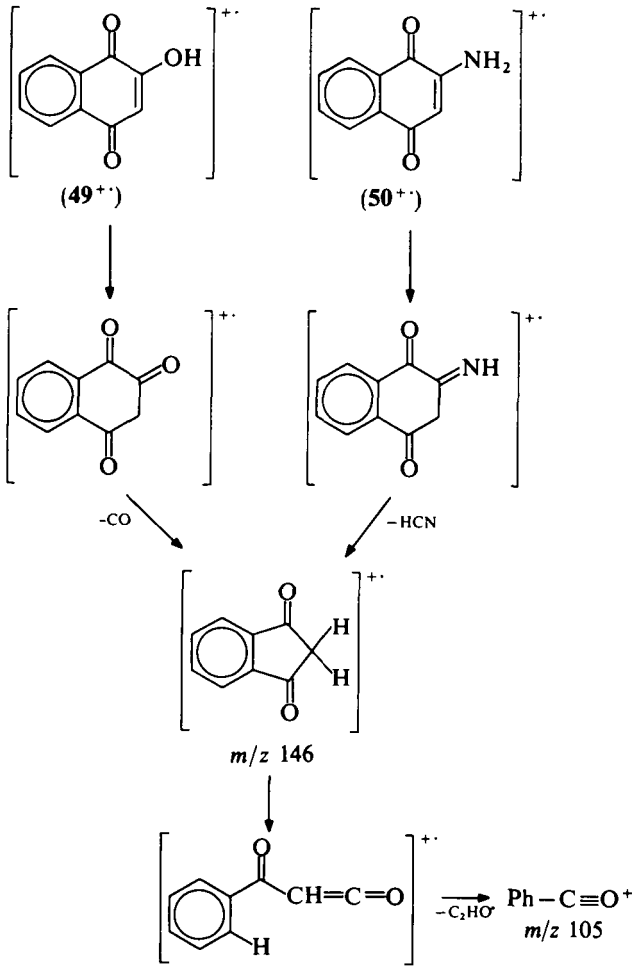
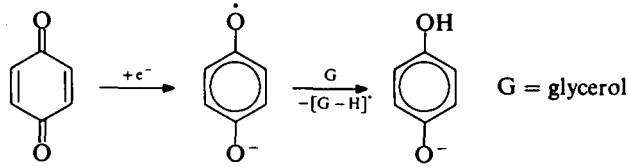


FIGURE 5. (a) $+E$ mass spectrum derived from the 1,4-naphthoquinone molecular anion in the second field-free region (sample pressure ca. 3×10^{-5} torr). The values given are readings on the mass scale corresponding to m_2^2/m_1; values in parenthesis refer to the fragment ion mass m_2. (b) Conventional positive-ion mass spectrum of 1,4-naphthoquinone. *Reproduced from J. H. Bowie and T. Blumenthal,* J. Am. Chem. Soc., **97**, 2959 (1975), *by permission of the American Chemical Society. Copyright* (1975) *American Chemical Society*

$+E$ spectrum this process contributes more substantially. A particular example is afforded by 2-hydroxy-1,4-naphthoquinone (**49**) and 2-amino-1,4-naphthoquinone (**50**). The positive-ion spectra of **49**[1] and **50**[41] are dominated by the process $(M^{+\cdot}\text{–CO}) \rightarrow (M^{+\cdot}\text{–CO})\text{–}C_2HO^{\cdot}$ and $(M^{+\cdot}\text{–HCN}) \rightarrow (M^{+\cdot}\text{–HCN})\text{–}C_2HO^{\cdot}$, respectively. In the $+E$ counterparts peaks due to the final product ion of these sequences at m/z 105 are present, however, of low abundances.



Benzoquinone when ionized by fast atom-beam bombardment (FAB) in a glycerol matrix is able to capture an electron to produce the semiquinone radical anion (rel. intensity ca. 60 %)[43]. This process is followed by hydrogen abstraction from glycerol to yield the monoanion of hydroquinone representing the base peak. The formation of these ions is of general importance for the theory of ion formation under fast atom-beam bombardment, since it indicates that in addition to protonation and proton abstraction electron capturing and hydrogen abstraction may also contribute to the formation of ions in a FAB source.



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CHAPTER 4

Chiroptical properties and absolute configurations of chiral quinones

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I. INTRODUCTION

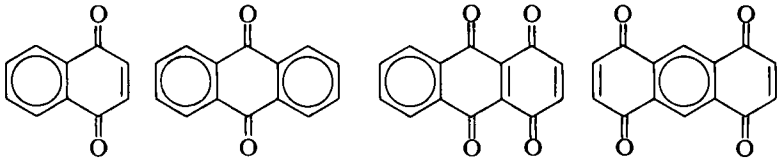
In his classical work on the chiroptical properties of chemical substances, Lowry[1] reviewed the early history of rotatory power measurements. Thus from the very beginning Biot and Louis Pasteur made such measurements using light of various wavelengths in the visible part of the spectrum, the rotatory power of a substance over a spectral range being known as its optical rotatory dispersion (ORD)[1]. After Biot's death in 1862 and the introduction about 1866 of the Bunsen burner as a light source, it became much easier to work with the nearly monochromatic light of the sodium flame (589 nm), and the more laborious study of ORD was largely abandoned. As a matter of convenience then, the chiroptical property most frequently reported for chiral substances is their rotatory power for sodium D light[2].

Useful compilations of this chiroptical property have appeared, and Thomson[3] in his very important review of naturally occurring quinones has presented their physical properties, including the specific rotations of naturally occurring chiral quinones. More recently the absolute configurations of a host of chiral substances, including chiral quinones, have been given in two collections[4,5]. In one of these[4], the absolute configurations of approximately 6000 compounds, the method by which each configurational assignment was made, the sign of the rotatory power for a particular enantiomer, and appropriate literature references are given. In the other[5], the absolute configurations, the sign of the rotatory powers for given states (liquid or as solutions in various solvents) and literature references are tabulated for nearly 6000 compounds. This latter collection has limited value for chiral quinones since it is restricted to compounds with one chiral center (asymmetric carbon atom), and many chiral quinones have more than one such center or are chiral as the result of restricted rotation about a single bond (atropisomerism[6]) and thus do not have any chiral center.

The rotatory powers (with sodium D light) of chiral organic compounds, including chiral quinones, are useful as the means for their characterization, both as a physical property which distinguishes one enantiomer from the other but also as the means by which the optical purity (percent enantiomeric excess, % ee) of particular samples can be easily determined.

Prior to 1950 rotatory powers were occasionally used for the determination of absolute configurations (rotatory power comparisons)[7], but most of these assignments were made by chemical correlations[4,5]. Certainly rotatory power measurements are not as reliable as ORD and circular dichroism (CD) methods[8] for absolute configurational assignments by comparison, but before 1950, ORD curves were measured only with ease in the visible spectral region (380–780 nm) and with great difficulty in the near ultraviolet region (200–380 nm)[1]. In 1953, a commercially manufactured spectropolarimeter capable of routine ORD measurements from 700 to 280 nm became available[9] and now measurements are easily made to 185 nm[8]. Circular dichroism (CD) curves were measured in the visible spectral region during the nineteenth century[1], but they were not common before 1960[9]. The description of the first recording circular dichrograph[10] led to a rapid development in this field and to commercial availability of instruments capable of routine CD measurements in the visible and the near ultraviolet spectral regions (180–600 nm)[8,11].

The main focus of this chapter then is a brief outline of the use of ORD and CD measurements in the visible and near ultraviolet spectral region for the establishment of the absolute configurations of chiral quinones, occurring for the most part as natural products[3]. Other chiroptical measurements such as far ultraviolet circular dichroism[12] (FUVCD), vibrational (infrared) circular dichroism[13] (VCD) and Raman optical activity[14] (ROA) are just beginning to have an impact on stereochemical problems, but they have not been used with chiral quinones and will not be discussed here. Magnetic circular dichroism



(1) (2) (3) (4)

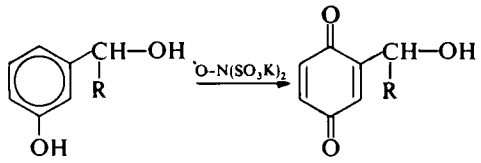
(MCD) measurements using 1,4-naphthoquinone[15] (**1**), anthraquinone[16] (**2**) and 1,4,9,10- (**3**) and 1,4,5,8-anthracenetetrone[15] (**4**), linear dichroism studies of 1,4-naphthoquinone and several substituted 1,4-napthoquinones[17] and induced circular dichroism observations on 1,4-naphthoquinone in β-cyclodextrin[18] have been reported but only in connection with studies of the electronic absorption (EA) spectra of quinones[15, 17, 18] and of the MCD of aromatic carbonyl compounds[16].

It is to be recognized, however, that the absolute configuration of a chiral quinone can be assigned with ORD and CD measurements only on the basis of empirical comparison with model compounds of similar structures of known absolute configurations. In what follows, the chiral quinones are grouped for convenience into the usual types of quinones and for each type as classes of natural products, and part of the discussion for each class concerns the establishment of the absolute configurations of model compounds by rotatory power comparison, chemical correlation, or X-ray techniques. For completeness, the absolute configurations of a few types of important naturally occurring quinones are discussed although these absolute configurations were not determined by chiroptical methods or were not used for other chiroptical studies.

II. BENZOQUINONES

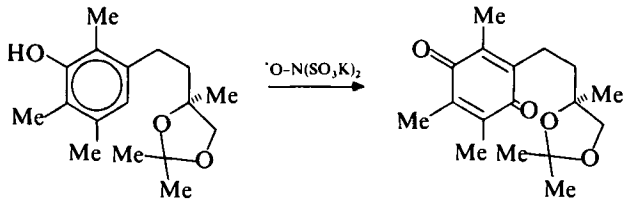
A. Synthetic *p*-Benzoquinones

Usually chiral benzoquinones occur as natural products[3], but a few chiral *p*-benzoquinones have been prepared and studied as their enantiomers. Thus oxidation of 1-(*m*-hydroxyphenyl)ethanol (**5**) and 1-(*m*-hydroxyphenyl)propanol (**6**) with Fremy's



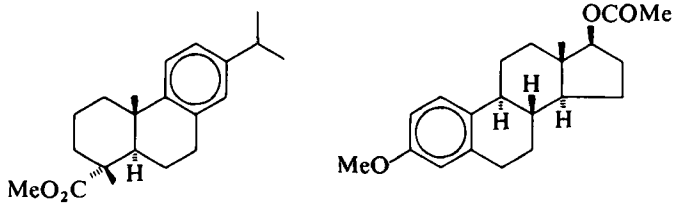
(**5**, R = Me) (**7**, R = Me)
(**6**, R = Et) (**8**, R = Et)

salt[19, 20] gave the respective racemic 1'-hydroxyethyl- (**7**) and 1'-hydroxypropyl-*p*-benzoquinone (**8**)[21] and using the β-cyclodextrin inclusion complexes, one enantiomer of each was obtained in low enantiomeric excess, 27% for **7**[21]. Using Fremy's salt and a pure enantiomer of a chiral phenol such as **9**, the optically pure *p*-benzoquinone was obtained in very high chemical yield, 98% for **10**. The reaction proceeded in almost as high a chemical yield (91%) with the phenol diol corresponding to **9**[22]. Hydrogen peroxide trifluoroacetic



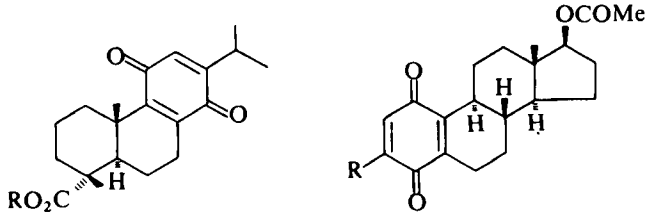
(9) (10)

acid oxidation of the methyl ester of the dehydroabietic acid **11** and of 17β-acetoxy-3-methoxyestrane (**12**) in chloroform gave the corresponding *p*-benzoquinones, **13**, **14** and



(11) (12)

15 in low chemical yield, 10%, 10% and 1% respectively[23]. Compound **12** gave both **14** and **15**[23]. Benzoquinone **13** was prepared in connection with the possibility that the acid **16** is an intermediate in the degradation of dehydroabietatic acid[23].



(**13**, R = Me) (**14**, R = MeO)
(**16**, R = H) (**15**, R = H)

The EA spectra of **13–15** (Figure 1) show maxima near 450, 340 and 260 nm which are assigned, respectively, to an $n \rightarrow \pi^*$ of the carbonyl groups, an electron transfer transition and an $\pi \rightarrow \pi^*$ transition[3]. The CD spectra of **13–15** (Figure 2) also show similar Cotton effects (CEs), a negative maximum near 460 nm followed by a positive maximum in the 340–380-nm region[23]. That the CD spectra of the three *p*-benzoquinones are very similar can be seen by comparison of the non-traditional representation of **13** as stereoformula **17** with those of **14** and **15**. In all of these, the chiral centers alpha and beta to the *p*-benzoquinone chromophore have the same absolute configuration. Thus these CD spectra constitute a set of model spectra for the assignment of the absolute configurations of *p*-benzoquinones similar in structure to **13–15**[23].

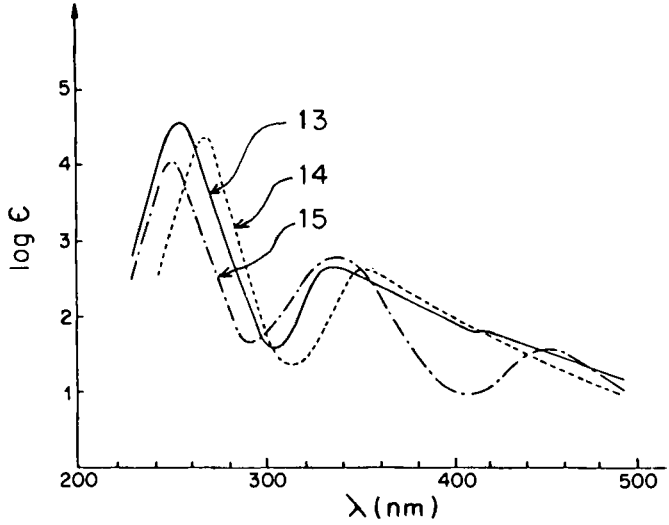
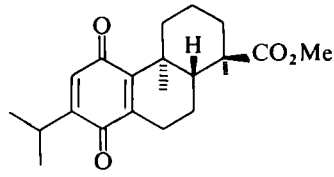
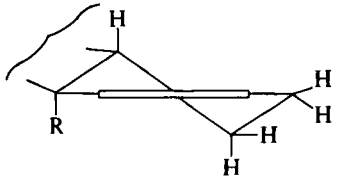


FIGURE 1. Electronic absorption (EA) spectra for the *p*-benzoquinones **13**, **14** and **15** in ethanol. *Adapted from Ref. 23 by permission of the French Chemical Society*

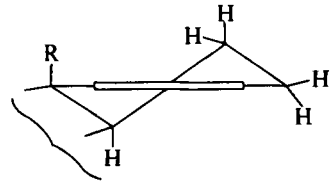
Since the signs of the observed CEs in the CD spectra of **13–15** reflect the chirality of the half-chair cyclohexene ring attached to the *p*-benzoquinone chromophore (**18**) as imposed



(**17**)



(**18**)



(**19**)

by the alpha and beta chiral centers, the benzoquinone **16** should show a CD spectrum similar to those of **13–15**. Reversal of the chirality of the half-chair cyclohexene ring with respect to the benzoquinone chromophore (**19**) will result in a change in sign of the observed Cotton effects near 460 and 360 nm.

B. Neoflavanoids. Dalbergiones

A number of chiral *p*-benzoquinones was isolated from the heartwood of trees (African Blackwood, Senegal Ebony, Mozambique Ebony) of various species of the genus

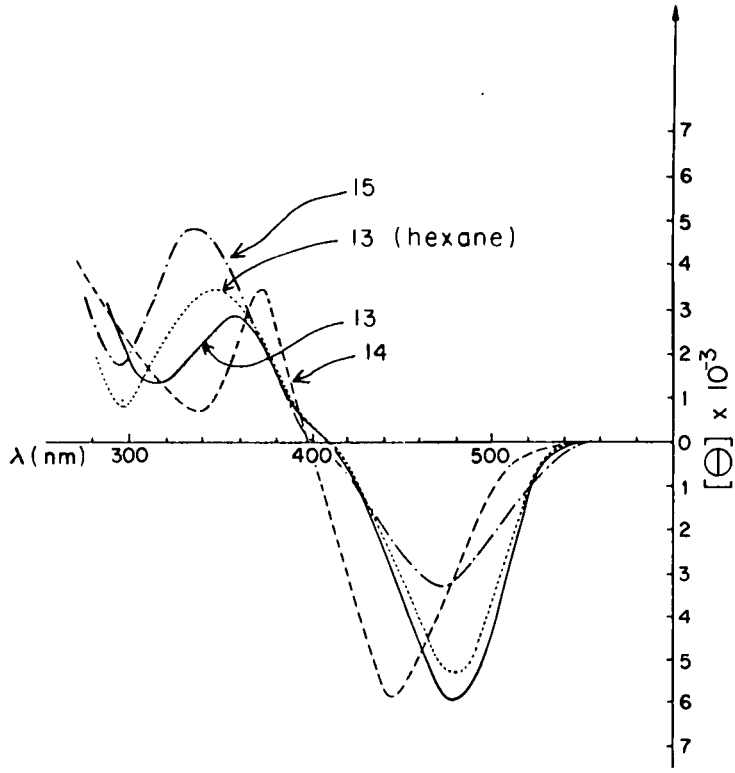
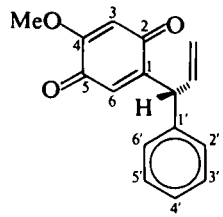
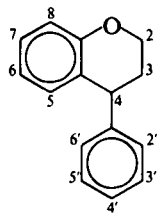


FIGURE 2. Circular dichroism (CD) spectra of the *p*-benzoquinones **13**, **14** and **15** in ethanol and of **13** in hexane. *Adapted from Ref. 23 by permission of the French Chemical Society*

Dalbergia[24]. These compounds were given the general name dalbergiones[24] and the simplest member of the group, initially called dalbergione[24], was shown to have the structure and absolute configuration shown in stereoformula **20**[24]. These *p*-benzoquinones, although not heterocyclic compounds, belong to a class of natural products called neoflavanoids to emphasize their relationship to the heterocyclic natural products with the 4-arylchroman structure (**21**) to which has been given the name neoflavanoid[25]. Since the first report of the structures and configurations of the

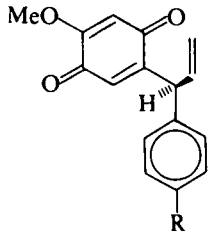


(20)

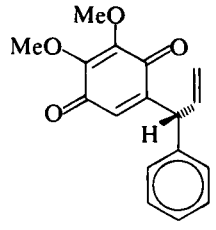


(21)

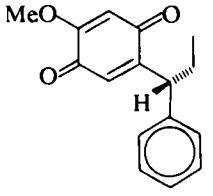
dalbergiones[24], the nomenclature has been changed, and **20** is now named (*R*)-4-methoxydalbergione[25]. Other members of the group, isolated from *Dalbergia*[25, 26] and *Machaerium*[27] species, are (*S*)-4-methoxy-[25], (*S*)-4,4′-dimethoxy-[25], (*S*)-4′-hydroxy-4-methoxydalbergione[25] (**22**–**24**, respectively) and (*R*)-3,4-dimethoxydalbergione[27] (**25**). Catalytic reduction of **20** and **23** gave the corresponding dihydro compounds, **26** and



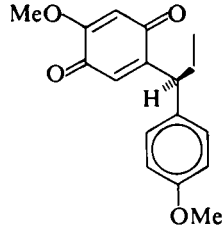
(**22**, R = H)
(**23**, R = OMe)
(**24**, R = OH)



(**25**)



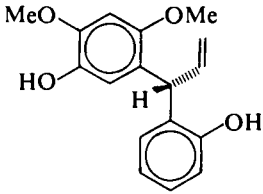
(**26**)



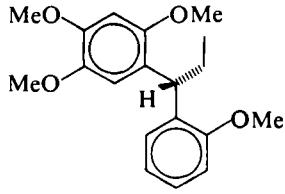
(**27**)

27[24, 25] which on ozonolysis gave, respectively, (*R*)-α-phenyl and (*S*)-α-(*p*-methoxyphenyl)-*n*-butyric acid, and thus the absolute configurations of **20**, **23**, **26** and **27** were firmly established by chemical correlation[24, 25]. The absolute configuration of **24** was established as *S* by comparison of its ORD curve with those of **22** and **23**[25]. As seen in Figure 3, the dalbergiones (**20**, **23**) and dihydrodalbergiones (**26**, **27**) with the *R* and *S* configurations give essentially enantiomeric ORD curves, the presence of a methoxyl (or an hydroxyl group[25]) at C(4′) having little effect on the ORD curves[25]. The same is true for the EA and CD spectra[25]. The absolute configuration of **25** was also established by comparison of its ORD curve and CD spectrum with the ORD curve of **20**[27].

Another isoflavanoid isolated from a *Dalbergia* species is latifolin (**28**), and although not



(**28**)



(**29**)

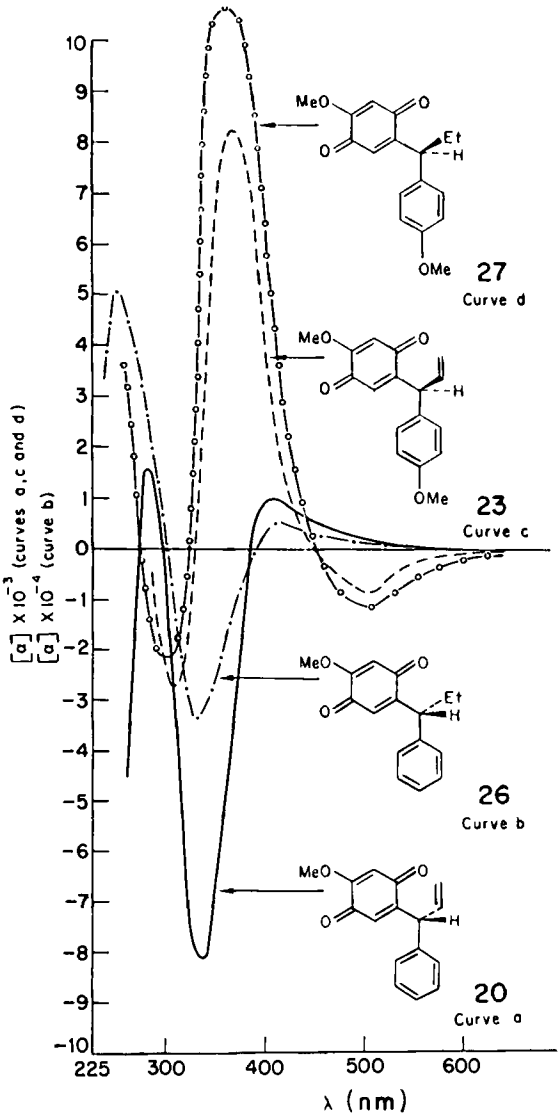
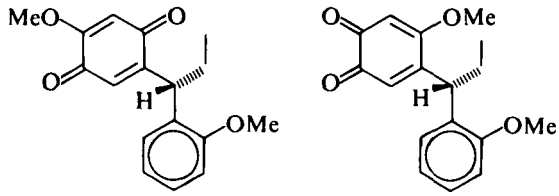


FIGURE 3. Optical rotatory dispersion (ORD) curves of (*R*)-4-methoxydalbergione (**20**), (*S*)-4,4'-dimethoxydalbergione (**23**), (*R*)-dihydro-4-methoxydalbergione (**26**) and (*S*)-dihydro-4,4'-dimethoxydalbergione (**27**) in dioxan. *Adapted from Ref. 25 by permission of Pergamon Press*

a dalbergione, it is a close structural relation[28]. Conversion of **28** to its dihydrodimethyl derivative (**29**) and oxidation of the latter with chromic acid in acetic acid gave (*R*)-dihydro-2',4-dimethoxydalbergione (**30**) and the isomeric *o*-benzoquinone **31**[28]. The absolute configurations of **30** and **31** and thus **28** and **29** were all established as *R* on the



(30) (31)

basis of a comparison of the ORD curves of **30** and **31** with that of (*R*)-4-methoxydalbergione (**20**). Finally the absolute configuration of latifolin (**28**) was independently established by comparison of its ORD curve and those of some of its derivatives with those of related quinol diacetates derived from various dalbergiones[29]. As part of this work, the ORD curves of the four dalbergiones **23–25** and **30** were examined in some detail. In these curves, at least three apparent CEs occur which overlap one another and thus the curves can only be compared on an empirical basis. It is not possible to interpret the results without analysis of the curves into their single transition components. The CE centered in the ORD curve at about 336 nm (Figure 3), positive for those with the *S* configuration (**23**, **24**) and negative for those of the *R* configuration (**25**, **30**), however, can be used with confidence to assign the absolute configuration of chiral *p*-benzoquinones of similar structure[29].

C. Isoflavanoids. Mucroquinone and Claussequinone

Also isolated from a *Machaerium* species, *M. mucronulatum*, is a levorotatory, orange compound to which was assigned a methoxy-*p*-benzoquinone structure and the name mucroquinone[30] (**32**). Since **32** has the 3-arylchroman structure, it is a member of the class of natural products to which has been given the name isoflavanoid.

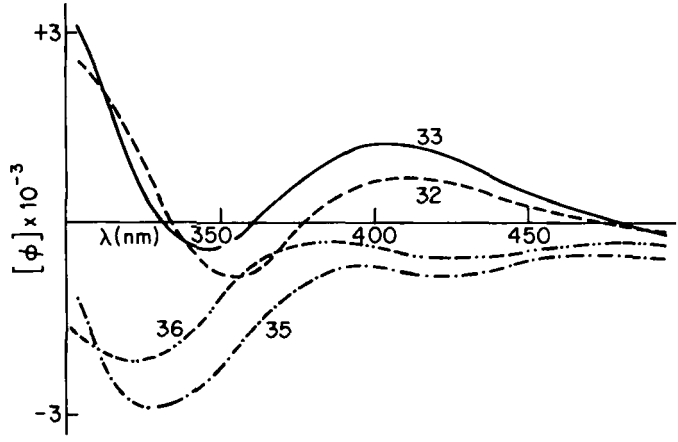
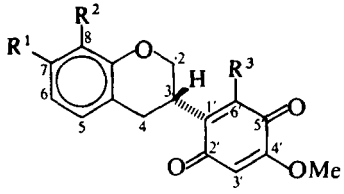


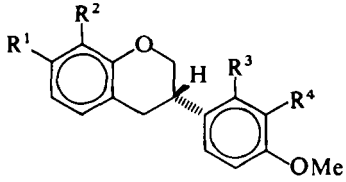
FIGURE 4. Optical rotatory dispersion (ORD) curves of mucroquinone (**32**), (*S*)-7,4′-dimethoxyisoflavan-2′,5′-quinone (**33**), (*S*)-7-hydroxy-8,4′,6′-trimethoxyisoflavan-2′,5′-quinone (**35**) and (*S*)-7,8,4′,6′-tetramethoxyisoflavan-2′,5′-quinone (**36**). *Adapted from Ref. 32 by permission of the Royal Society of Chemistry*

The absolute configuration of levorotatory mucroquinone (**32**) isolated from *M. mucronulatum*[30] and *M. villosum*[31] was established as *S* by comparison of its ORD characteristics with those of the isoflavanquinone **33**, the ORD curves for both **32** and **33** being very similar from 330 to 450 nm (Figure 4)[32]. The absolute configuration of **33** follows from its preparation by oxidation of the corresponding isoflavan **34** which was shown to have the *S* configuration[32]. Although the ORD curves for the configurationally



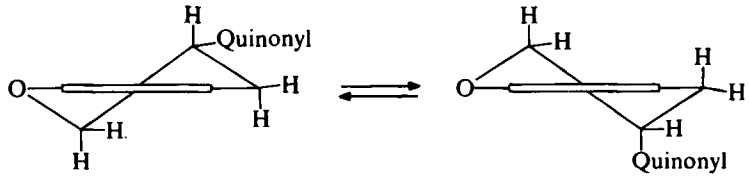
(**32**, R^1 = OH, R^2 = OMe; R^3 = H)
(**33**, R^1 = OMe, R^2 = R^3 = H)
(**35**, R^1 = OH, R^2 = R^3 = OMe)
(**36**, R^1 = R^2 = R^3 = OMe)

related isoflavans such as **34**, **37** and **38** display a consistent pattern, caution must be exercised in the interpretation of the ORD curves for the isoflavanquinones and



(**34**, R^1 = OMe; R^2 = H; R^3 = OH; R^4 = H)
(**37**, R^1 = OH, R^2 = R^3 = OMe; R^4 = OH)
(**38**, R^1 = OMe; R^2 = R^3 = R^4 = H)

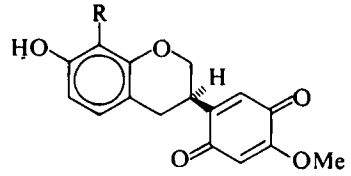
comparison of curves is clearly limited to closely related structural types[32, 33]. The isoflavanquinones **35** and **36**, although known to have the *S* configuration from their preparation from the corresponding isoflavan **37**, have ORD curves (Figure 4) in the 400–500-nm region which are almost enantiomeric to those of **32** and **33**[32, 33]. This at first sight could be just a consequence of the different chromophores of the two pairs of quinones, but the proton nuclear magnetic resonance (^{1}H-NMR) spectra of the dihydropyran ring protons show that there are also conformational differences between the pairs of compounds[32, 33]. The dihydropyran ring in **32**, **33**, **35** and **36** is expected to assume a preferred half-chair conformation. It is not possible on the basis of conformational arguments to state which of the two conformers, **39a** or **39b**, is of lower energy, since the axial 3-quinonyl substituent in **39b** does not result in the destabilizing 1,3-diaxial interaction of axial-substituted cyclohexane and cyclohexene systems. The vicinal coupling constants for the protons of the dihydropyran ring for the isoflavanquinones **35** and **36** are consistent with those expected for the half-chair conformation **39a** in which the 3-quinonyl substituent occupies an equatorial position[33]. The observed vicinal coupling constants for the corresponding protons in the isoflavanquinone **32** are, however, different and are consistent with the values expected from a conformational equilibrium in which **39b** with an axial 3-quinonyl substituent is the major contributor[33]. This conformational



(39a) (39b)

difference between quinones **32** and **33**, which lack the 6'-methoxy group, and quinones **35** and **36**, which have a 6'-methoxy group, is clearly related to the difference in the ORD curves shown by **32** and **33** on the one hand and those shown by **35** and **36** on the other (Figure 4)[32].

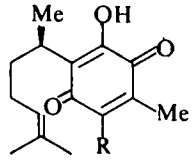
(*R*)-Mucroquinone (**40**), the enantiomer of **32**, and claussequinone (**41**) were both isolated from species of the genus *Cyclolobium*, **41** so named because of its occurrence in the heartwood of *C. clausseni*[34]. The absolute configurations of both of these isoflavanquinones were established by comparison of their ORD curves with that of (*S*)-mucroquinone (**32**)[34], the curves of **40** and **41** being essentially enantiomeric to that of **32**[32].

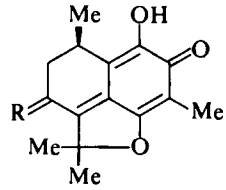


(**40**, R = OMe)
(**41**, R = H)

D. Sesquiterpenes. Perezone

Although monoterpene *p*-benzoquinones occur as natural products, none so far known is chiral, but chiral sesquiterpene *p*-benzoquinones are known[3, 35]. An important one with the bisabolene structure is perezone (**42**) which was found as a plant constituent and





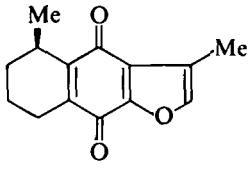
(**42**, R = H)
(**43**, R = OH)

(**44**, R = H_2)
(**45**, R = O)

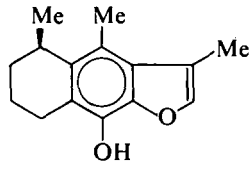
characterized as a *p*-benzoquinone many years ago[36, 37]. The structure for perezone as originally proposed[37] was subsequently revised[38], but the earlier work in connection with its absolute configuration[37, 39] still establishes its absolute configuration as *R*[39].

Optical rotatory dispersion measurements were reported for perezone as well as a number of its derivatives[40, 41]. Among the latter was hydroxyperezone (**43**), isolated as a

natural product[3] but also prepared from perezone[37,42] (**42**). Others were the *p*-benzoquinone methides, perezinone (**44**) and oxoperezinone (**45**), formed, respectively, by dehydration of hydroxyperezone[37,42] and oxidation of perezinone[43]. Included in one of these chiroptical studies was the ORD curve of the norquinone[41] **46**, an oxidation product of cacalol[44] (**47**), the latter a sesquiterpene with a structure[44] different from that assigned earlier[45]. The *R* configuration for **46** and for **47** was originally assigned on the basis of a comparison of the ORD curve of **47** with those of a number of chiral 1-substituted indans[41]. It is to be noted, however, that although **47** and the indans all incorporate benzene chromophores, the substantial difference in the structure of **47** from those of the indans suggests that comparison of the ORD curve of **47** with those of the chiral 1-substituted indans is not justified. Hence the configurational assignment for **47** and also for **46** must be recognized as not firmly established.



(**46**)

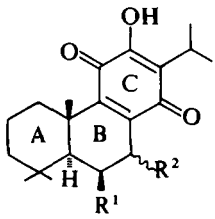


(**47**)

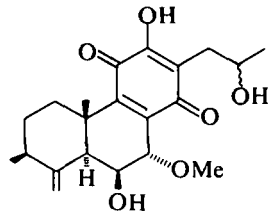
E. Diterpenes

1. Royleanones

As reviewed by Eugster[35], a vast number of diterpenoid pigments occurs in nature, some of which incorporate the *p*-benzoquinone chromophore. Important among these is royleanone (**48**), a benzoquinone with the abietane carbon skeleton and isolated from the root of *Inula royleana*, a perennial shrub that grows in the western Himalayas[46]. Royleanone has been found in other plants, and it has given its name to a group of related diterpenes, the royleanones[35]. The approximately sixteen compounds which comprise this group have the basic royleanone carbon skeleton and chromophore but have hydroxyl



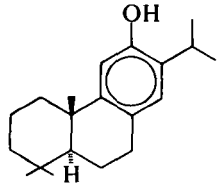
(**48**, $R^1 = R^2 = H$)
(**49**, $R^1 = H$; $R^2 = \beta$-OH)
(**50**, $R^1 = H$; $R^2 = \alpha$-OH)
(**51**, $R^1 = OH$; $R^2 = \alpha$-OH)



(**52**)

substituents on various positions of rings A and B[35]. Important ones are taxoquinone (**49**), horminone (**50**) and 6β-hydroxyhorminone (**51**)[35]. Occasionally a rearranged abietane skeleton (**52**) is encountered[35].

The structure and configuration of royleanone (**48**) follows its formation by oxidation of ferruginol (**53**) with hydrogen peroxide in acetic acid-sulfuric acid[46]. The CD spectrum



(**53**)

(Figure 5) of **48** was reported in connection with stereochemical studies of related compounds[47] and may be compared with those of **13–15** (Figure 2) (Section II.A). The spectra of **48** and of **13–15** show substantial differences in both the wavelength and intensity of their respective CD maxima. This again emphasizes the requirement that, for comparison of ORD curves and CD spectra in configurational studies, comparison must be made between compounds of very similar structures unless differences in the structures are known to have no substantial effect on the ORD curves and CD spectra as among **22–24**[25].

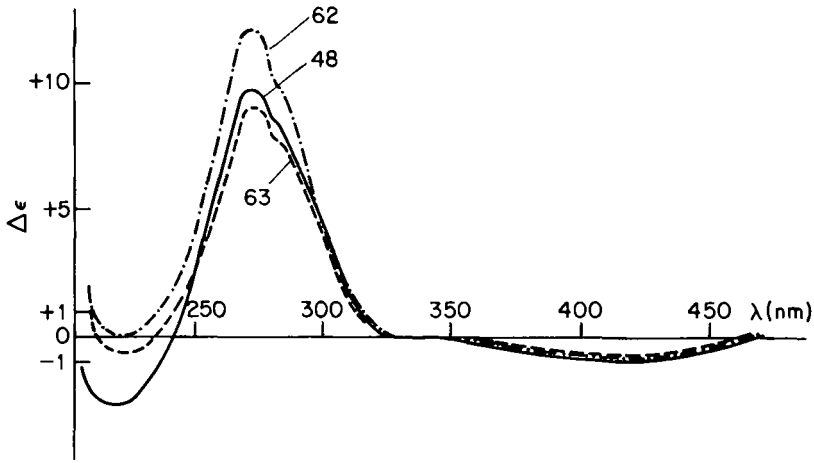


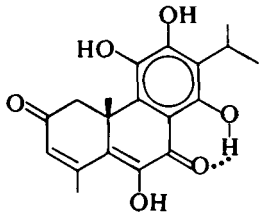
FIGURE 5. Circular dichroism (CD) spectra of royleanone (**48**) and the *p*-benzoquinones **62** and **63** from coleone E (**61**) in dioxan. *Adapted from Ref. 47 by permission of the Swiss Chemical Society*

The CD spectra for royleanones other than **48** have not been reported, but it is anticipated that an hydroxyl, methoxyl, or acetoxyl group on rings A or B will have only a small effect on their CD spectra.

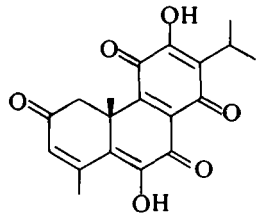
2. *Coleones*

Another group of diterpene pigments is the coleones, so named because they were first found in the glands of *Coleus* species[48]. These substance, by 1977 over 70 compounds[35], have a great structural diversity, but almost all can be derived from abietane. Among these is the hydroquinone coleone B[49] (**54**), so named because it was the second coleone found[35]. Coleone Z was reported in 1979[50].

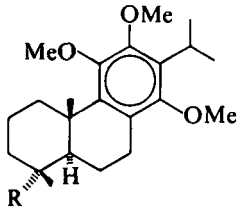
Coleone B (**54**) on oxidation yields coleone-B-quinone (**55**)[49]. The absolute configuration of **54** and thus that of **55** were assigned on the basis of the similarity of the ORD curves of the trimethyl ethers **56** and **57**, derived, respectively, from royleanone (**48**) and coleone B (**54**)[49].



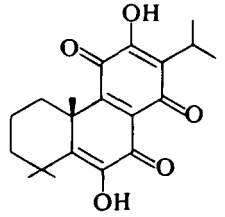
(**54**)



(**55**)



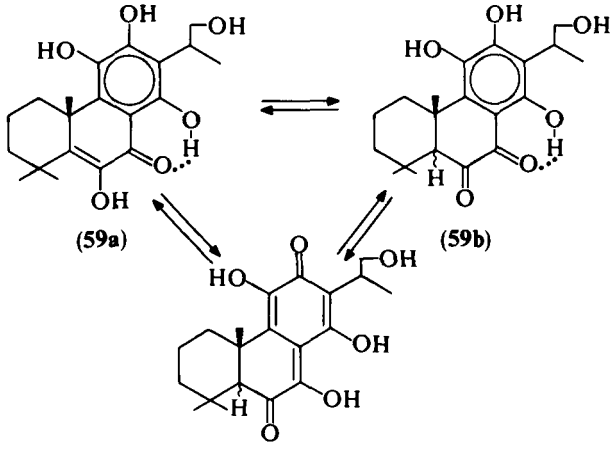
(**56**, R = Me)
(**57**, R = H)



(**58**)

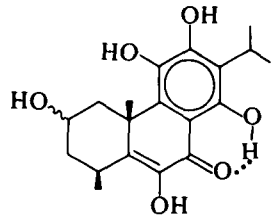
The CD spectrum of coleone-B-quinone (**55**) has not been reported, but a quinone similar to **55**, coleone-U-quinone (**58**), has recently been isolated from the red leaf glands of *Plectranthus agentatus*[51]. The absolute configuration and CD spectrum of **58** were reported[51].

A substance related to coleone B (**54**) is coleone C (**59**) which on isolation is a bright yellow, sharp melting, crystalline solid[52]. On the basis of its electronic absorption



(**59a**) (**59b**)

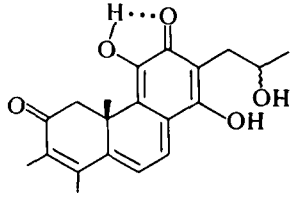
(**59c**)



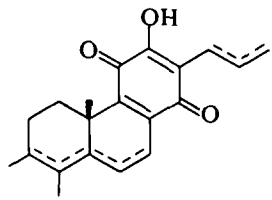
(60)

spectrum in ethanol with a strong absorption maximum near 400 nm and other spectral and chemical evidence[52], **59** in solution is assigned tautomeric structures such as **59a–c**, including the quinone methide **59c**. The absolute configuration of **59** follows from a comparison of its CD spectrum in dioxan (Figure 6) with that of dihydrocoleon-B-alcohol (**60**) which on the basis of its spectral properties must also have a tautomeric structures in dioxan similar to those of **59**[52].

Some of the members of the coleone group are in fact fully conjugated quinone methides[47, 53]. Coleone E[47] (**61**) is a deeply red substance, and in its EA spectrum has a



(61)



(62)

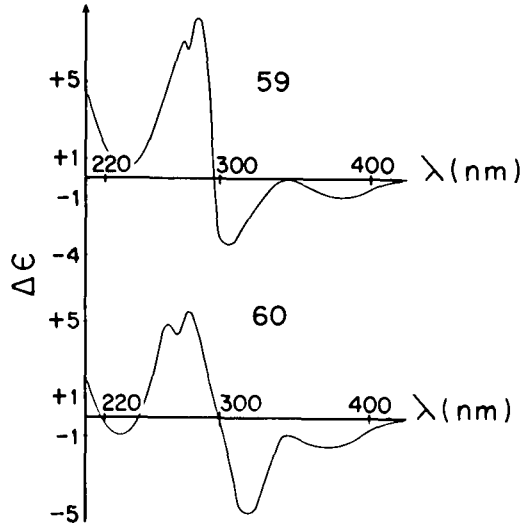
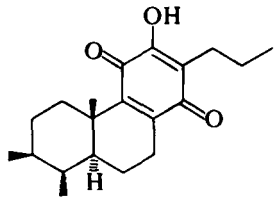


FIGURE 6. Circular dichroism (CD) spectra of coleone C (**59**) and dihydrocoleone-B-alcohol (**60**) in dioxan. *Adapted from Ref. 52 by permission of the Swiss Chemical Society*

strong absorption maximum near 440 nm[47]. Conversion of **61** to the *p*-benzoquinone **62** and then reduction to **63**, and comparison of the CD spectra of **62** and **63** with that of

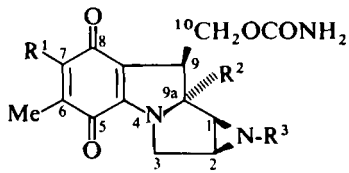


(63)

royleanone (**48**) (Figure 5) fixes the configuration of the angular methyl group at C (10) in both **62** and **63** and thus also in coleone E (**61**)[47].

F. Mitomycin Antibiotics

In the search for new antibiotics produced by actinomycetes, a group of closely related substances was isolated from *Streptomyces caespitosus*[54]. This mixture had substantial antitumor activity and was called mitomycin[54]. Chromatography and recrystallization gave pure mitomycins A and B[54]. These substances are reddish violet and violet, respectively, and have electronic spectra with an absorption maximum near 550 nm indicating the presence of a *p*-benzoquinone chromophore[54]. Mixtures of four mitomycins, mitomycins A, B, C and porfiromycin (**64–67**, respectively) are also produced by strains of *S. verticillatus*[55] and their structures and relative configurations were established

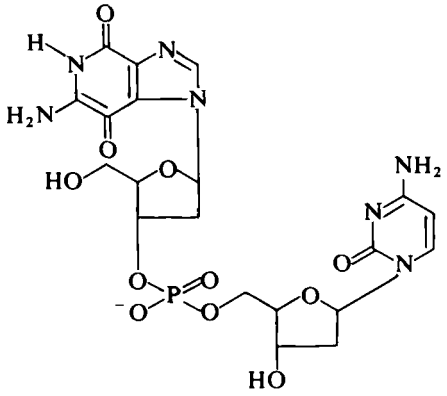


(**64**, $R^1 = R^2 = OMe$; $R^3 = H$)
(**65**, $R^1 = OMe$; $R^2 = OH$; $R^3 = Me$)
(**66**, $R^1 = NH_2$; $R^2 = OMe$; $R^3 = H$)
(**67**, $R^1 = NH_2$; $R^2 = OMe$; $R^3 = Me$)

by chemical, spectrophotometric, and X-ray methods[55–58]. An early X-ray determination of the absolute configuration of mitomycin A[59] (**64**) was later corrected[60]. This revision was based on the direct X-ray determination of absolute configuration of mitomycin C[60] (**66**) which has been stereochemically related to **64** and porfiromycin (**67**). Since mitomycin B (**65**) has not been derived directly from or converted to any of the others, its absolute configuration was also determined by the X-ray method using 7-demethoxy-7-*p*-bromoanilinomitomycin B[61]. Thus, all of the mitomycin antibiotics have the same absolute configuration.

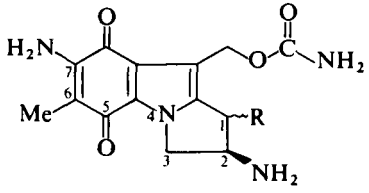
The importance of the mitomycin antibiotics and especially mitomycin C (**66**) is their antitumor activity, with **66** currently in clinical use. It interacts with DNA *in vivo* and *in vitro*, resulting in covalent linkage of the drug to DNA as well as in the formation of covalent cross-links between the two complementary DNA strands[62]. These modifications of DNA are generally thought to be primary events in the antibiotic and antitumor activity

of **66**. The drug requires acidic or reductive activation, and it is known that high guanine and cytosine content of DNA promotes cross-link formation[62]. In model studies, the reaction of **66** with 2′-deoxyguanylyl-(3′ → 5′)-2′-deoxycytidine [d(GpC)] (**68**) was studied in some detail[63]. Enzymatic degradation of the mitomycin-d(GpC) adducts yielded one major mitomycin–deoxyguanosine adduct. A combination of ^{1}H-NMR, Fourier transform infrared, and circular dichroism spectroscopic techniques established its structure

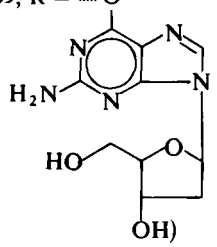


(**68**)

and configuration as 1,2-*trans*-1-[O^6-(2′-deoxyguanosyl)]-2,7-diaminomitosene (**69**)[63], compound **70** having the trivial name 2,7-diaminomitosene[56]. The stereochemistry of the adduct **69** was determined to be *trans* by comparison of its CD spectra with those of the diastereomeric 2,7-diamino-1-hydroxymitosenes (**71** and **72**)[63] (Figure 7). The relative stereochemistry at C(1) and C(2) in **71** and **72** had been previously established[64], but the



(**69**, R = ⁞⁞⁞O



(**70**, R = H)
(**71**, R = ━OH)
(**72**, R = ⁞⁞⁞OH)

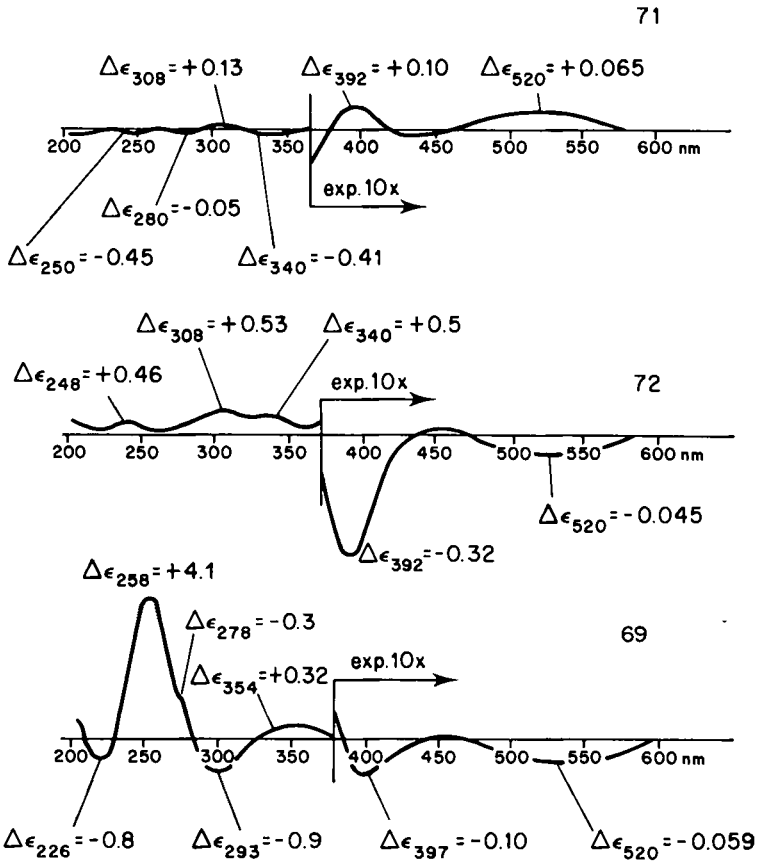


FIGURE 7. Circular dichroism (CD) spectra of 1,2-*trans*-1-[O^6-(2'-deoxyguanosyl)]-2,7-diaminomitosene (**69**), *cis*-2,7-diamino-1-hydroxymitosene (**71**), and *trans*-2,7-diamino-1-hydroxymitosene (**72**) in methanol. *Adapted with permission from M. Tomasz, R. Lipman, J. K. Snyder and K. Nakanishi*, J. Am. Chem. Soc., **105**, *2059 (1983). Copyright (1983) American Chemical Society*

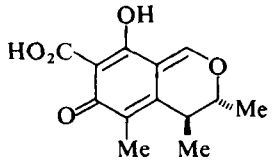
absolute configuration of the mitosene moiety in **69–72** is different from that reported earlier[63]. In **69–72**, the absolute configurations conform to those required by the recent X-ray studies on the absolute configuration of mitomycin C (**66**)[60].

The mitosene and guanine chromophores in adduct **69** both have EA in the 200–300-nm region[63] and hence the intense CD Cotton effects in **69** in the region below 400 nm (Figure 7) can certainly be ascribed to coupled oscillator interactions[65]. However, since the directions of the electric transition moments of the two interacting chromophores are unknown, and the conformation of the guanosine moiety with respect to the mitosene chromophore is not clear, the CD maxima can not be used for absolute configurational assignments[63]. A more extensive study of the weak CD Cotton effects displayed by 1,2-*cis/trans* isomers of 1-substituted 2-aminomitosene in the 530-nm region (Figure 7)[66] shows that a positive CE is associated with a 1β configuration (**71**) while a negative one is

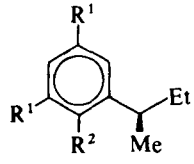
associated with a 1α configuration (**72**). When C(1) is unsubstituted, as in **70**, the 530-nm CE is absent, indicating that the substituent at C(2) exerts no influence. These results establish that observation of the sign of the 530-nm CE constitutes a non-ambiguous method for deducing the C(1) configuration of mitosenes. This CD method was then used to establish the stereochemistry of mitosenes derived from the acid-catalyzed solvolysis of porfiromycin[66] (**67**) and applied[66] to a minor mitosene–deoxyguanosine adduct formed on reductive alkylation of d(GpC) by mitomycin C (**66**)[63]. The CD method was thus shown to be applicable to mitosene products from metabolic reactions of **66** as well as to nucleoside–mitosene adducts[66].

G. Fungal Quinone Methides

Although the mitomycins are the most important benzoquinone fungal metabolites, those with the benzoquinone methide structure have been of interest for many years[67]. The structure of citrinin[68] (**73**) as a *p*-benzoquinone methide has recently been definitively established by an X-ray diffraction study[69] and its absolute configuration was established earlier by application of the Prelog atrolactic acid method using citrinin degradation



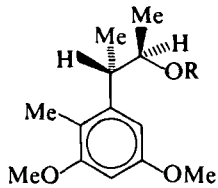
(**73**)



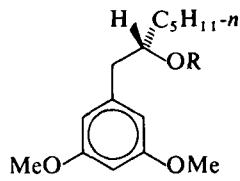
(**74**, $R^1 = R^2 = H$)
(**75**, R^1 = OMe; R^2 = Me)

products[70]. This assignment has some, but not unequivocal confirmation by comparison of the ORD curve of (*R*)-2-phenylbutane (**74**) with that of 2-(3,5-dimethoxy-2-methylphenyl)butane (**75**)[71], also obtained as a degradation product of **73**[71]. Since both **74** and **75** show plain negative dispersion curves from 600 to 350 nm, **75** was assigned the *R* configuration and thus the corresponding chiral center in **73** has the *S* configuration. Correlations of this type must be used with extreme caution since the ORD and CD associated with the longest wavelength benzene transition (^1L_b) at about 260 nm depend on the spectroscopic moments and the positions of the benzene ring substituents[72].

The configuration of the chiral center in **73** was, however, firmly established using the

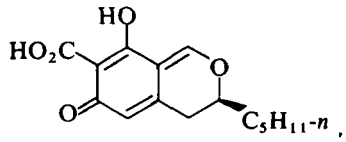


(**76**, R = CS_2Me)
(**77**, R = H)



(**78**, R = CS_2Me)
(**79**, R = H)

CD of the methyl xanthate derivative **76** of the alcohol **77**, a degradation product of **73**[73]. The CD of the methyl xanthate derivative **78** of the alcohol **79** derived from pulvilloric acid (**80**) was also used to establish the absolute configuration of this *p*-benzoquinone methide.



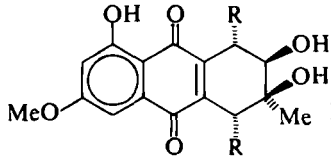
(80)

Thus each methyl xanthate exhibits a strong Cotton effect at 355 nm, positive and negative for **76** and **78**, respectively.

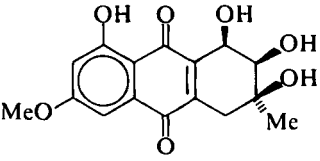
III. NAPHTHOQUINONES

A. Tetrahydroanthraquinones

A few chiral tetrahydroanthraquinones of the basic emodin structure (see Section IV.A) are known. Notable are altersolanols A[74,75] (**81**) and B[75] (**82**) and bostrycin[76] (**83**), but no



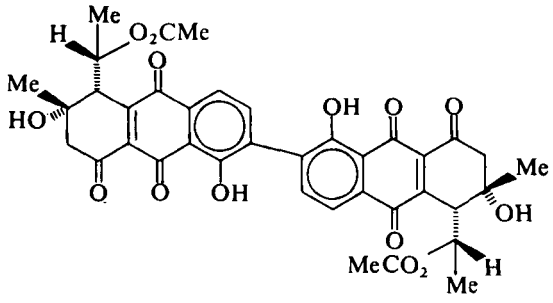
(**81**, R = OH)
(**82**, R = H)



(**83**)

CD spectrum or ORD curve has been reported for these substances. For the altersolanols (**81, 82**), both red pigments from *Alternaria solani*, a pathogen of solanaceous plants[75,77], the absolute configurations have not been reported, but their relative configurations were assigned on the basis of chemical and proton nuclear magnetic resonance evidence[77]. The absolute configuration of bostrycin (**83**) rests on an X-ray study of a *p*-bromobenzoate derivative[78].

The antiviral antibiotic julimycin B-II[79] (**84**) also incorporates reduced tetrahydroanthraquinone moieties. An X-ray study using a bromine derivative[80] gives the absolute configurations at its six chiral centers. There is no indication, however, if there is substantial restricted rotation (atropisomerism[6]) about the single bond connecting the two naphthoquinone groups so that **84** has a particular configuration about this bond much the same as is encountered with the bianthraquinones (see Section IV. B).

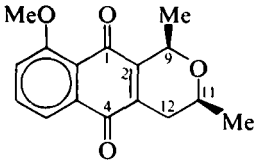


(**84**)

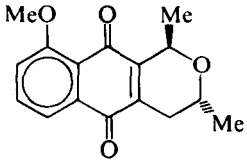
B. Pyranonaphthoquinones

1. *Eleutherins*

The first pyranonaphthoquinones (benzoisochromanquinones) to be reported were eleutherin (**85**) and isoeleutherin (**86**)[81, 82]. Compounds **85** and **86** are diastereomers since

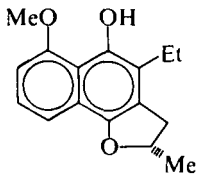


(**85**)

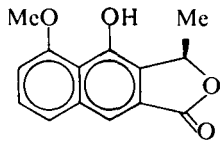


(**86**)

in phosphoric acid **85** gives the enantiomer of **86** (alloeleutherin)[82]. Under similar conditions, the enantiomer of **85** (alloisoeleutherin) can be obtained from **86**[82]. That **85** and **86** epimerized at C(9) was established by the observation that on Clemmensen reduction, both **85** and alloisoeleutherin (enantiomer of **86**) gave the same enantiomer of

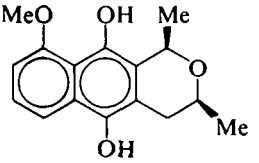


(**87**)

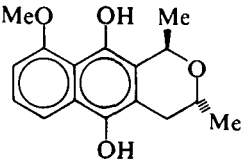


(**88**)

the dihydrofuran **87**[83]. The absolute configuration at C(11) was established by degradation of **87** to (*S*)-β-hydroxybutyric acid. The configuration at C(9) was deduced by reference to (*R*)-eleutherol (**88**) which was degraded to D-lactic acid[83]. Correlation of the molecular rotations of various *O*-methyl and *O*-acetyl derivatives of leucoeleutherin (**89**) and leucoisoeleutherin (**90**) with similar derivatives of (*R*)-eleutherol (**88**) indicate that **89** and **90** have the same absolute configuration at C(9) as does **88**[83]. Subsequent ^{1}H-NMR spectral measurements support the relative configurational assignments for **85** and **86**[84].



(**89**)

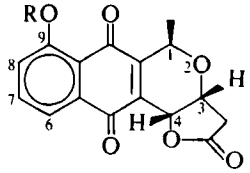


(**90**)

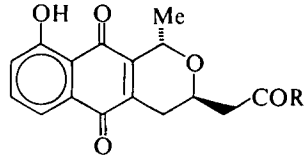
2. *Nanaomycin antibiotics*

A number of antibiotics also have the pyranonaphthoquinone structure. Kalafungin[85] (**91**) and nanaomycins A[86, 87] (**92**), B[86, 87] (**93**), C[88] (**94**) and D[89] (enantiomer of **91**) are closely related to the eleutherin pyranonaphthoquinones. That kalafungin and nanaomycin D are enantiomers was shown by the coincidence of their physical properties except that the ORD curve of nanaomycin D shows a trough at 355 nm and a peak at

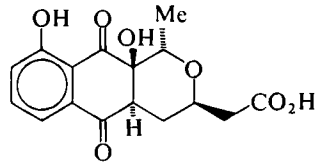
292 nm while the curve of kalafungin is enantiomeric with a peak at 355 nm and a trough at 292 nm[89]. Thus the genus *Streptomyces* produces the two enantiomers of the same antibiotic.



(**91**, R = H)
(**95**, R = Me)



(**92**, R = OH)
(**94**, R = NH_2)



(**93**)

The structure and relative configurations of the three chiral centers in kalafungin were established by X-ray studies[90] and chemical and other physical properties support these assignments[90]. The absolute configuration of kalafungin (**91**) was assigned on the basis of the comparison of the ORD curves of 9-*O*-methylkalafungin (**95**) with that of isoeleutherin (**86**) (Figure 8), both curves showing significant similarities[90]. Since the C(1) methyl group in **95** and the corresponding one in isoeleutherin (**86**) at C(9) are, on the basis of conformational arguments[90], pseudoaxial, the two ORD curves then should be similar if

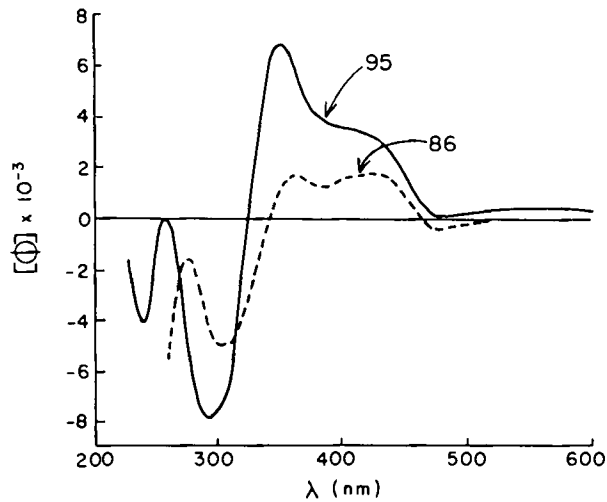


FIGURE 8. Optical rotatory dispersion (ORD) curves of isoeleutherin (**86**) and 9-*O*-methylkalafungin (**95**). *Adapted from Ref. 90 by permission of the Japan Antibiotics Research Association*

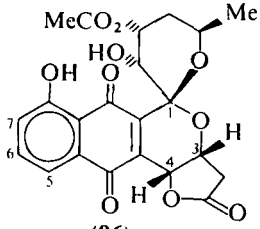
95 has the 1*R*,3*R*,4*R* configuration[90]. If 9-*O*-methylkalafungin (**95**) has the 1*S*,3*S*,4*S* configuration, its ORD curve would be enantiomeric to that observed in Figure 8.

The structure of nanaomycins A (**92**) and B[91] (**93**) and nanaomycin C[88] (**94**) were established on chemical and spectroscopic grounds. Their absolute configurations follow from the air oxidation of nanaomycin A (**92**) to nanaomycin D (enantiomer of **91**)[89]. Since **93** and **94** have been configurationally related to **92**[88,91], the absolute configurations of **93** and **94** were also established.

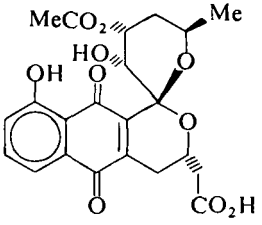
It is to be noted, however, that the absolute configurations established for the nanaomycin antibiotics (**91–94**) all depend on the configurational correlation of 9-*O*-methylkalafungin (**95**) with that originally established for isoeleutherin (**86**). This latter assignment was made only on the basis of a comparison of the rotatory powers (sodium D line) of *O*-methyl and *O*-acetyl derivatives of leucoeleutherin (**89**) and leucoisoeleutherin (**90**) with the rotatory powers of similar derivatives of (*R*)-eleutherol (**88**)[83]. Verification of these configurational assignments for **91–94** by another method would thus be of value.

3. *Griseusin antibiotics*

Two other pyranonaphthoquinone antibiotics, also isolated from a genus of *Streptomyces*, are griseusins A[92] (**96**) and B[92] (**97**). The structure and relative configurations of **96** and **97** were established on chemical and spectroscopic evidence[93]. The absolute configurations were originally assigned incorrectly, however, on the basis of a



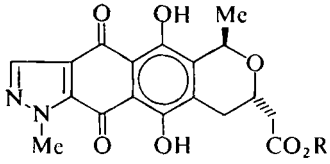
(**96**)



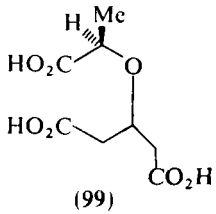
(**97**)

comparison of their respective CD spectra with that of actinorhodinindazolquinone[93] (**98**) (Figure 9). The absolute configuration of this latter compound was assigned by a chemical correlation with (*R*)-3-(1-carboxyethoxy)glutaric acid (**99**)[94]. The configuration of **99** follows from its ORD spectrum which is enantiomeric to that of (*S*)-lactic acid[94]. The absolute configurations of **96** and **97** have subsequently been established correctly by an X-ray study utilizing 5,7-dibromogriseusin A[95].

That actinorhodinindazolquinone (**98**) can not serve as a model compound for the assignment of the absolute configurations of **96** and **97** by a CD comparison may be due to a substantial difference in the chromophore in **96** and **97** as compared to that in **98**. An



(**98**, R = H)
(**102**, R = Me)



(**99**)

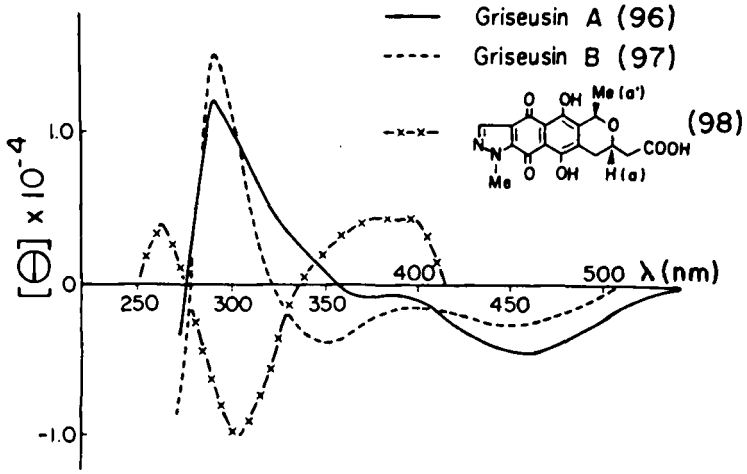
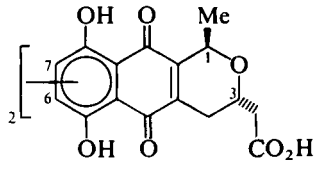


FIGURE 9. The circular dichroism spectra of griseusin A (**96**), griseusin B (**97**) and actinorhodinindazolquinone (**98**). *Adapted from Ref. 93 by permission of Pergamon Press*

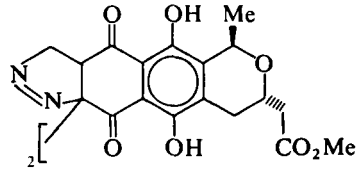
alternative difficulty may be that for corresponding absolute configurations at C(1) and C(3) in **96–98**, a preferred chirality of the half-chair pyrano ring with respect to the naphthoquinone chromophore in **96** and **97** may be opposite to that in **98** because the substituents at C(1) in **96** and **97** are different from those at C(1) in **98**.

4. Actinorhodin antibiotic

The structure and configuration of actinorhodinindazolquinone (**98**) is of some interest in that it is a degradation product of another pyranonaphthoquinone antibiotic, actinorhodin[94] (**100**). For this binaphthoquinone, each naphthoquinone moiety has a structure similar to nanaomycin A (**92**), but the absolute configurations at C(1) and C(3) in **100** are opposite those in **92**. It is not known, however, if **100** is the 6,6′- or 7,7′-dimer. If the former, the diazomethane adduct with the dimethyl ester of **100** has structure **101**.



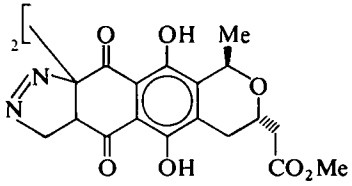
(**100**)



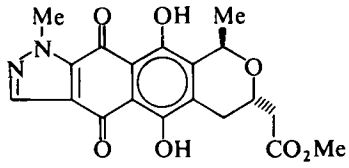
(**101**)

Oxidation of **101** and then *N*-methylation gives the methyl ester of **98** (**102**). If **100** is the 7,7′-dimer, the structure of the diazomethane adduct of the dimethyl ester of **100** is **103**. Oxidation of **103** and then *N*-methylation gives **104**.

In connection with the configurational assignments for other isochromanquinone antibiotics[96], the respective indazolquinones degradation products similar to **102/104** were assigned their respective absolute configurations at C(3) on the basis of their CD spectra,



(103)

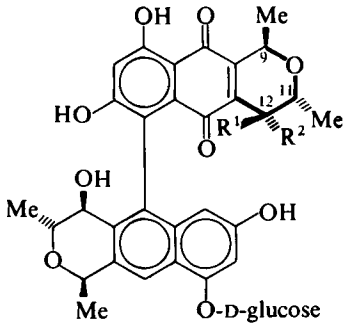


(104)

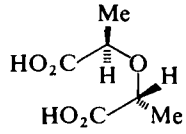
each showing a strong positive or negative maximum at 300 nm depending on the configuration at C(3)[96].

5. *Protoaphins and aphins*

Some of the most highly condensed aromatic compounds found as natural products are the extended quinones[3]. One group of these is the aphins, formed on intramolecular condensation of the protoaphins[97]. The latter are yellow water soluble substances which occur in aphids and incorporate a pyranonaphthoquinone moiety (**105–107**). The chirality of some of their chiral centers are preserved in the aphin group of extended quinones.



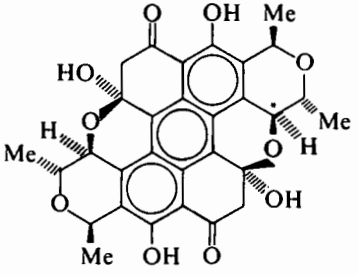
(**105**, R^1 = OH, R^2 = H)
(**106**, R^1 = H, R^2 = OH)
(**107**, R^1 = R^2 = H)



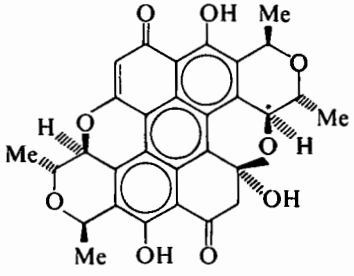
(**108**)

The three protoaphins so far reported are protoaphin-*fb*[98] (**105**), protoaphin-*sl*[98] (**106**) and deoxyprotoaphin[99] (**107**), the suffix in **105** and **106** indicating the species from which the protoaphin was first isolated, ***Aphis fabae and Tuberolachnus salignus***, respectively[3]. Deoxyprotoaphin (**107**) was isolated from various aphid species of the genus *Dactynotes*[99]. The structure and absolute configuration of each of the tricyclic systems in **105** and **106** were established by degradation, the first step of which was mild reductive cleavage of the binaphthyl system[97,98]. The same glucoside was obtained from each protoaphin, but a different quinone, each of the latter having the same carbon skeleton and the same absolute configurations at C(9) and C(11) as was found for isoeleutherin (**86**). Hydrolysis of the glucoside obtained on reductive cleavage of the binaphthyl system and oxidation of the aglycone gave the same quinone as was obtained directly from **105**. The absolute configurations of the chiral centers at C(9) and C(11) in the three quinones were established by their oxidation to (*R*, *R*)-dilactic acid (**108**)[98]. Nuclear magnetic resonance studies established other structural and configurational features[84].

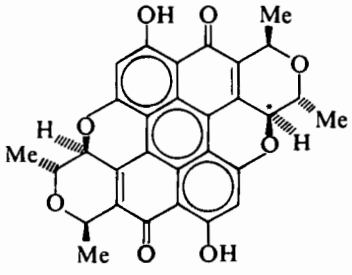
Under the influence of an enzyme system, each protoaphin is converted to a particular series of aphins, successively a xanthoaphin, a chrysoaphin, and an erythroaphin[99]. In the



(109)



(110)



(111)

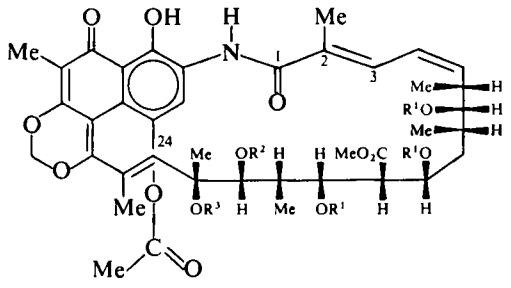
case of protoaphin-*fb* these are xanthoaphin-*fb* (**109**), chrysoaphin-*fb* (**110**) and finally erythroaphin-*fb* (**111**)[100]. The corresponding aphins from protoaphin-*sl* have a different configuration at a single chiral center shown with an asterisk in **109–111** because of the difference in the chirality of the corresponding center in the protoaphin[101].

It is to be noted that in the protoaphins **105–107**, the two tricyclic units cannot attain coplanarity and this introduces into these molecules an additional element of chirality (atropisomerism[6, 100]). On the basis of an analysis of the steric demand for the cyclization of protoaphin-*fb* (**105**) and protoaphin-*sl* (**106**) to xanthoaphin-*fb* (**109**) and xanthoaphin-*sl*, respectively, the chirality of the restricted rotation in both **105** and **106** was assigned as *S*. This chirality is shown in **105** and **106** with the non-aromatic ring of the naphthoquinone moiety out of the plane of the paper toward the observer[100]. Because of the condensation of deoxyprotoaphin (**107**) by an enzymic extract of *A. fabae* to a compound analogous to a xanthoaphin, it is presumed that the absolute configuration of **107** about the binaphthyl linkage is the same as that in protoaphin-*fb* (**105**)[99]

C. Ansamycin Antibiotics

A somewhat large group of antibiotics some of which incorporate a naphthoquinone or naphthoquinone derived group are the ansamycins[102], so called because each contains an aliphatic bridge connecting two non-adjacent positions of an aromatic nucleus. The term *ansa* is used to designate *meta*- and *para*-bridged aromatic, usually benzene, compounds.

Various types of this class of antibiotics have been identified: the rifamycins, the streptovaricins, the tolypomycins and the naphthomycins[102,103]. The rifamycins and naphthomycins incorporate a naphthoquinone group[103] while the streptovaricins have a naphthoquinone methide moiety[102]. An important one of the latter type is streptovaricin C (**112**) for which the stereochemistry and circular dichroism have been studied in some



(**112**, $R^1 = R^2 = R^3 = H$)
(**113**, R^1 = MeCO; $R^2R^3 = \!>\!BC_6H_4Br\text{-}p$)

detail[104]. Stereoformula **112** shows the absolute configurations for the various chiral centers in streptovaricin C as well as that of the helix with *P* configuration for which the acetoxyl group at C(24) is below the *ansa* bridge[104]. When streptovaricin C (**112**) was boiled in toluene overnight, an equilibrated mixture of **112** and atropisostreptovaricin C was obtained[104]. Atropisostreptovaricin C is a diastereoisomer (atropisomer[6]) of **112** in which the chiral centers have the same absolute configurations but the acetoxyl group at

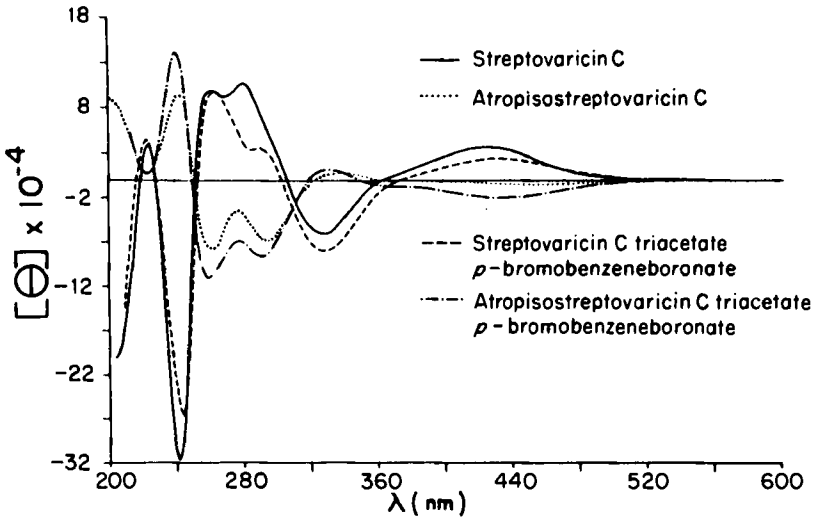


FIGURE 10. Circular dichroism (CD) spectra of streptovaricin (**112**), atropisostreptovaricin C, streptovaricin C triacetate *p*-bromobenzeneboronate (**113**) and atropisostreptovaricin C triacetate *p*-bromobenzeneboronate. *Adapted with permission from K. L. Rinehart, Jr., W. M. J. Knöll, K. Kakinuma, F. J. Antosz, I. C. Paul, A. H.-J. Wang, F. Reusser, L. H. Li and W. C. Krueger,* J. Am. Chem. Soc., **97**, *196 (1975). Copyright (1975) American Chemical Society*

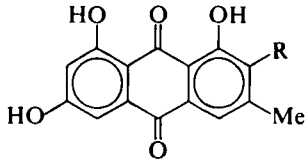
C(24) now is above the *ansa* ring. The helix so formed has the *M* absolute configuration. The nature of the isomerism of **112** and atropisostreptovaricin C was established by the nearly mirror image relationship of their CD spectra (Figure 10)[104]. A similar equilibration of streptovaricin C triacetate *p*-bromobenzeneboronate (**113**) with its atropisomer was also obtained and the atropisomers also show enantiomeric CD curves (Figure 10). An X-ray investigation was used to establish the absolute configuration of **113**. On the basis then of the respective CD curves, the *P* helicity of streptovaricin C (**112**) and the *M* helicity of its atropisomer were also assigned.

The apparent CD couplets in the spectra of **112** and **113** and their atropisomers in Figure 10 indicate that the source of the high rotational strength in the 200–300-nm region is the chirality of the *ansa* bridge unsaturated polarizabilities with the naphthoquinone methide polarizabilities. A striking confirmation of this was given in a recent CD study of rifamycin *S* and its tetrahydro and hexahydro derivatives[105]. Thus in the 200–300-nm spectral range, the CD intensity of the hydrogenated derivatives is much lower in comparison to the intensity shown by rifamycin *S*.

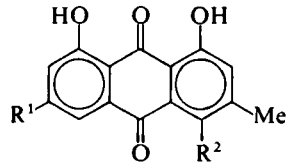
IV. ANTHRAQUINONES

A. Simple Anthraquinones

Simple anthraquinones form the largest group of naturally occurring quinones, and their occurrence and structures have been reviewed by Thomson[3]. The majority of these substances, which are assumed to be elaborated by the acetate–malonate pathway, conforms to the emodin (**114**) pattern formed by folding and condensation of a polyketide chain derived from eight acetate units. In endocrocin (**115**), the terminal carboxyl group is retained.

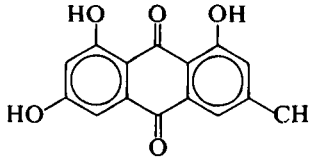


(**114**, R = H)
(**115**, R = CO_2H)

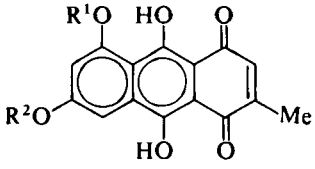


(**116**, $R^1 = R^2 = H$)
(**117**, $R^1 = H$; $R^2 = OH$)
(**118**, $R^1 = R^2 = OH$)

Numerous variations of the basic emodin structure (**114**) exist, resulting from *O*-methylation, side-chain oxidation, chlorination and the introduction or omission of nuclear hydroxyl groups. Examples of some of these anthraquinones are chrysophanol (**116**), islandicin (**117**), catenarin (**118**) and ω-hydroxyemodin (**119**). In addition, three 1,4-anthracenedione pigments, two of which are viocristin (**120**) and isoviocristin (**121**), have



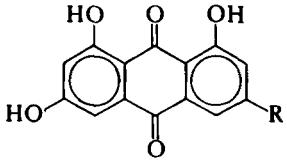
(**119**)



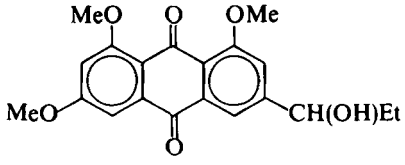
(**120**, R^1 = Me; R^2 = H)
(**121**, R^1 = H; R^2 = Me)

recently been found as natural products[106]. These anthraquinones and 1,4-anthracenediones (**114–121**), however, are symmetrical and show no chiroptical properties.

In a few cases the usual β-methyl group is replaced by a three- or a five-carbon substituent[107,108] and in rhodoptilometrin[107,108] (**122**) and isorhodoptilometrin[107] (**123**), this side chain is oxidized such that both of these anthraquinones contain a chiral center. In rhodoptilometrin (**122**), isolated from a crinoid[107], the configuration was

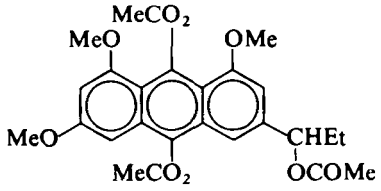


(**122**, R = CH(OH)Et)
(**123**, R = $CH_2CH(OH)Me$)



(**124**)

assigned as *S* on the basis of an empirical rule relating the configuration of the side chain to the rotatory powers of the trimethyl ether (**124**) and the so-called trimethyl ether leucoacetate (**125**)[107]. Lacking confirmation of the configurational assignment for **124** or **125**, the configurational assignment for **122** is not conclusively established.



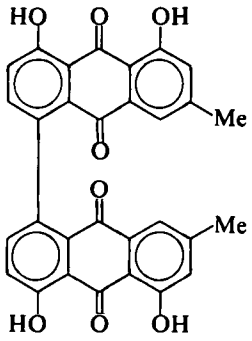
(**125**)

Other anthraquinones with chiral centers in attached side chains have been reported[3,109] but aside from their rotatory powers at the sodium D line their chiroptical properties have not been studied. As noted above (Section I), magnetic circular dichroism (MCD) of anthraquinone (**2**), however, has been reported as part of a general study of the electronic absorption of aromatic compounds[16].

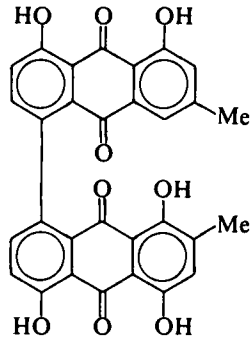
B. Bianthraquinones

One interesting group of pigments derived from simple anthraquinones are the bianthraquinones isolated from several strains of *Penicillium islandicum*[110,111]. The structures of these natural products were established as 1,1′-dimers of simple anthraquinones by the reductive cleavage with alkaline sodium dithionate and ^{1}H-NMR spectral analysis of the respective acetates. Thus (+)-dianhydrorugulosin [(+)-**126**)] yields two equivalents of chrysophanol (**116**) on reductive cleavage[110]. Four other bianthraquinones are 1,1′-dimers of one particular simple anthraquinone with structures **114**, **117**, **118** and **119**[111]. Seven others, such as (+)-roseoskyrin [(+)-**127**] are 1,1′-dimers of two different simple anthraquinones. Thus on reductive cleavage, (+)-roseoskyrin [(+)-**127**] gives one equivalent each of chrysophanol (**116**) and islandicin (**117**)[111].

All of the dimeric anthraquinones from *P. islandicum*[110] and from other fungi and lichens[111] are optically active as the result of the restricted rotation about the C(1)–C(1′) bond (atropisomerism[6]). Chirality due to a similar steric effect is well known[6] and both



(126)



(127)

(*R*)- and (*S*)-2,2'-dimethyl-1,1'-bianthraquinonyl [(*R*)- and (*S*)-**128**] have been prepared[112, 113].

The ORD curves and CD spectra of the bianthraquinones isolated from *P. islandicum* show the same features with Cotton effects associated with the EA spectrum from 350 to 500 nm (Figure 11). In each ORD curve, the extremum at the longest wavelength is positive[110, 111]. That this extremum is positive is indicated by the attachment of a

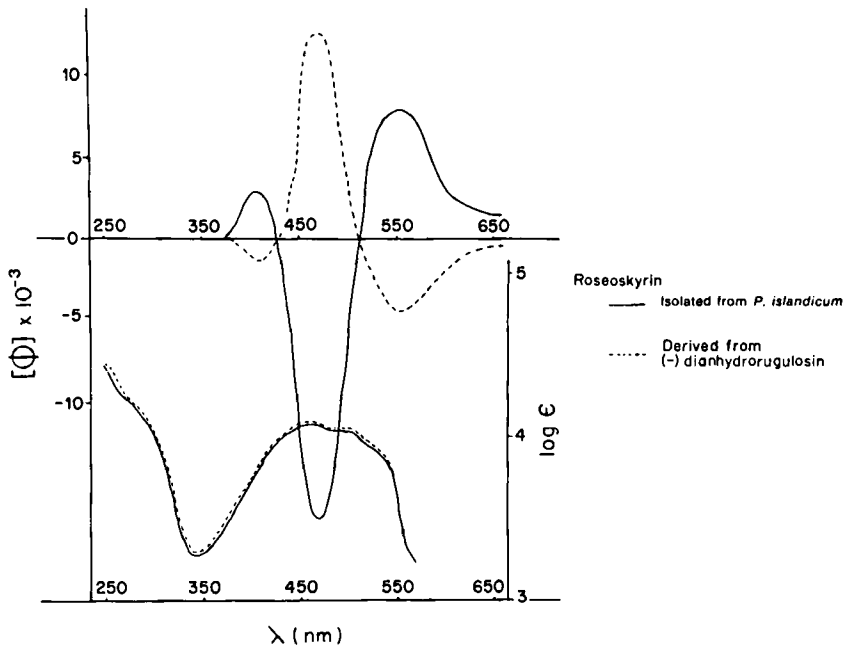
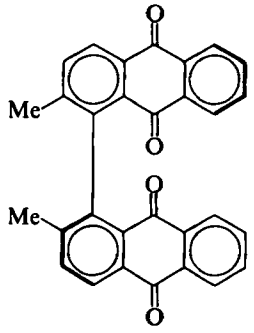


FIGURE 11. Electronic absorption (EA) spectra and optical rotatory dispersion (ORD) curves in dioxan of (+)-roseoskyrin [(+)-**127**] from *Penicillium islandicum* and (−)-roseoskyrin [(−)-**127**] derived from (+)-rugulosin [(+)-**129**] by way of (−)-dianhydrorugulosin [(−)-**126**]. *Adapted from Ref. 111 by permission of Pergamon Press*

(+) prefex to the name. For the bianthraquinones isolated from all *Penicillium* species, the similarity of their ORD curves suggests that they all have the same absolute configuration

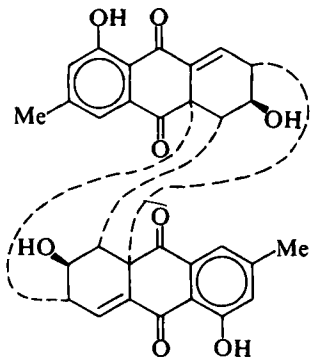


[(*R*)-**128**]

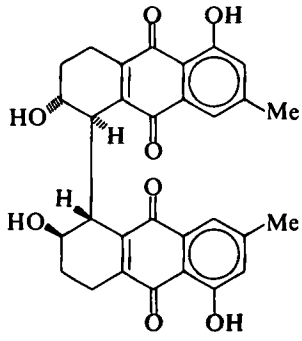
and arise by a stereospecific oxidative coupling of the monomeric anthraquinones, the latter also occurring in these fungi.

The ORD curves of these pigments[110,111] (Figure 11) show two Cotton effects in the 350–550-nm region which are due to exciton interaction[65] between the two anthraquinonyl chromophores. The nature and direction of the relevant transition moments giving rise to these Cotton effects, however, are not established[114] and hence the absolute configuration of a bianthraquinone can not be determined on the basis of the chiral exciton coupling mechanism[65]. Further, neither the ORD curve nor CD spectrum of (*R*)- or (*S*)-**128** has been reported, and thus model spectra are not available for the possible assignment of absolute configuration of the natural products by a comparison of their ORD curves or spectra CD with that of a model.

Also occurring in *P. islandicum* and other fungi is a group of modified bianthraquinones[111,115], which in fact are not anthraquinones at all but are included here because of their structural and biogenetic relationship to the bianthraquinones. An important modified bianthraquinone is (+)-rugulosin [(+)-**129**] for which the absolute configuration was established by an X-ray study of its dibromodehydrotetrahydroderivative[116] and which could be formed biogenetically by the base-catalyzed Michael-type intramolecular condensation of a hypothetical, partially reduced bianthraquinone (**130**).



[(+)-**129**]



(**130**)

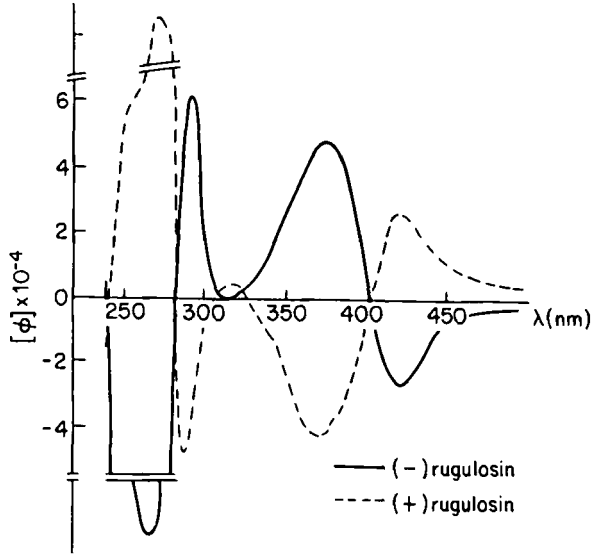
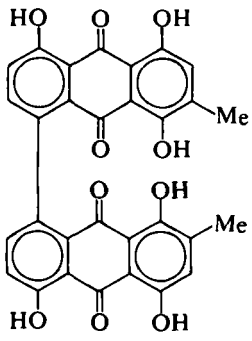


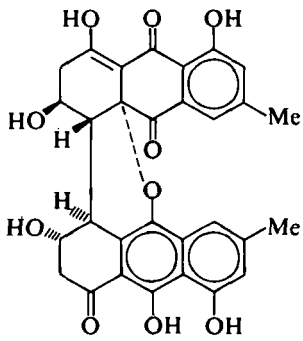
FIGURE 12. Optical rotatory dispersion (ORD) curves in dioxan of (+)-rugulosin [(+)-**129**] isolated from *Penicillium brunneum* and (−)-rugulosin [(−)-**129**] derived from (−)-flavoskyrin [(−)-**132**]. *Adapted from Ref. 117 by permission of Pergamon Press*

The stereochemistry of (+)-**129**, which shows a strong positive Cotton effect centered at 400 nm and a strong negative one at about 280 nm in its ORD curve (Figure 12)[117], is of interest. Thus (+)-**129** on dehydration with thionyl chloride and pyridine at 0°C affords (−)-dianhydrorugulosin [(−)-**126**] which on oxidation with pertrifluoroacetic acid in methylene chloride at 0°C gives (−)-iridoskyrin [(−)-**131**] and (−)-roseoskyrin [(−)-(**127**)][111]. The ORD curve of (−)-**127** is enantiomeric to that of the naturally occurring (+)-**127** (Figure 11)[117] and thus the chiralities about the respective C(1)–C(1′) bonds are enantiomeric. The respective chiralities of the related bianthraquinones, however, can not be inferred from this transformation in combination with the known absolute configuration of (+)-**129**.

(−)-Flavoskyrin [(−)-**132**] is another type of modified bianthraquinone also occurring



(**131**)



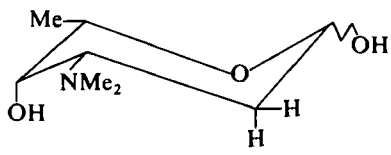
[(−)-**132**]

in *P. islandicum*[117]. This compound, with a positive Cotton effect centered at 415 nm and a negative one at 276 nm[117], almost enantiomeric to that of (+)-rugulosin, forms, on treatment with pyridine, (−)-rugulosin [(−)-**129**] and (+)-dianhydrorugulosin [(+)-**126**]. It is to be noted that these chemical transformations relate the absolute configuration of (−)-**129**][111] to that of (−)-**132** but not to that of (+)-**126**. Thus the absolute configurations of (−)-flavoskyrin is established as in stereoformula (−)-**132**[117], but the absolute configurations of (+)-**126** and the other chiral bianthraquinones from *P. islandicum*[110, 111] remain unknown.

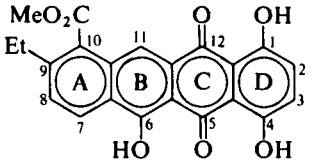
C. Anthracyclinones

In the search for new antibiotics, the screening of many hundreds of *Streptomyces* bacteria revealed numerous pigments. One group of about 30 anthraquinones, studied extensively by Brockmann and his associates[118], is the anthracyclinones, occurring either free or as the glycosides (anthracyclines) of various sugars including amino sugars such as rhodosamine[3, 118](**133**). While these substances are found mostly in *Streptomyces*, one has been found in another genus[119]. Only a few anthracyclinones, such as η-pyrromycinone (**134**), are fully aromatic and in most cases ring A of the naphthacenequinone system is such that the anthracyclinones are in effect 2,3-dialkylpolyhydroxyanthraquinones with chiral centers in ring A.

Brockmann[118] introduced a trivial nomenclature which is used in association with the number and position of the hydroxyl substituents of the anthraquinone moiety (cf. **135–140**). Individual members of the various groups are distinguished according to the

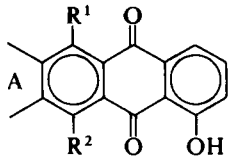


(**133**)

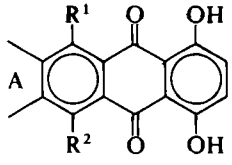


(**134**)

order of increasing R_f values. Originally α-rhodomycinone was the rodomycinone (**137**) with the lowest R_f value, but other still lower values were found later and were designated α_1-, α_2- and α_3-rhodomycinones.

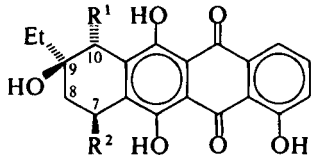


(**135**, R^1 = H; R^2 = OH)
Aklavinones
(**136**, R^1 = OH; R^2 = H)
Citromycinones
(**137**, R^1 = R^2 = OH)
Rhodomycinones

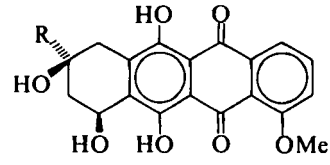


(**138**, R^1 = OH; R^2 = H)
Rhodomycinones
(**139**, R^1 = H; R^2 = OH)
Pyrromycinones
(**140**, R^1 = R^2 = OH)
Isorhodomycinones

The structure and 7*S*, 9*R*, 10*R* configuration of ring A in β-rhodomycinones (**141**) is the same as that of other anthracyclinones with a few variations: the hydroxyl group at C(10) may be replaced by a methoxycarbonyl group as in ε-rhodomycinone (**142**) or be absent; the hydroxyl group at C(7) may be absent as in γ- (**143**) and ζ-rhodomycinone (**144**) or may have the 7*R* configuration as in α-rhodomycinone; and the ethyl group at C(9) may be replaced by an acetyl group as in daunomycinone (**145**) or by an hydroxyacetyl group as in adriamycinone (**146**)[118].



(**141**, R^1 = OH; R^2 = OH)
(**142**, R^1 = CO_2Me; R^2 = OH)
(**143**, R^1 = OH; R^2 = H)
(**144**, R^1 = CO_2Me; R^2 = H)



(**145**, R = MeCO)
(**146**, R = $HOCH_2CO$)

On the basis of chemical evidence and the CD spectra of various pyrromycinones (**139**), rhodomycinones (**137**) and isorhodomycinones (**140**), Brockmann Jr and Legrand[120, 121] suggested that all of the anthracyclinones had the same absolute configuration for the chiral centers in ring A. Thus for the compounds examined, the CD spectra all showed the same characteristic S-shape curve in the 270–390-nm region (Figure 13), a spectral region where

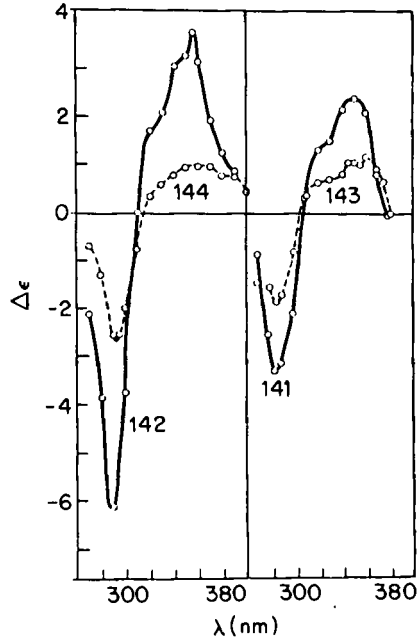
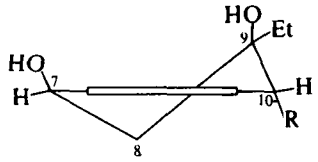
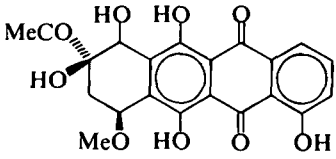


FIGURE 13. Circular dichroism (CD) spectra of β-rhodomycinone (**141**), ε -rhodomycinone (**142**), γ-rhodomycinone (**143**) and ζ -rhodomycinone (**144**) in dioxan. *Adapted from Ref. 121 by permission of Pergamon Press*

all of these pigments show similar absorption characteristics[121]. Initially it was recognized that the CD spectra for a number of anthracyclinones were similar because of the same absolute configuration and the same preferred half-chair conformation of ring A[120]. Thus in **141** and **142**, the ethyl group at C(9) occupies an equatorial position (**147**, **148**) while the



(**147**, R = OH)
(**148**, R = CO_2Me)



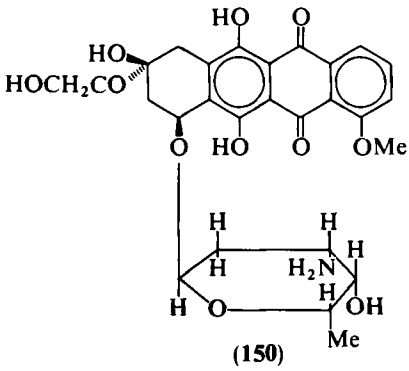
(**149**)

conformation of the hydroxyl groups at C(7) and C(10) in **141** are both pseudoaxial (**147**) and the hydroxyl group at C(7) and the methoxycarbonyl group at C(10) in **142** are also both pseudoaxial (**148**)[121]. The same preferred conformation of ring A exists for those anthracyclinones in which the ethyl group at C(9) is replaced by an acetyl or an hydroxyacetyl group (**145**, **146**) and results from the preference of an ethyl or acetyl group at C(9) to be equatorial. A preferred pseudoaxial conformation for a substituent at C(7) and C(10) is suggested by ^{1}H-NMR studies with 3,5-dichlorobenzylamine[122] and 3,5-dibromoethylbenzene[123] and calculations using empirical potential functions[124] for the conformational distribution in 1-phenylethanol. These studies show that for these compounds the conformation of the substituent group about its attachment bond in which one hydrogen atom eclipses the plane of the benzene ring is lower in energy than those in which an amino, methyl or hydroxyl group eclipses the ring plane.

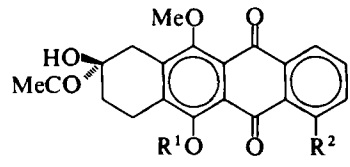
The CD spectra of an anthracyclinone then depends only on the substitution pattern of the saturated ring A and not on the number and positions of the phenolic hydroxyl groups in the anthraquinone part of the molecule[125]. The relative configurations of the chiral centers at C(7), C(9) and C(10) are supported by extensive chemical and ^{1}H-NMR spectral evidence[125]. It is to be noted, however, that the absolute configurations of the anthracyclinones was not and in fact could not be established on the basis of their CD spectra. Rather the absolute configuration of this group of natural products was based on the oxidative degradation of 7-*O*-methyldesmethyldaunomycinone (**149**) to (*S*)-methoxysuccinic acid[126]. The configurational assignment for the anthracyclinones was later confirmed by X-ray anomalous scattering using γ-rhodomycinone[127] (**143**).

The CD spectrum of an anthracyclinone can be used as an aid for the assignment of the relative configurations of the substituents on ring A[125]. Thus, on the assumption that the conformation of ring A (**147**, **148**) does not depend on whether a C(7) hydroxyl group is present or not, the relative configuration of an hydroxyl group at C(7) can be deduced by comparison of the CD spectrum with that of the corresponding 7-desoxy compound[125], an hydroxyl group at C(7) with the *S* configuration causing the S-shaped CD curve in the 270–390-nm region to be increased in intensity[125] (Figure 13).

As outlined above, the early efforts for structural and stereochemical characterization of the anthracyclines, the glycosides of the anthracyclinones, began in the 1950s. The discovery of adriamycin (**150**) and recognition of its unusual potential efficacy in treatment of human cancers in 1969[128, 129] have spawned an enormous interest in anthracycline synthesis. This was stimulated by a quest for synthetic anthracyclines which retain the efficacy of adriamycin but lack its severe toxicity in cancer chemotherapy[130]. The synthesis of anthracyclines can be divided into three parts: formation of the anthracyclinone,



(150)



(151, R^1 = H; R^2 = OMe)
(152, R^1 = Me; R^2 = H)

preparation of the sugar, and coupling of the two. It is the synthesis of the anthracyclinones, however, which has particularly engaged the interest of synthetic organic chemists, and has been the subject of a recent symposium-in-print[131] and another review[132]. In many of these syntheses one enantiomer of the anthracyclinone is prepared[133] and the rotatory power at the sodium D line is used for evaluating the optical purity of these preparations[134]. The specific rotations (sodium D line) of anthracyclinones, however, exhibit dramatic variation induced by protic solvents and there are reports of purportedly optically pure anthracyclinones having dramatically different reported specific rotations when measured under seemingly identical conditions[134]. The origin of this variation was traced to the purity of the solvent used in the determination of specific rotations[134]. Figure 14 shows that the presence of polar organic oxygen solvents, in particular ethanol and methanol, can dramatically alter the magnitude of specific rotations determined for

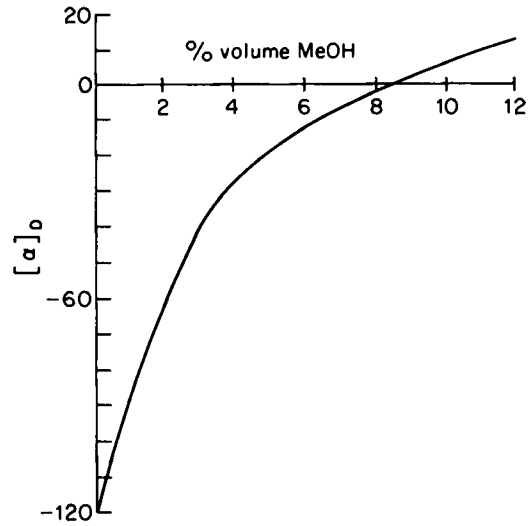


FIGURE 14. Variation of $[\alpha]_D$ for 7-desoxy-11-*O*-methyldaunomycinone (**151**) in chloroform with increasing concentration of methanol. *Reproduced from Ref. 134 by permission of Pergamon Press*

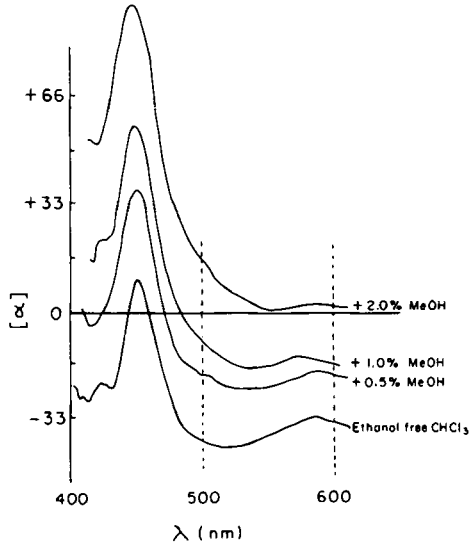
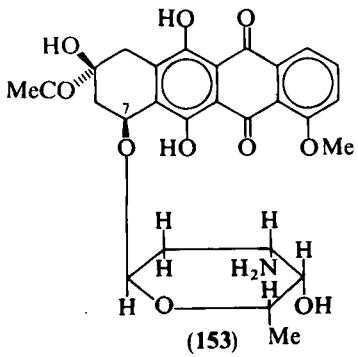


FIGURE 15. Optical rotatory dispersion (ORD) curve of 4,7-didesoxy-6-*O*,11-*O*-dimethyldaunomycinone (**152**) in chloroform and chloroform–methanol. *Revised from Ref. 134 by permission of Pergamon Press*

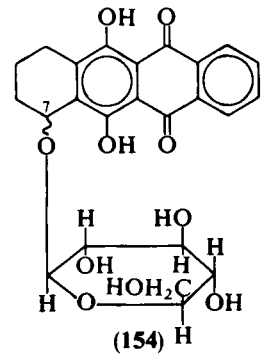
chloroform solutions of 7-desoxy-11-*O*-methyldaunomycinone (**151**). This problem can be overcome by determining specific rotations in a 1 : 1 methanol–chloroform mixture[134]. The origin of the solvent dependency is reflected dramatically throughout the visible ORD curve of 4,7-didesoxy-6-*O*,11-*O*-dimethyldaunomycinone (**152**) (Figure 15), this curve being a revision[135] of that reported earlier[134]. It is not clear, however, whether the effect originates from conformational changes or molecular aggregation[134].

D. Anthracyclines

Although much earlier work focused on the structure and stereochemistry of the anthracyclinones, the structure and stereochemistry of the anthracyclines were also of interest[118]. The structure[136,137] and the absolute configuration[126] of the antitumor antibiotic daunomycin (**153**) were of prime importance. Since for the establishment of the



(153)



(154)

absolute configuration of **153**, the latter was converted by hydrolysis to 7-*O*-methyldesmethyldaunomycinone (**149**) and in **149** it is possible that the configuration at C(7) was altered in the conversion of **153** to **149**. That this was not the case is indicated by comparison of the CD curve of daunomycin and daunomycinone which are very similar in the 280-nm region[137]. Removal of the hydroxyl group at C(7) gives 7-desoxydaunomycinone, which exhibits a very weak dichroic effect, and implies that the substantial effect in the CD curves of daunomycinone and daunomycin is largely contributed by the substituent at C(7)[137].

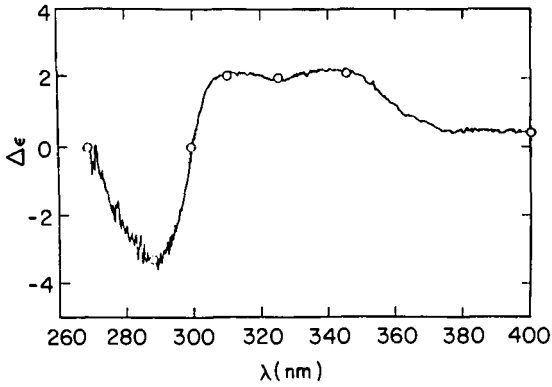
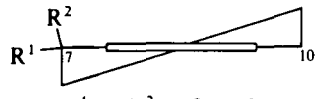


FIGURE 16. Circular dichroism (CD) curve of daunomycin (**153**) in dioxan. *Adapted from Ref. 138 by permission of the Royal Society of Chemistry*

The CD spectra of daunomycin (**153**) was also reported[138] (Figure 16) and was used to establish the configuration at C(7) of two D-glucosides (**154**) of the anthraquinone analog of daunomycinone. These isomers were prepared to explore the structure–activity relationship in the anthracycline cytotoxic antibiotics. Reaction of the racemic aglycone of **154** with acetobromoglucose in the presence of mercuric cyanide gave the two diasteromeric tetraacetates of **154**. Removal of the acetyl groups with methanolic sodium methoxide and then preparative thin layer chromatography gave the two stereoisomers with structure **154**[138]. The CD spectra (Figure 17) of these isomers are essentially enantiomeric and reflect the enantiomeric nature of two half-chair conformations **155** and **156**. In both isomers, the substituent at C(7) is preferentially either pseudoequatorial (R^1 in **155** and **156**) or pseudoaxial (R^2 in **155** and **156**) and the ring conformation depends only on the configuration at C(7). That isomer with its CD spectrum showing a negative



(**155**, R^1 or R^2 = *O*-D-glucose)

(**156**, R^1 or R^2 = *O*-D-glucose)

maximum near 290 nm, similar to that for daunomycin (Figure 16), was assigned the 7*S* configuration[138]. Thus the glucoside substituent, represented by R^2, is pseudoaxial in both **155** and **156**, the conformation at C(7) also being pseudoaxial in daunomycin[121]. If, however, the glucosidic substituent in the isomers of **154** is pseudoequatorial (R^1 in **155** and **156**), that isomer with a positive maximum near 290 nm would have the 7*S* configuration.

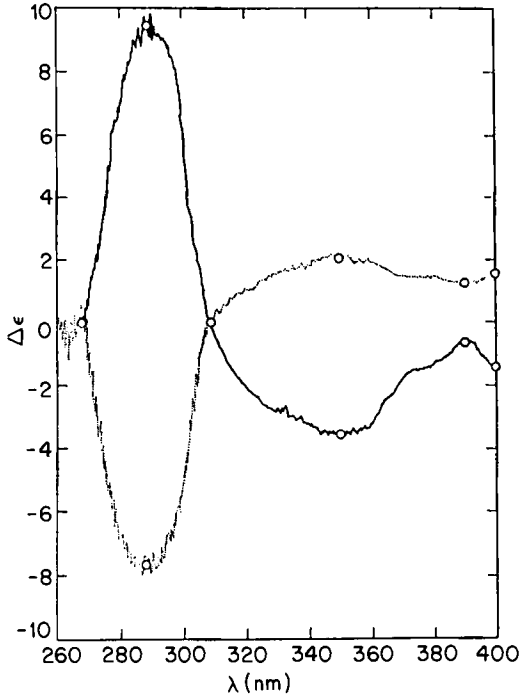


FIGURE 17. Circular dichroism (CD) spectra of the glucoside of diastereomeric anthraquinone analogs of daunomycinone (**154**) in dioxan. *Adapted from Ref. 138 by permission of the Royal Society of Chemistry*

As discussed above in connection with preferred half-chair conformation for anthracyclinones (Section IV.C), ^{1}H-NMR measurements[122,123] and calculations using empirical potential functions[124] indicate that the pseudoaxial conformation (R^2 in **155** and **156**) for a substituent at C(7) and C(10) is slightly lower in energy than is the pseudoequatorial conformation (R^1 in **155** and **156**). Thus, the assignment of the 7*R* and 7*S* configurations to the D-glucosidic isomers which show positive and negative CEs near 290 nm, respectively, has some experimental and theoretical justification.

V. DEDICATION AND ACKNOWLEDGEMENT

This chapter is dedicated to my late brother, Charles A. Smith, Jr. He was a good friend to me, and I will miss him. Also, I thank the many authors and copyright holders for permission to reproduce the respective figures.

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CHAPTER 5

Photoelectron spectra of quinonoid compounds*

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I. INTRODUCTION

In the original Quinone volume, the leading chapter ('Theoretical and general aspects' by G. J. Gleicher) cited just two experimental ionization energies for quinonoids: 9.68 eV for *p*-benzoquinone (PBQ) and 9.34 eV for 9,10-anthraquinone (AQ), both taken from Vilesov and coworkers[1]. Furthermore, only two theoretical works, one by Newton and coworkers[2] and the other by Aussems and coworkers[3a], both of which used SCF-MO theory to predict the ionization potentials of PBQ[3], 1,4-naphthoquinone (NQ)[3b] and AQ[3], were quoted†. Today, merely a dozen years later, we find it necessary to write an entire chapter on the photoelectron spectroscopy of quinonoid compounds! Nothing less would do justice to the enormous growth of the field or to the pertinence of the electronic structure of these molecules to modern organic chemistry. Hence, this essay.

The interpretation and assignment of the spectra of quinonoid compounds has caused much headache for both photoelectron spectroscopists and quantum chemists. For example, it is now known that the two lowest-energy ionization events in PBQ are connected with the removal of oxygen lone-pair electrons and are best denoted $I(n_{\pm})$. However, the path leading to this conclusion is exceedingly tortuous[1-27], so much so that it provides a chastening example for all spectroscopists of theoretical bent. For that reason, we have illustrated the twists and turns, along a time-line beginning in 1966, of the spectroscopic assignments for the four lowest-energy ionization events in *p*-benzoquinone. The total number of possible assignments is 4! The reader will note that most of these 4! permutations are represented in Figure 1.

The four relevant ionization events of Figure 1 correspond to the removal of electrons from two oxygen lone-pair orbitals, $I(n_+)$ and $I(n_-)$, and two benzenoid (or ring) orbitals, $I(\pi_+)$ and $I(\pi_-)$. All assignments of Figure 1 embrace these four orbital characterizations, virtually all of them being heavily influenced by the results of quantum chemical calculations. Such calculations have served very well in organic chemistry. Yet, in *p*-benzoquinone, they fail dramatically.

The reasons for all these difficulties seem to be the following:

(1) Quinones are oxidants; that is, they tend to accept (or extract) electrons from their environment. Photoelectron spectroscopy, on the other hand, measures the exact opposite process, namely the release (or injection) of electrons into the continuum. This disparity is the source of some problems.

(2) As with most electron acceptors, quinonoid compounds usually possess tightly-bound virtual orbitals, a point that is amply substantiated by the absorption spectroscopy[28-34] of these compounds. These low-lying virtual orbitals generate low-energy excited states and play an important role in the photoionization act, in the sense that they and the continuum may be simultaneously populated by a single X-ray excitation photon.

† Incidentally, both of these calculations predicted, quite wrongly it should be emphasized, that the lowest-energy ionization events were of π nature. Despite the mis-assignments, 'good' agreement was obtained between the measured[1] and calculated values[3b] for PBQ and AQ. Thus, the prediction of energy and assignment for the unknown, lowest-energy ionization event in NQ was taken, again quite wrongly, to be reliable. Finally, as if to add insult to injury, the experimental value $I = 9.68$ eV for *p*-benzoquinone is now known to be erroneous.

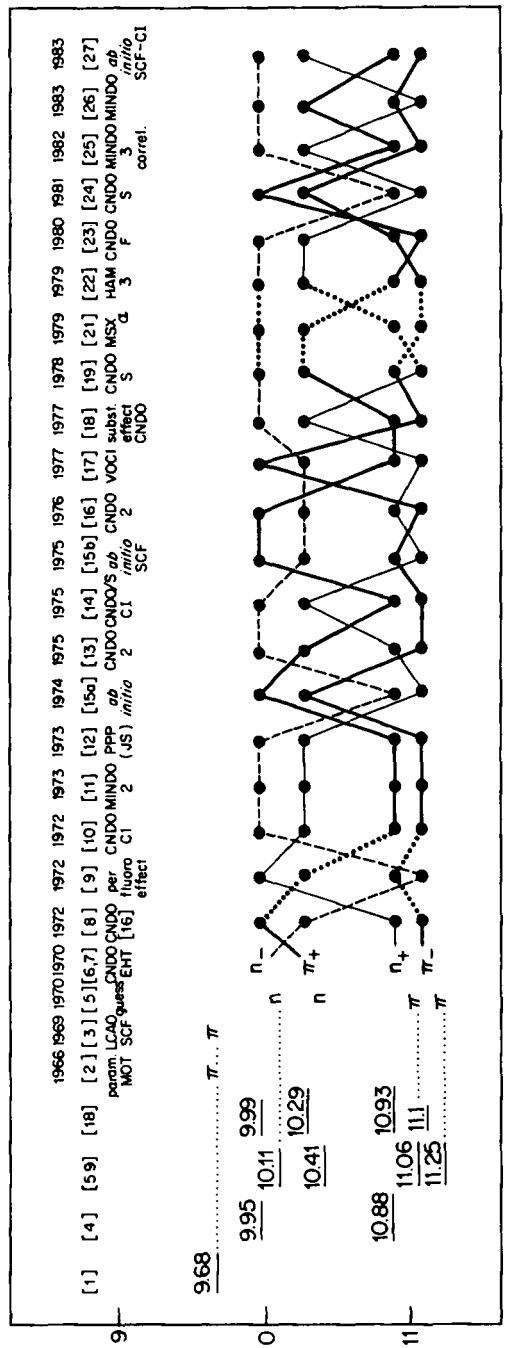


FIGURE 1. Assignments of ionization energies in *p*-benzoquinone by year from 1966 to 1983. References are bracketed. The comments under the references refer to the quantum chemical method used in the cited work except for that under [9], which refers to the empirical use of the perfluoro effect. The variation of the experimental measurements is represented in the first 4 columns, the data under [18] being now generally accepted. Differentiated assignments begin in 1970. The correct assignments are those of [10], [11], [12], [13], [18], [22], [25] and [27]

That is, the photoelectron spectrum may contain 'shake-up' events. The presence of such events in the photoelectron spectrum imposes serious difficulties on the empirical assignment process.

(3) The presence of low-lying virtual orbitals, as discussed in (2), implies a high density of low-energy electron configurations. This, in turn, implies a high probability of Koopmans' breakdown. That is, the extensive configuration interactions that may occur as a result of the energetic proximity of singly and doubly excited configurations to the ground configuration invalidates almost all the approximations inherent in the Koopmans derivation. Consequently, ionization energy no longer relates to an orbital energy. In specific, Koopmans' theorem[35] is certainly inapplicable to *p*-benzoquinone and certain other quinonoid compounds. Since this point is so important for the interpretation of the valence photoelectron spectra of quinonoids, we will discuss it briefly in the next section.

II. KOOPMANS' THEOREM: ITS CONSEQUENCES FOR PHOTOIONIZATION PROCESSES, PHOTOIONIZATION ENERGIES AND ELECTRONIC STRUCTURE[35-37]

The release of an electron from any chemical system constitutes ionization of that system. We confine ourselves here to the ionization of free atoms and molecules in the gas phase caused by electromagnetic radiation (photons). Such events are known as 'photoionization' processes, the released electrons are termed 'photoelectrons' and the technique used to determine their excess kinetic energy is referred to as 'photoelectron spectroscopy', or PES. If the photon energy exceeds the ionization energy, the surplus excitation is transferred to the ejected electron as a kinetic energy, E_k. The techniques that measure E_k are referred to as 'X-ray or UV photoelectron spectroscopy' or, for short, XPS and UPS, respectively. When E_k is plotted against the number of ejected photoelectrons, the result is a photoelectron (PE) spectrum, from which ionization energies I_k may be obtained using the equality

$$I_k = h\nu - E_k;\ k = 1, 2, \ldots w;\ I_w \leqslant h\nu$$

In the MO picture, the photoelectrons are supposed to originate in individual electronic orbitals of the molecular ground state configuration. If spin-orbit coupling is small, each non-degenerate orbital is occupiable by two electrons of opposite spin (Figure 2). However, the photoionization spectrum need not consist solely of the set of single-event processes that supposedly describes the UPS and XPS processes. Indeed, electron excitation can accompany electron ejection ('shake-up'); two electrons can be ejected simultaneously ('shake off'); or a second electron can be subsequently ejected from the original highly-excited ion produced in the XPS process (Auger event).

A. The First Part of Koopmans' Theorem

The connection of theory and experiment is given by Koopmans' theorem, which states that the electronic wave function of a singly-ionized state is adequately described by Slater determinants based on the set of $N-1$ ground state, self-consistent field (SCF), molecular spin orbitals (MSOs). That is, if

$$\Psi^N = |\phi_a(1)\phi_b(2) \ldots \phi_n(N)|$$

is a good descriptor for the ground state, then

$$\Psi^{N-1} = |\phi_a(1)\phi_b(2) \ldots \phi_m(N-1)|$$

is a good descriptor for the singly ionized state. The ionization energy, then is

$$I_n = E(\Psi^{N-1}) - E(\Psi^N) = \langle \Psi^{N-1}|H^{N-1}|\Psi^{N-1}\rangle - \langle \Psi^N|H^N|\Psi^N\rangle = -\varepsilon_{nn}$$

where H^{N-1} and H^N are the SCF hamiltonians for the $(N-1)$ and N electron systems, respectively. This statement, namely that the ionization energy equals the negative of the orbital energy of the ejected electron, $-\varepsilon_{nn}$, is the first part of Koopmans' theorem.

B. The Second Part of Koopmans' Theorem

Now, the function Ψ^{N-1} is by no means optimal. The optimal function may be written as the CI (configurational interaction) expansion

$$\Psi^{N-1} = \sum_{k \in occ} \Psi_{-k} C_k + \sum_{\substack{k,l \in occ \\ u \in unocc}} \Psi^u_{-kl} C^u_{kl}$$

where, for example, Ψ_{-k} denotes a determinant Ψ_0 in which spin-orbital ϕ_k has been deleted; Ψ^u_l is one in which ϕ_l has been replaced by ϕ_u; and where we have dropped the $N-1$ superscripting to avoid crowding. The function Ψ^u_{-kl}, as is obvious, is a shake-up configuration (Figure 2). Simplification of Ψ^{N-1} might consist of truncation to

$$\Psi^{N-1} = \sum_{k \in occ} \Psi_{-k} C_k$$

However, what we really desire is

$$\Psi^{N-1} = \Psi_{-k}$$

This gross simplification is equivalent to the demand that we find an orthogonal transformation of the set of Hartree–Fock MSOs so that the cationic state can be represented by one single determinant constituted from this set, namely Ψ_{-k}, and the neutral ground state can be represented by one single determinant constituted from the same set, namely Ψ_0. Koopmans' theorem asserts this possibility and, furthermore, it identifies the appropriate MSO set as the canonical Hartree–Fock set.

This latter assertion is the second, and more important, part of Koopmans' theorem. It may be rephrased alternatively: the only allowed ionizations are those which remove an

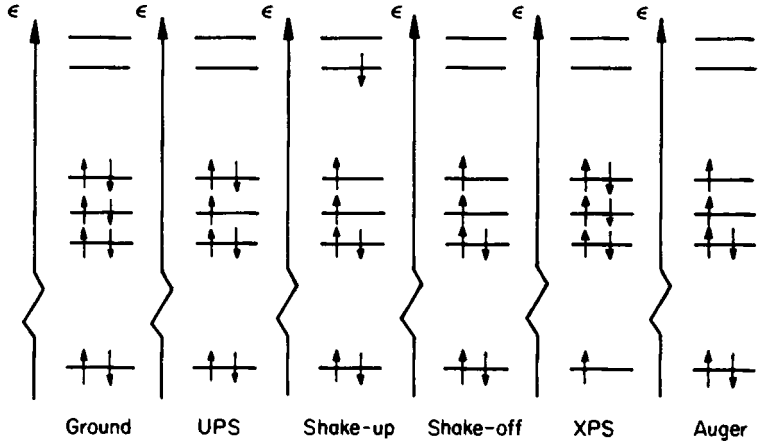


FIGURE 2. A depiction of various types of ionization processes in an MO format. Orbital energy is denoted by ε. The jogs in the vertical arrows connote a large energetic separation of core and valence orbitals. The two topmost orbitals are the virtual orbitals

electron from an MSO (or shake-up and shake-off transitions are forbidden). If spin-orbit coupling is small (< 20 meV), a further restatement becomes possible: the only allowed ionizations are those which remove one electron from an MO.

C. The Deficiencies of Koopmans' Theorem

Koopmans' theorem provides a salient experiment/theory interface. Consequently, it is well to specify the approximations inherent in its derivation. These are as follows.

1. Fixed-nuclei approximation

The Born–Oppenheimer approximation permits the notion of 'molecular geometry'. It is understood that the cationic $N-1$ electron system, which is the immediately terminal state of the process

$$N \text{ electron system} + h\nu = (N-1) \text{ electron system} + e^-$$

is identical in all geometric detail to the initial state of the N electron system. This, of course, is the Franck–Condon approximation. Consequently, Koopmans' theorem applies only to vertical ionization events.

2. The correlation energy

The neglect of correlation energy is intrinsic to the Hartree–Fock approximation. The correlation energy is caused by the fact that electrons adjust their motions to the instantaneous charge distribution, and not to an average charge distribution (as is assumed in the Hartree–Fock equations). In fact, the correlation energy is the difference between the correct energy and the Hartree–Fock energy associated with any given Hamilton operator. If relativistic effects are small, the latter is well known; and the 'correct energy' is the same as the experimental energy. Thus, correlation energies are often readily determinable.

Electrons of opposite spin usually tend to stay considerably further apart (i.e. correlate their motions better) than a single determinantal wave function will allow and, as a result, correlation energies can be quite substantial. Nonetheless, while large for any one state, it is only the difference between two states, namely between the initial N and terminal $(N-1)$ electron states, which is of significance to photoelectron spectroscopy. This difference may well be small. Koopmans' theorem implies that it is zero.

3. The relaxation energy

The same set of spin-orbitals is used to construct the Slater determinants for the N and $(N-1)$ electron systems. This supposition implies that the electrons of the cation do not adjust or relax in order to accommodate the changes of interelectronic repulsions which characterize the $(N-1)$ electron system. This supposition is known as the 'frozen-core (fc)' or 'frozen orbital (fo)' approximation.

4. The non-relativistic approximation

This approximation is not a consequence of deficiencies in the wave functions; it is, rather, a defect caused by the omission of relativistic terms from the Hamilton operator. We have omitted these terms solely for convenience. The various relativistic terms—for example, spin-orbit or spin–spin interactions—might have been included in the Fock operator in a way which would not have altered any of our conclusions. In fact, in his

original paper, Koopmans included relativistic effects explicitly—and to no ill effects whatsoever.

5. Restriction to closed-shell systems

Koopmans' theorem is restricted to closed-shell N electron systems. Thus, at least in the form expressed here, it is specifically inapplicable to non-closed-shell systems (e.g. most transition metal complexes).

The relationships between the experimental ionization energy, the MO energy and the Hartree–Fock ionization energy are schematized in Figure 3. The correlation energy is always negative and is shown to be slightly larger for the system with the larger number of electrons. The reorganization energy for the cation (i.e. $\Delta E^+(\text{fc}) \equiv [E^+(\text{Koopmans}) - E^+(\text{HF})]$) will almost always be positive. Hence, there is a tendency for $|\Delta E^+(\text{fc})| + |\Delta E^+(\text{corr})|$ to equal (approximately, of course) $|\Delta E_0(\text{corr})|$. It is this tendency which is responsible for the moderate successes of Koopmans' theorem.

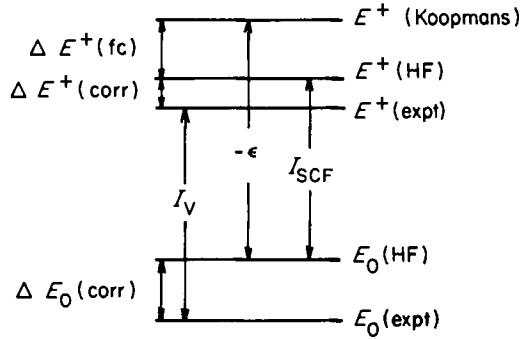


FIGURE 3. The relation between experimental vertical ionization energy, I_v, the Koopmans MO energy, ε, and the Hartree–Fock self-consistent field ionization energy, I_{SCF}. The symbol E^+ denotes cation energy; E_0 denotes the neutral molecule energy; $\Delta E(\text{corr})$ denotes the correlation energy; and $\Delta E(\text{fc})$ denotes the frozen-core energy correction

D. The Interface of Experiment and Koopmans' Theorem

The second part of Koopmans' theorem implies an isomorphism of the set of ionization potentials of the neutral molecule and the set of canonical MO energies. The first part of Koopmans' theorem specifies the connectors for this isomorphism. This, of course, is a very desirable state of affairs: it dictates the mapping of the UPS data set onto the HF-SCF MO set as an order-isomorphism in the energies. Not only that, it is well established that this particular isomorphism is usually correct; that is, the assignment of a given ionization event as the removal of an electron from an MO of given charge distribution (i.e. symmetry) is usually correctly rendered.

Such a rendering, however, is not always correct. First, the deficiencies of Koopmans' approximation can readily induce an uncertainty of ± 1 eV in the energy match and, second, the MO computations may not (in fact, are usually not) of HF-SCF quality. Nonetheless, a very large category of publication exists in which a set of UPS energies is mapped onto a set of MO energies obtained by some algorithmic quantum chemical scheme. We think this to be unfortunate. Such a mapping is valid only when vested in other

empirical informations. Among these, we list:

(1) cross-sections as a function of the ionizing photon energy.
(2) vibronic structure of the UPS band (i.e. normal modes active in the ionization event).
(3) energies and intensities of Rydberg series which terminate on specific cationic states.
(4) perturbation techniques based on relatively innocuous chemical substitution, such as substitution of a methyl group, an SiH_3 group, or even a fluorine atom (i.e. the perfluoro effect). Such substituents usually exert the largest effect on the ionization event associated with a specified MO when substituted at that locus at which the MO in question possesses the largest electron density. Indeed, the nature of the substituent can be used to gauge relative σ/π contributions to the electron density at the locus in question. Thus, an adroit use of substituent effects can be used to define shape and constitution (i.e. σ, π or relative σ/π admixture) of an MO. In a sense, then, this technique can be considered to be a chemical MO mapping procedure. It is also expected that even an algorithmic quantum chemical calculation, even if only moderately 'good', should mimic the observed perturbative effects. Hence, a new projective element is added to the Koopmans' isomorphism, namely MO shape and constitution.
(5) correlative studies based on the supposition that the spectrum of certain molecules should be a composite of the spectra of their constituent parts. For example, it is reasonable to suppose that the set of ionization events for nitroaniline should be related in some way to those of NH_3, HNO_2 and benzene.

The higher the ionization energy (that is, the deeper the MO from which electron ejection occurs), the greater is the chance for breakdown of this simple one-electron picture. Therefore, different levels of sophistication for the assignment of PE spectra using quantum chemical calculations do exist. These are:

(1) At the first stage, the canonical MO energies are correlated directly to ionization energies. Both parts of Koopmans' theorem are applicable at this stage.
(2) At the second stage, SCF calculations are performed for both the ground and the radical cation states and the energy differences of these states, which we denote ΔE_{SCF}, are correlated with the ionization energies. Only the second part of Koopmans' theorem is applicable at this stage.
(3) At the third stage, extensive configurational mixing is imposed. One usually includes configurations that are singly and doubly excited relative to all electron configurations of primary interest. No part of Koopmans' theorem retains validity at this level of sophistication. Indeed, finite intensity predictions for non-Koopmans' transitions (shake-up and shake-off) are intrinsic to this level and these predictions are of considerable help in tracking these low-intensity PES bands in an otherwise very intense spectrum.
(4) At the fourth stage, the calculations focus on the dynamic nature of the PES transition, even to the extent of including the effects of nuclear motion (i.e. vibronic and Coriolis coupling). This approach, which was elaborated by Cederbaum and coworkers[38], is well documented and there is no doubt that it is especially important for the determination of PES band shapes and intensities. It is also pertinent in those situations in which studies at any of the prior three stages suggest serious non-Koopmans behavior of the ionization energies. Fortunately, these latter instances are not very plentiful and they appear to be largely confined to small molecules—fortunately, that is, because the magnitude of the computational effect makes this approach impractical for large molecules.

In a somewhat naive picture, the canonical MOs and their energies may be supposed to represent the 'molecular electronic structure' of the molecule of interest. If this be so, then one of the consequences of being forced into a stage four discussion is that the PES technique will have lost much of its ability to probe this structure, becoming no more than

a means of measuring ionization energies. Luckily, however, the applicability of Koopmans' theorem seems to be reasonably general, with the result that the PES technique retains its virtues as a good probe of 'molecular electronic structure'.

III. QUINONES, QUINONOIDS AND QUINOID STRUCTURES

The contemporary reference literature (e.g. *Chemical Abstracts*) does not contain much information under the subject listing 'quinones'. The reason lies in the fact that the term 'quinone', as well as a number of other related terms, is not uniquely defined. In a chemical sense, a 'quinone' is readily defined as a cyclic dicarbonyl compound, Q, which, (*a*), by addition of two electrons (and two protons) is converted into a hydroquinone, HQ, as follows

$$Q + 2e^- + 2H^+ \rightarrow HQ$$

and (*b*) which possesses a positive electron affinity, EA[39]. It is not generally agreed that the resulting hydroquinone should be conjugated or even that it should possess more than one resonant (Kekulé) structure. We advocate the definition: a *quinone is either a cyclic or polycyclic conjugated diketone*. This definition introduces certain complications. For example, such a well-known compound as camphorquinone is not a quinone and is misnamed. On the other hand, this definition does ensure that every cyclic diketone is not, wrongly, considered to be a quinone.

Those quinones and their analogs in which one or both of the oxygens in the carbonyl group have been replaced by a valence-equivalent atom or group (e.g. $=CH_2$, $=NH$, $=S$ etc.) will be termed 'quinonoids'. *A quinonoid, then, is a cyclic or polycyclic conjugated compound with two exocyclic double bonds.*

We wish to reserve the term 'quinoid' for structures as opposed to molecules. Thus, we define a *quinoid as a cyclic or polycyclic conjugated structure that must contain two exocyclic double bonds.*

It must be emphasized that the ability to write a quinoid structure for a given compound does not imply that the compound in question is quinonoid. That is a matter that must be decided by appropriate computation and/or experiment. A good example of the computational approach happens to be available for the xylylenes, for which one may write at least 4900 structural formulas. It has recently been shown by sophisticated quantum chemical calculations that the quinoid structure constitutes 55% of the ground state of *o*-xylylene and 64% of the ground state of *p*-xylylene[40]. In other words, if the ground state is represented as a linear combination of valence bond structures, there being at least 4900 such structures, the weighting factor of the quinoid structures in this state is 55%/64% for *o*-xylylene/*p*-xylylene. Therefore, it would not be erroneous to refer to *p*-xylylene as quinonoid. In order to make the discussion more concrete, the most important valence structures for *o*- and *p*-xylylene are shown in Figure 4.

Some quinones have been found to possess considerable anti-cancer activity[41]. Therefore, the question of the number and relative stability of the quinones that might be generated from a polycyclic aromatic is not simply an academic exercise. Graph theoretical and computer enumeration techniques (e.g. those used above to determine the number of Kekulé structures pertinent to a given molecule; those used to specify the number and structure of alkane and polycyclic aromatic hydrocarbon isomers; those used to enumerate the total set of alkyl-substituted polyaromatic hydrocarbons[42]; etc.) could contribute much to the solution of this problem[43].

IV. X-RAY PHOTOELECTRON SPECTROSCOPY OF QUINONOIDS

We have found only two reports on the XPS of quinonoids[44,45]. The few available spectra contain no surprises and they also suggest that none is expected.

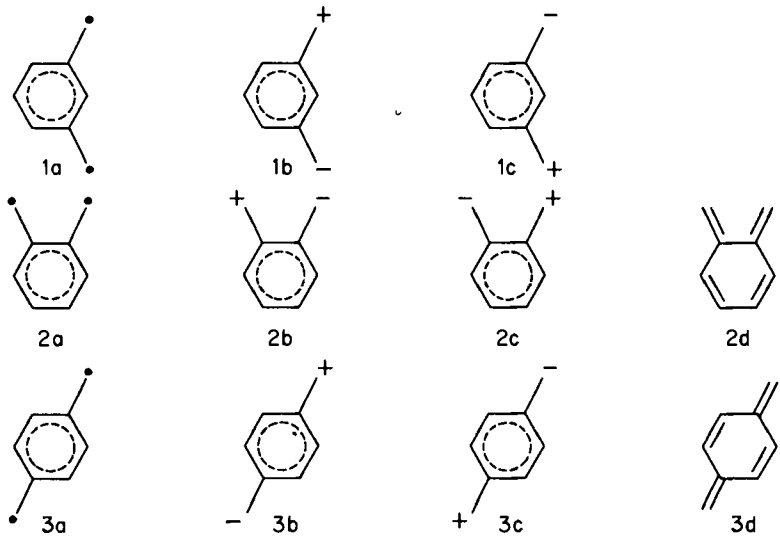
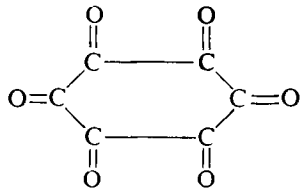


FIGURE 4. Structural formulas important to the ground state of *m*-xylylene (top), *o*-xylylene (middle) and *p*-xylylene (bottom). Quinoid structures are important in *o*-xylylene (see structure 2d) and *p*-xylylene (see structure 3d) but not in *m*-xylylene (see Ref. 40)

The XPS technique is used to determine ionization energies of inner, core electrons associated with specific atomic nuclei of the molecule in question. The experimental quantity of primary interest is known as the 'chemical shift', namely the change of ionization energy relative to that for the free unbound atom. A knowledge of this shift leads to considerable information about the composition and structure of the molecule. In the case of *p*-benzoquinone and its tetrahalogenated derivative, two C_{1s} peaks of intensity ratio 2:1 (Figure 5), one O_{1s} peak and several halogen ns, np, and nd peaks were observed. The energies for these peaks are given in Table 1. Application of the Gelius method[46] permits a ready conversion of the chemical shifts into a theoretical molecular charge distribution.

The correlation of the calculated shifts, ones based on charge densities calculated by the CNDO/2 algorithm, with binding energies yields the linear relation of Figure 6. This linearity also encompasses the C_{1s} chemical shift for triquinoyl (TQ).



Because of the low resolution that still limits XPS accuracies, even simple computational schemes usually provide good correlation with experiment[47] and good predictive power.

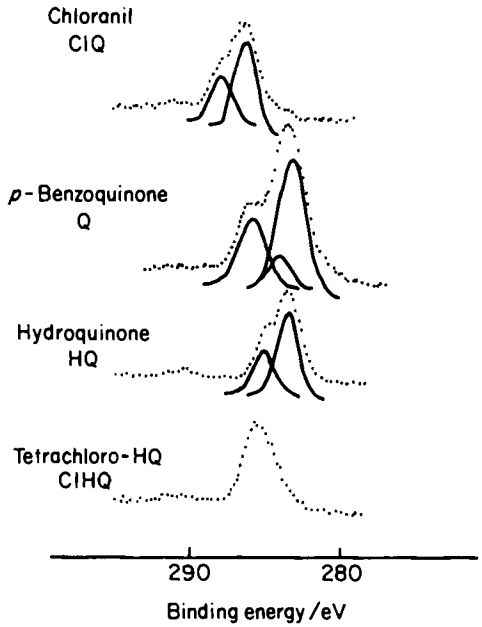


FIGURE 5. Carbon 1s X-ray photoelectron spectra taken from reference 45. The two main peaks, ratio 1/2, refer, in PBQ, to carbons with oxygen substituents and carbons with hydrogen substituents, respectively (i.e. a 2/4 ratio). Chlorine substitution for the hydrogens, as in chloranil, ClQ, moves the more intense peak to higher energies. Hydrogenation of the oxygens, as in HQ, moves the less intense peak to lower energies. Thus, it is not unexpected that both peaks should become coincident in tetrachlorohydroquinone, ClHQ

TABLE 1. XPS energies for some quinones, hydroquinones and triquinoyl*

	C_{1s}					
Molecule	C_O	C_X	O_{1s}	ns	np	nd
Chloranil	287.7	286.1	531.5	270.9	200.2	
Bromanil	287.5	285.6	531.4		183.4	70.1
Iodanil	286.7	284.4	531.0	187.2	123.0	50.1
p-Benzoquinone	286.0	283.4	530.8			
Hydroquinone	285.1	283.5	532.2			
Tetrachlorohydroquinone	285.5		532.5	270.7	200.0	
Triquinoyl	288.5					

* Energies are in eV. The C_O peak is the C_{1s} energy for the carbons to which an oxygen atom or hydroxyl group is attached. The C_X peak is the C_{1s} energy for the carbons to which an atom X = H, Cl, Br or I is attached. The principal quantum number is n = 2, 3 & 4 for chlorine, bromine and iodine, respectively. The C_O and C_{Cl} peaks are accidentally degenerate in tetrachlorohydroquinone and truly degenerate in triquinoyl.

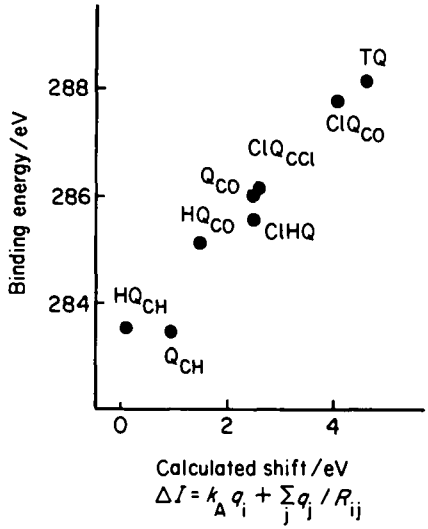


FIGURE 6. Binding energy (eV) for C_{1s} core electrons versus calculated chemical shifts (eV) for *p*-benzoquinone (PBQ), hydroquinone (HQ), tetrachlorohydroquinone (ClHQ), chloranil (ClQ) and triquinoyl (TQ). The circles refer to C_X and to C_O values of Table 1. This material is taken from Refs 44 and 45 of the text. The chemical shift at center i is $\Delta E_i = k_A q_i + \sum_j q_j / R_{ij}$ where q_i is the charge on center i, q_j that on center j and R_{ij} the distance between centers i and j

V. THE INTERACTIONS OF VALENCE ELECTRONS IN QUINONES

Quinones, as stated, are cyclic, conjugated, dicarbonyl compounds. The composite molecule method provides an apt means to discuss the electronic structure of such molecules: a knowledge of the low-energy levels and their electronic structure for the constituent parts (i.e. the carbonyl group and an unsaturated cyclic hydrocarbon) can be used to reconstitute the quinone and, in the process, to induce considerable insight into its electronic structure.

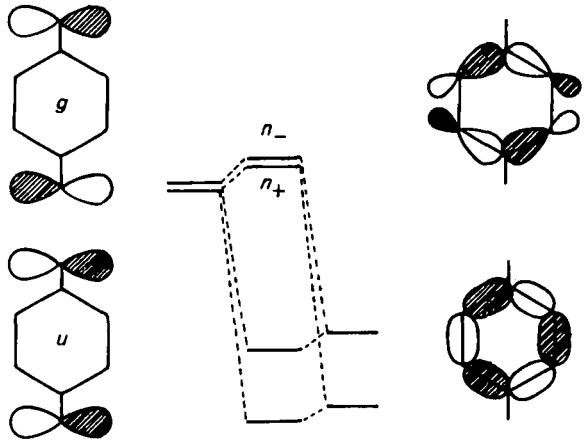
An isolated carbonyl group is characterized by two lone-pair orbitals, one of p-type and the other of s-type, of widely different energy. Only the orbital of low binding energy, the p orbital (which also is the highest-energy occupied σ orbital in simple ketones and aldehydes), is of interest for the present considerations. This p orbital is referred to also as an n orbital, where n denotes 'non-bonding'.

If a molecule contains more than one equivalent carbonyl group, the group orbitals must be combined into molecular orbitals in order to fit the requirements imposed by the point symmetry of the molecule. Unfortunately, these symmetry impositions, while mandatory, provide little or no information about either the extent of the group orbital interactions, the degree of their delocalization over the entirety of the composite molecule or even the magnitude by which the initial zero-order degeneracies are split in the actual molecule.

Quinones also possess group orbitals of a cyclic hydrocarbon π-orbital nature, and these orbitals are energetically very similar to the lone-pair n orbitals. It is our aim, in this section, to schematize the qualitative factors that influence the relative energetic disposition of the various orbitals. As examples, we will choose *p*-benzoquinone (PBQ) and *o*-benzoquinone (OBQ).

A. *p*-Benzoquinone

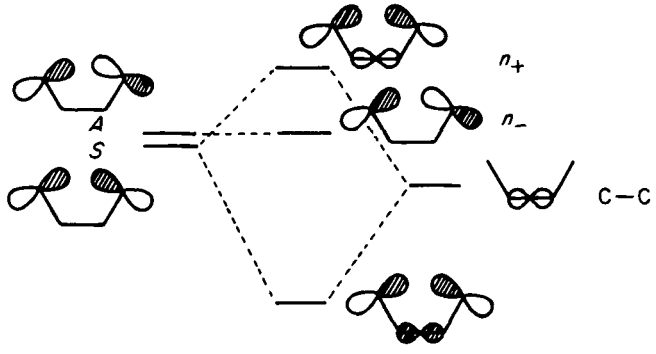
In PBQ, the two oxygens are situated far apart. Thus, although we can anticipate the need for n_+ and n_- linear combinations of the σ lone pairs, their direct through-space (TS) interaction should be quite negligible. To the extent that any splitting occurs, it is expected that n_- should be of lower binding energy than n_+. To this point, the interactions of the $n_\pm$ orbitals with the σ orbitals of the six-membered ring have been neglected. Since some of these σ orbitals are of appropriate symmetry to interact with the n_+/n_- orbitals, such neglect is unjustified. The σ-ring orbitals are well known in benzene or 1,4-cyclohexadiene[48]. They and the $n_\pm$ orbitals are schematized below.



The orbital of g symmetry, which corresponds to the ~ 11.5 eV ionization event in benzene, is of lower binding energy than the orbital of u symmetry which appears at $I > 12$ eV. Since the g orbital can interact only with n_-, which already lies above n_+, the final result of this interaction is expected to maintain the original energetic order and to contribute only moderately, perhaps a few tenths of an eV, to the final splitting. This ring-orbital/n-orbital interaction is often referred to as through-bond (TB) interaction.

B. *o*-Benzoquinone

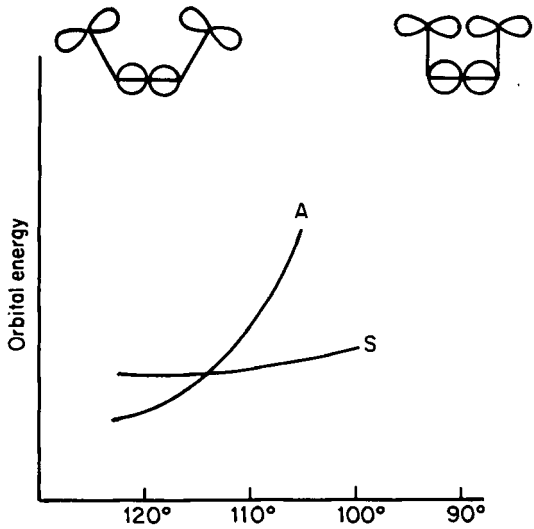
In the case of OBQ, the pure TS interaction should cause the antisymmetric (A) combination to be of lesser binding energy than the symmetric (S) combination. However,



since this interaction should be quite weak, the two levels should be almost degenerate. The additional TB interaction which operates through the joint C–C bond and, for symmetry reasons, affects only the (S) combination of n orbitals causes a reversal of the zero-order situation. This situation is schematized above.

The TB interaction in OBQ is expected to be much stronger than in PBQ. Thus, there is little doubt that the n_+ orbital is the highest-energy occupied MO in OBQ and that the n_+/n_- split is quite large. As a result, the $I(\pi)$ events, which are largely unperturbed and associated with the conjugated hydrocarbon part of the molecule, usually lie between the $I(n_+)$ and $I(n_-)$ lone-pair ionization events.

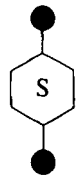
The effects of variation of the angle between the two coplanar carbonyl groups on the zero-order $I(n)$ events is of some interest and is shown below[6]. From the initial ideal angle



of 120° to the limiting 90° case, in which the two p orbitals point directly at each other, the binding energy of the A combination is expected to decrease consistently. The energy of the S (antibonding) combination, on the other hand, experiences compensation between increased bonding of the oxygen orbitals and increased antibonding carbon–oxygen interactions, the result being that the energy of this level remains largely invariant to angle. Calculations also predict that, at some angle close to 90°, the energy of A will cross over that of the π^* virtual antibonding MO, providing another example of the inability to form a four-membered ring by thermal reaction methods (Woodward–Hoffmann rules).

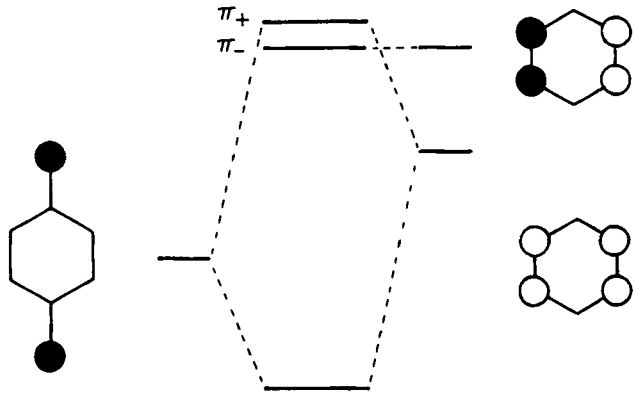
C. The π-MOs

The nature of the π-MOs of PBQ are best visualized as follows. Consider two p orbitals, one on each of the two oxygen centers. These are shown below, the positive lobes lying



below the plane of the paper. Consider also two cyclohexadiene group orbitals, one symmetric and one antisymmetric, as shown below. The interactions of these three group

orbitals is quite straightforward, the cyclohexadiene group orbital denoted A (or π_-) converting directly into a molecular orbital without any significant change of energy. The interaction of the S group orbitals, however, is extensive and it is this mixing which yields $I(\pi_+) < I(\pi_-)$. These mixings are shown below.



D. Summary

In sum, then, one predicts for PBQ that $I(n_-) < I(n_+)$ and $I(\pi_+) < I(\pi_-)$. The shapes of these orbitals, as obtained from CNDO/2 calculations, are shown in Figure 7. However, qualitative considerations cannot specify the n_+/n_- splitting, the π_+/π_- splitting or even the relative order of the n and π subsets. Indeed, as will be discussed *in extenso* in the next section, we will show that simple computations tend to predict that $I(\pi) < I(n)$ whereas experimental arguments usually bespeak a reverse ordering.

VI. THE *p*-BENZOQUINONE STORY

The history of PES assignments for *p*-benzoquinone has been long and tortuous. Specifically, while the assignment of the four lowest-energy PES events to the ionization processes $I(n_+)$, $I(n_-)$, $I(\pi_+)$ and $I(\pi_-)$ has been generally accepted, virtually every one of the 4! permutations of these processes has been advocated at one time or another. This situation has produced much confusion and some discord. In a sense, the turns and twists of the PBQ PES assignments provide an object lesson in the need for scientific sobriety, particularly the desirability of leavening semiempirical quantum chemical results with large doses of empiricism. For that reason, we will devote some space to history.

The lowest-energy ionization of PBQ was first reported as $I_1 = 9.67$ eV in 1957 by Vilesov and coworkers[1]. Dewar and Worley[4] reported a set of ionization energies, $\{I_j\} = \{9.95, 10.88, 13.26, 14.05, 16.44, 18.65, 19.19\ \text{eV}\}$, in which I_1 differed substantially from that of Vilesov. Turner and coworkers[5], using higher resolution, showed that each of

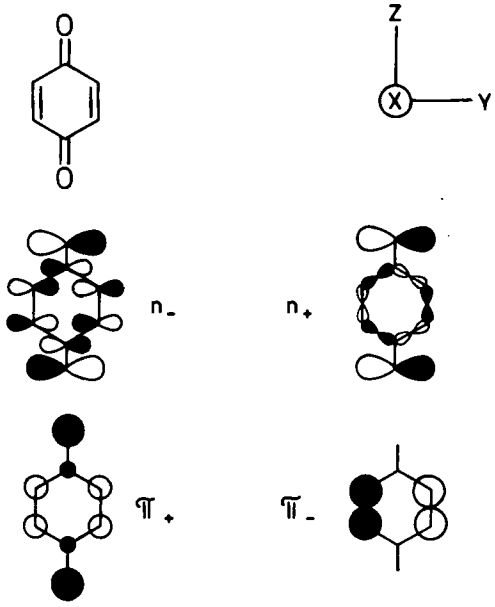


FIGURE 7. CNDO/2 computed molecular orbitals[18] for PBQ. Only the n_+, n_-, π_+ and π_- molecular orbitals are shown

the two lower Dewar–Worley values actually consisted of two close-lying bands, one pair at 10.11 and 10.41 eV and the other at 11.06 and 11.25 eV. Turner and coworkers also provided a correct assignment for the lowest set of ionization energies, namely $I(n), I(n) < I(\pi), I(\pi)$, but they gave no information concerning the method used to make these attributions. These assignments were all the more remarkable because prior calculations had unanimously predicted the topmost-filled MO (HOMO) of PBQ to be a π-MO[2, 3]. As will be seen, this predictive tendency is a common but wrong characteristic of most quantum chemical calculations for PBQ.

Swenson and Hoffmann[6] investigated the TS and TB lone-pair interactions of the oxygens in 1970 and correctly predicted that $I(n_-) < I(n_+)$ for PBQ. However, their CNDO/2 and EHT calculations overestimated the degree of interaction of the lone pairs and, as a result, they predicted an $I(n_+)$–$I(n_-)$ gap much greater than the 0.3 eV posited by Turner. This, in turn, led Cowan and coworkers[7] to an assignment $I(n_-) < I(\pi_+) < I(n_+) < I(\pi_-)$, all four transitions fitting into the I_4–I_1 gap of ~ 1 eV observed by Turner.

Trommsdorf[8], Brundle and coworkers[9] and Stevenson[10] independently proposed very different assignments in 1972. Trommsdorf's assignment, based mainly on a CNDO calculation by Merienne-Lafore and Trommsdorf[16], yielded the order $I(\pi_+) < I(n_-) < I(n_+) < I(\pi_-)$. Brundle and coworkers[9] obtained improved spectra for PBQ and its tetrafluoro derivative but, unfortunately, they seem not to have calibrated their instrument. Furthermore, the PES of tetrafluoro-PBQ was so complex that the use of the perfluoro effect as an assignments device was largely vitiated. Nevertheless, on the assumption that the perfluoro effect stabilized the σ-MOs by as much as 5 eV and the π-MOs but slightly, they made the following assignments: $I(n_+) = 10.11, I(n_-) = 11.5, I(\pi) = 10.41$, $I(\pi) = 11.06$ eV and $I(\sigma) = 13.43$ eV. The assignments $I(n_+)$ and $I(n_-)$,

tentative to begin with, were reversed in all later quotations of this work[9] so that the ordered set became $I(n_-) < I(\pi) < I(\pi) < I(n_+)$. However, the availability of the Brundle spectrum rapidly led to three correct assignments: (1) the Stevenson[10] assignment, $I(n_-) < I(n_+) < I(\pi_+) < I(\pi_-)$, based on CNDO-CI calculations; (2) the Gleghorn–McConkey[11] assignment based on a MINDO/2 calculation, which even gave numerical results {9.90, 10.58, 11.16 and 11.47 eV} in remarkable agreement with experiment; and the Hojer and coworkers[12] assignment based on a Pariser–Parr–Pople calculation (with Jensen–Skancke parameters for oxygen[49]) which yielded remarkable numerical agreement with experiment, namely 10.21, 10.51, 11.03 and 11.12 eV.

Kobayashi[13] initiated a rash of new work with the publication of improved, calibrated spectra for PBQ, *p*-toluquinone and 2,5-dimethyl-PBQ. Kobayashi paid particular attention to the band shifts induced by methylation and he concluded that the order was $I(n_-) < I(\pi_+) < I(n_+) < I(\pi_-)$ for both PBQ and methyl-PBQ and $I(n_-) < I(n_+, \pi_+) < I(\pi_-)$ for 2,5-dimethyl-PBQ. These assignments produced rather large $I(n_+)$–$I(n_-)$ splittings of 0.95, 0.59, and 0.48 eV, respectively. These splittings were immediately questioned by Lauer and coworkers[14] who had just recorded new spectra for PBQ, NQ and AQ, from which they concluded that the lone-pair splitting was less than 0.4 eV—a conclusion that also agreed with deductions from the electronic spectroscopy of neutral PBQ, namely that $I(n_+)$–$I(n_-) < 0.25$ eV[8, 50].

Lauer and coworkers[14] also pointed out the invalidity of Koopmans' theorem for the $n_-/^2B_{3g}$ and $n_+/^2B_{2u}$ ionic states of PBQ. They showed that configuration interaction of

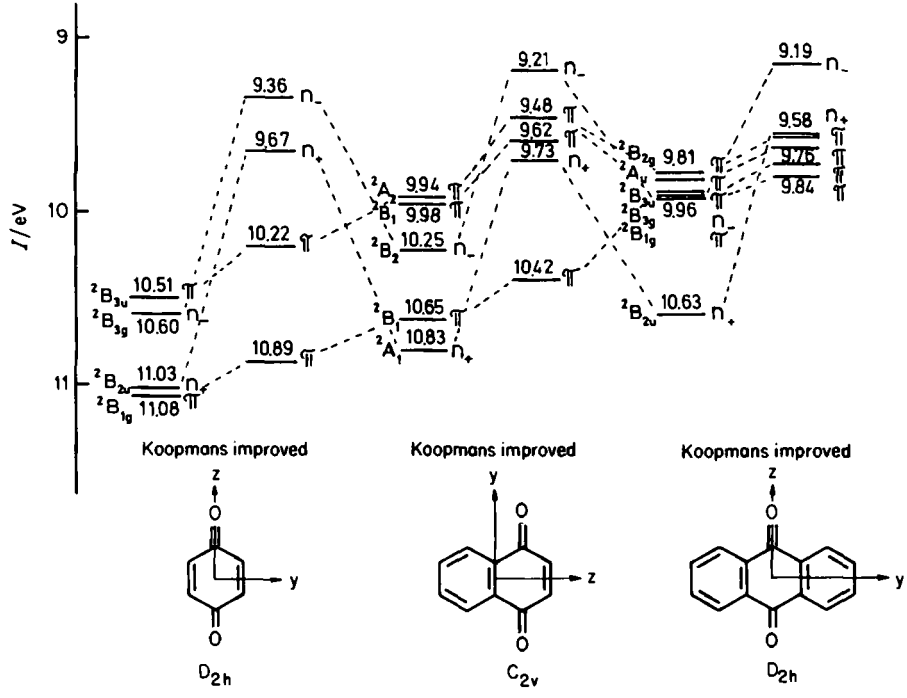


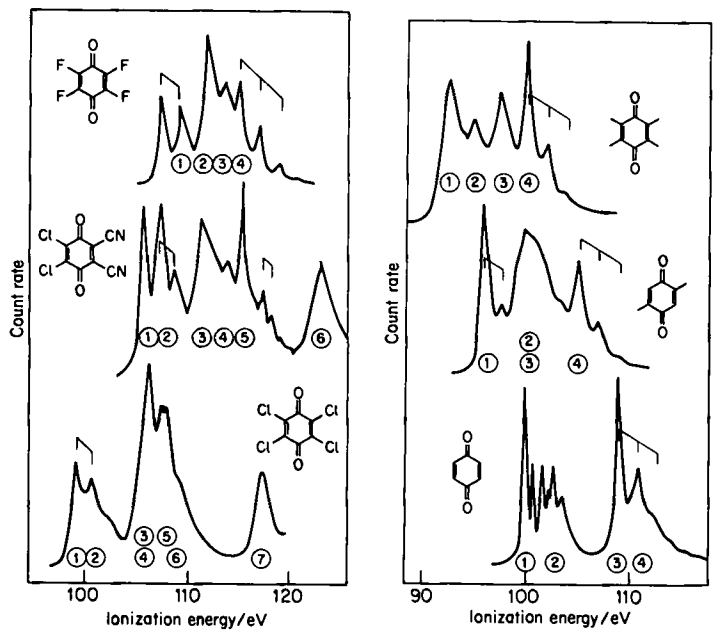
FIGURE 8. The assignment of the lowest-energy ionization events in PBQ, NQ and ANQ, according to Lauer and coworkers[14]. The 'improved' set refers to a situation in which configuration interaction was introduced

the ionic states was prerequisite to generation of the correct order of ionzation energies $I(n_-) < I(n_+)$ (Figure 8). Finally, a series of extensive computations pointed up the sensitivity of the computed results to the assumptions of the computational method.

Two *ab initio* SCF studies of PBQ[15a, b] produced the quite different MO sets $\{-10.91\ (\pi_+),\ -11.37\ (\pi_-),\ -11.75\ (n_-),\ -12.35\ (n_+)\}$ and $\{-8.30\ (\pi_+),\ -9.23\ (n_-),\ -9.67\ (\pi_-),\ -9.95\ (n_+)\}$, respectively. Since a small gaussian basis and a minimal Slater orbital basis were used in these calculations, it was not surprising that the agreement with experiment should be unsatisfactory. However, the discord of the two sets was surprising. This surprise was emphasized when it was found that contraction of the already small (6, 3/3) gaussian basis to a (4, 2/2) basis and the application of a restricted SCF method in the full D_{2h} symmetry yielded $\{-10.42\ (\pi_+),\ -10.53\ (\pi_-),\ -11.04\ (n_-),\ -11.23\ (n_+)\}$ whereas a local description in C_{2v} symmetry yielded $\{-8.60\ (n_-$ and $n_+),\ -10.06\ (\pi_-$ and $\pi_+)\}$.

Bunce and coworkers[17] investigated the excited states of several *p*-quinones (PBQ, duroquinone, AQ, chloranil and NQ). They used the virtual orbital configuration method (VOCI), which gives a good description of excited states and is an INDO variant[51]. However, it yields an ionization set for PBQ, namely $\{I(\pi_-) < I(n_-) < I(\pi_+) < I(n_+)\}$, which is clearly discordant with those discussed above.

Dougherty and McGlynn[18], in 1977, recorded the He(I) PE spectrum of PBQ in both low and high resolution; they reported spectra for several derivatives (i.e. tetrafluoro-PBQ, 2,5-dimethyl-PBQ, tetramethyl-PBQ (duroquinone), tetrachloro-PBQ (chloranil) and 2,3-dichloro-5,6-dicyano-PBQ); they provided a generally accepted recalibration of the low-energy PBQ bands; and they analysed a number of vibrational structures. Using a composite molecule approach and empirical data for band shapes, vibronic structures and



(a)

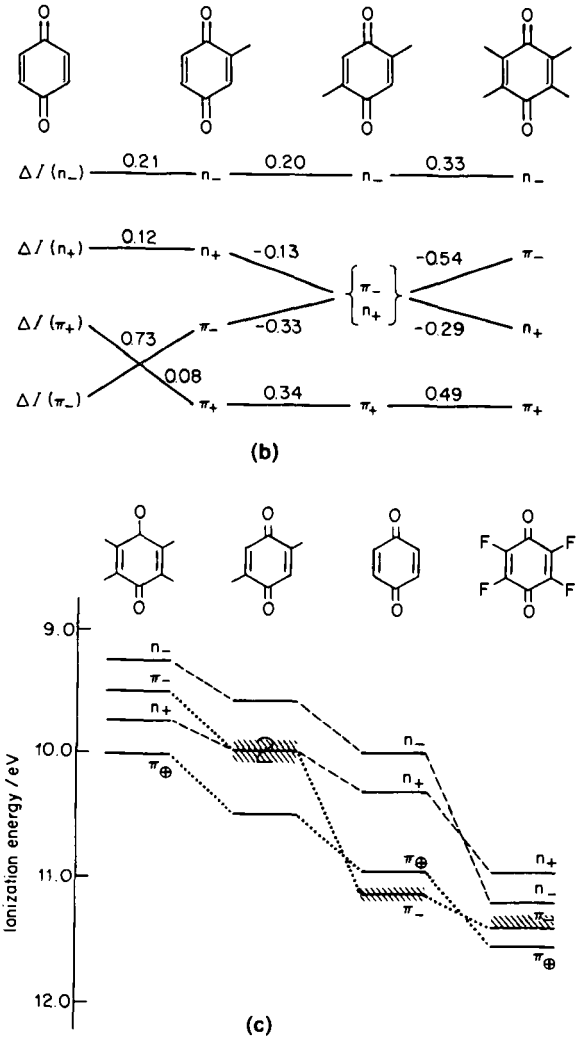


FIGURE 9. (a) The expanded scale He(I) photoelectron spectra of 1,4-benzoquinone, 2,5-dimethyl-1,4-benzoquinone, and tetramethyl-1,4-benzoquinone are given in the right side rectangle. Those of tetrafluoro-1,4-benzoquinone, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, and tetrachloro-1,4-benzoquinone are given in the left side rectangle. Vibrational spacings are indicated on the spectra[18]. (b) Schematic of the ionization energy differences between corresponding orbitals for 1,4-benzoquinone, toluquinone, 2,5-dimethyl-1,4-benzoquinone, and tetramethyl-1,4-benzoquinone[18]. (c) UPS correlation diagram for tetramethyl-1,4-benzoquinone, 2,5-dimethyl-1,4-benzoquinone, 1,4-benzoquinone and tetrafluoro-1,4-benzoquinone[18]

substituent shifts (Figure 9), these authors established the assignments $I(n_-) = 9.99 < I(n_+) = 10.29 < I(\pi_+) = 10.93 < I(\pi_-) = 11.1$ eV. In doing so, these authors aborted the details of their own CNDO/S calculations and placed primary reliance on empirical

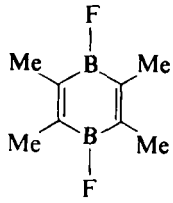
data correlations. This happenstance, however, seems not to have had much influence on succeeding computationists. As witness:

(1) Bigelow[19], in 1978, performed a CNDO/S calculation for PBQ and tetrafluoro-PBQ. He concluded, wrongly, that the assignment for PBQ was $I(n_-) < I(\pi_+) < I(\pi_-) < I(n_+)$ and for tetrafluoro-PBQ was $I(\pi_-) < I(\pi_+) < I(n_+) < I(n_-)$.

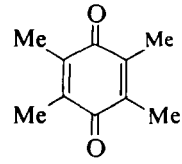
(2) Goodman and Brus[20] questioned the assignment of Dougherty and McGlynn[18] since they had found $|\Delta E(n_+ - n_-)| < 10^2\,cm^{-1}$ in the UV absorption spectrum, which they thought to be inconsistent with the 0.3 eV splitting observed (and assigned) in PES.

(3) Bloor and coworkers[21], using the MSX_α method, found the order $I(n) < I(\pi) < I(n) < I(\pi)$ for PBQ. They also noted that 'for the CNDO/S method, slight changes in geometry and/or the oxygen parameters enable one to change at will the order of the top four MOs'.

The PES spectra of PBQ and tetrafluoro-PBQ were recorded in 1979 by Åsbrink and coworkers[22] using He(II) excitation. They interpreted the spectrum using the semi-empirical MO method, HAM/3. For PBQ they found $I(n_-) < I(n_+) < I(\pi_+) \leqslant I(\pi_-)$ and for tetrafluoro-PBQ they found $I(n_+) < I(\pi_-) < I(n_-) < I(\pi_+)$, in agreement with Dougherty and McGlynn[18]. Bock and coworkers[23] reported spectra for the isoelectronic molecules 1,4-difluoro-2,3,5,6-tetramethyl-1,4-dibora-2,5-cyclohexadiene (B) and duroquinone (i.e. tetramethyl-PBQ):



B



tetramethyl-PBQ
(duroquinone)

Based on CNDO/F calculations, they obtained the following assignments $I(n_-) < I(n_+) < I(\pi_-) < I(\pi_+)$ (PBQ) and $I(n_-) < I(\pi_-) < I(\pi_+) < I(n_+)$ (duroquinone, B and its parent compound 1,4-difluoro-1,4-dibora-2,5-cyclohexadiene).

The ability of MO calculations to reproduce the UV spectra of PBQ was critically evaluated by Jacques and coworkers[24], their aim being to reparametrize the CNDO/S method and to resolve disagreements in the assignments of the low-energy ionizations. The parameters, which seemed to provide an adequate representation of the whole UV spectrum of PBQ and to improve the agreement between the calculated and experimental spectra of other carbonyl compounds as well, yielded the sequence $I(\pi_+) < I(\pi_-) < I(n_-) < I(n_+)$. The assignments of the PBQ spectrum, as given in Refs 19, 21 and 24, are compared in Figure 10.

Gleiter and coworkers[25a,b] discussed the relationship between tropoquinones and benzoquinones and quote the order $I(n_-) < I(n_+) < I(\pi_+) < I(\pi_-)$ for PBQ.

Bock and coworkers[26] produced the first evidence of PES nature for the formation of *p*-thiobenzoquinones. The thermal decomposition of 1,4-di(heteroallyl)-substituted benzenes ($H_2C{=}CH{-}CH_2X{-}C_6H_4X{-}CH_2{-}CH{=}CH_2$, with X = O or S) produces PBQ, monothio- or dithio-PBQ and 1,5-hexadiene in the gaseous phase. Because of the overlapping 1,5-hexadiene spectrum, only the two lowest-energy ionization events in dithio-PBQ, namely 8.5 and 9.1 eV, could be determined. Based on MNDO calculations, which for PBQ gave the order 10.9(n_-), 11.0(π_+), 11.2(π_-), 11.6(n_+), the assignment for the dithio-PBQ was given as $I(\pi_+) < I(n_-) < I(n_+) < I(\pi_-)$.

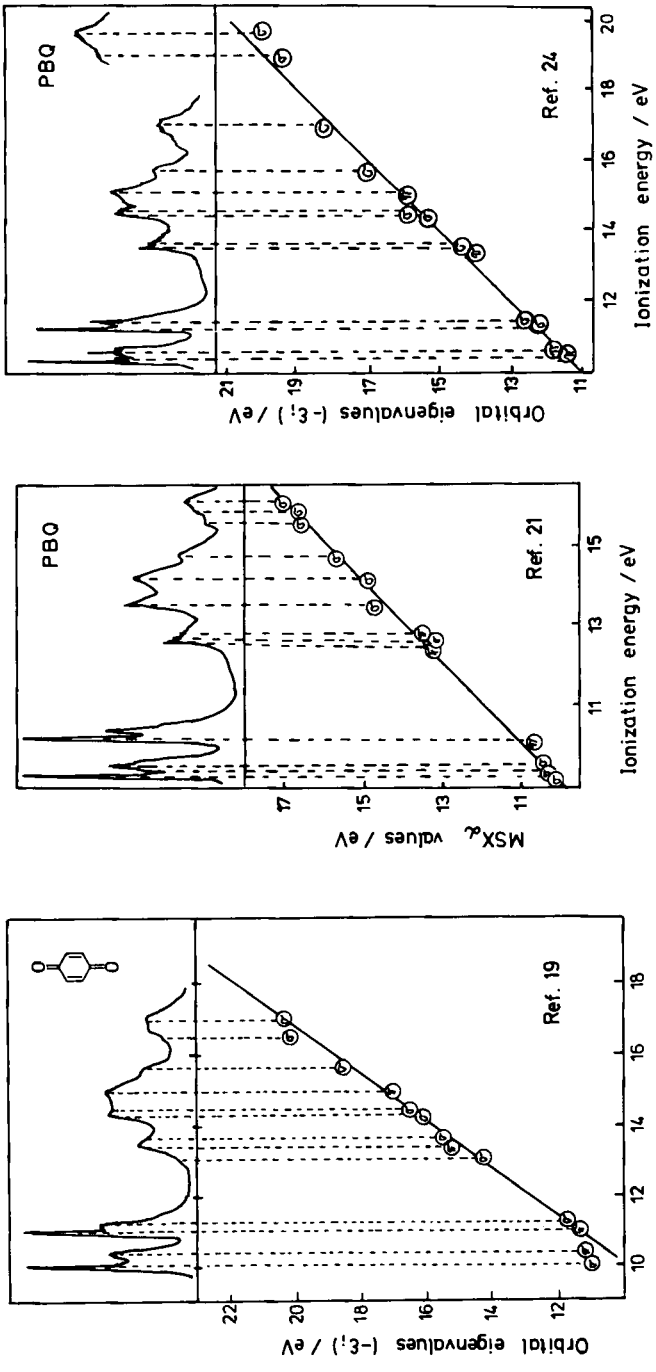


FIGURE 10. Alternative assignment of the photoelectron spectrum of PBQ, according to Refs. 19, 21 and 24. The orbital eigenvalues, leftmost and rightmost, are CNDO/S in nature. Those in the middle are MSX_α 'state' differences

Ha[27] reported extended CI calculations employing a gaussian set of double-zeta (DZ) quality for the ground, excited and ionized states of PBQ. The SCF calculations for the ground state (^1A_g) yielded the configuration

$$[\ldots\ (1b_{3u})^2(8a_g)^2(3b_{3g})^2(1b_{2g})^2(5b_{2u})^2(4b_{3g})^2(1b_{1g})^2(2b_{3u})^2]$$

and, therefore, $I(\pi_+) < I(\pi_-) < I(n_-) < I(n_+)$. A CI calculation was carried out for each state of interest, all single and double excitations of the valence shell electrons being included. The results are shown in Figure 11, in which the experimental ionization energies (EXPT) are compared with the calculated orbital energies, ε_i; with the SCF energy differences between the cations and ground state, ΔSCF; and with the CI energy differences between the cations and the ground state, ΔCI. The CI stage of calculation indicates that the effect of electron correlation is least for the two top π levels and that it effects a change of ionization order to one which remains unchanged in all multi-reference CI schemes which incorporate higher-order correlation (Davidson correction). This ordering, which is supported by experimental evidence, may not be obtained at the SCF level employing either Koopmans' theorem or the direct SCF differences between the ground state and the various cationic states. Thus, Ha's calculation indicates that the PBQ spectrum may be assigned $I(n_-) < I(n_+) < I(\pi_+) < I(\pi_-)$ when CI is imposed but that,

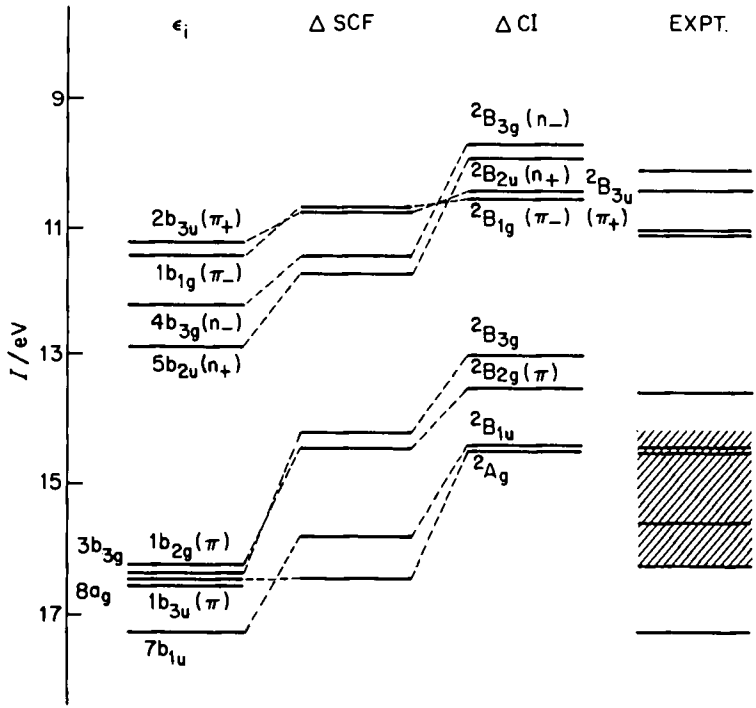
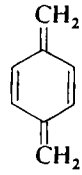


FIGURE 11. A comparison of the calculated ionization potentials in the SCF and CI levels with the experimental ionization energies, EXPT. ε_i is the orbital energy; ΔSCF is the SCF energy difference between the cations and the ground state; ΔSCI is the CI energy difference between the cations and the ground state. The hatched area stands for the PES region between 14.0 and 16.0 eV, which has an irregular fine structure

in the absence of CI, the MO order is probably $\varepsilon(\pi_+) > \varepsilon(\pi_-) > \varepsilon(n_-) > \varepsilon(n_+)$. Similar large changes of level ordering also take place in *p*-benzoquinodimethane as a result of CI (*vide infra*). Thus, to some extent at least, the root of the assignment problem has been uncovered.

VII. ALL ABOUT *p*-QUINODIMETHANE

The *p*-quinodimethanes can be defined[52] as even-membered, conjugated hydrocarbons. They are identical to the quinones except that $=CH_2$ groups replace the oxygens. *p*-Quinodimethane, for example, is understood to have the structure



(1)

It should be emphasized that *p*-quinodimethane is a colloquialism in the same way that 'quinone' is vernacular fo '*p*-benzoquinone'; other names are *p*-xylylene and *p*-benzoquinodimethane.

The He(I) photoelectron spectrum of *p*-(benzo)quinodimethane (**1**), as obtained by flash vacuum pyrolysis of [2,2]paracyclophane, was first analysed by Koenig and coworkers[53]. The PES of [2,2]paracyclophane had been reported by Pignataro and coworkers[54] and by Boschi and coworkers[55]. Contrary to [2,2]paracyclophane, which has a broad low-energy composite band (maximum at 8.00, shoulder at 8.5, sharp peak at 9.52 eV), the spectrum of **1** exhibits a sharp band at (7.87 ± 0.05) eV and a broad band at (9.7 ± 0.1) eV, the intensity ratio of these bands being 1:1.2. These latter bands have been assigned to the $^2B_{3u}$ and ($^2B_{1g} + {}^2B_{2g}$) states of the radical cation of **1**. However, an unperturbed $^2B_{2g}$ state, such as that assigned above, should lie at higher energy than a $^2B_{3g}$ state. Consequently, Koenig and coworkers[53] were forced to postulate that the energy of the $^2B_{2g}$ state was lowered by an interaction between ionic forms derived from both the quinoid and diradical structures that are present in the ground state. In effect, part of this broad band was assigned to a non-Koopmans, shake-up transition. This important and novel assignment was supported by Allan and coworkers[56], who showed that the valence bond (VB) scheme used by Koenig[53] was equivalent to a linear combination of bond orbitals (LCBO) model. In fact, the LCBO model yielded an excellent set of assignments for **1**.

State of 1^+	I_v (calc)/eV	I_v (obs)/eV
$^2B_{3u}$	7.94	7.87 ± 0.05
$^2B_{1g}$	9.80	9.7 ± 0.1
$^2B_{2g}$	10.00	
$^2B_{3u}$	12.86	(12.5?)

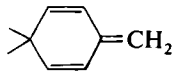
The LCBO model also performed equally well for anthraquinodimethane[56].

Tetracyanoquinodimethane (TCNQ) was the first derivative of **1** investigated by PES techniques: Ikemoto and coworkers[58] reported the gas phase spectrum; Grobman and

coworkers[59] reported the solid-state He(I) spectrum; and numerous authors[60,65,72] performed computations in an attempt to assign the spectrum. The available data for TCNQ are summarized in the Appendix. The agreement between experiment and theory seems to be satisfactory. The spectrum of TCNQ appears much like that of **1** but is displaced from it by ~ 1.4 eV because of the inductive effects of the CN groups[57].

The three lowest-energy ionizations of TCNQ appear to be of $I(\pi)$ nature. In addition, recent open-shell CNDO/S-CI calculations[72] indicate that, as in **1**, two non-Koopmans transitions, both of which arise from a mixing of the one-electron $b_{2g}(\pi)^{-1}$ Koopmans state and the non-Koopmans $b_{3u}(\pi)^{-1} \rightarrow 2b_{2g}(\pi^*)^{-1}$ valence excitation, should be observed at 11.44 and 12.84 eV. Being aware that such an assignment needs additional support, Koenig and Southworth[66] investigated the PES of 2,5-dimethyl-**1**, in which the accidental degeneracy of the second band might be expected to be removed. According to MO and structure representation (i.e. VB) arguments, dimethyl substitution should lower the energy of the first two ionization events (i.e. $^2B_{1u}$ and $^2B_{3g}$) but not that of the 'non-Koopmans' $^2B_{2g}$ state; thus, a weak band near 9.8 eV should evolve as a result of dimethylation. The PES spectrum of 2,5-dimethyl-**1** is shown in Figure 12. It actually exhibits the expected low-intensity band. However, these deductions did not go uncriticized: Dewar[67], for example, preferred the supposition that the weak bands were impurity related. However, in the interim, the evidence for non-Koopmans transitions has grown, even in simple conjugated hydrocarbons[68] such as were particularly questioned by Dewar.

In a subsequent work, Koenig and coworkers[69] showed that their assumption of non-Koopmans behavior for **1** and 2,5-dimethyl-**1** was supported by HAM/3-CI calculations. Bigelow[70–72] also studied the breakdown of Koopmans behavior in the PES of selected organic molecules such as 2,5-dimethyl-**1**, **1** and TCNQ as well as benzene, xylene, *s-trans*-1,3-butadiene, *p*-nitroaniline, *trans*-stilbene and acrolein, all within a semiempirical, open-shell RHF-CNDO/S(CI) approximation. Schulz and coworkers[73] investigated the low-energy non-Koopmans ion states of unsaturated hydrocarbons using a semiempirical PERTCI approach for **1**, *o*-xylylene, *iso*benzofulvene, *iso*benzofulvalene, 2,2-dimethyl-*iso*indene, benzocyclobutadiene, butadiene and 1,1,4,4-tetrafluorobutadiene. Their results[73] support the existence of non-Koopmans' shake-up ionizations in **1** and tetrafluorobutadiene and suggest their occurrence in certain new cases (*iso*benzofulvene, *iso*benzofulvalene and benzocyclobutadiene, for example) in which, unfortunately, the predicted intensities are so low as to inhibit observation. Finally, it has been shown for 2,2-dimethyl*iso*indene[74] and for 4,4-dimethyl-1-methylidene-2,5-cyclohexadiene[75] that the lowest-energy excited ion state is almost surely of non-Koopmans nature.



An *ab initio* SCF CI study of the ground and excited states of **1** was recently performed by Ha[76]. The results demonstrate that configuration mixing is as important to proper interpretation of the low-energy PES region as it is to the inner-valence, high-energy XPS region. A comparison of experiment with the calculated ionization energies at the SCF and CI stages is shown in Figure 13. Thus, the first ionization potential corresponds to

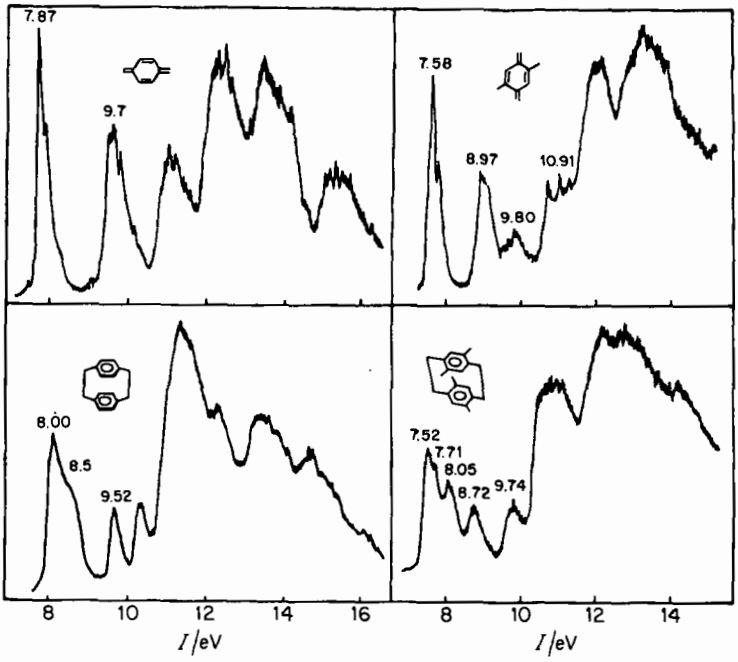


FIGURE 12. He(I) photoelectron spectra of *p*-benzoquinodimethane (**1**, upper left), 2,5-dimethyl-**1** (upper right), and of their corresponding paracyclophane precursors (below), according to Refs 53 and 66

ionization from a π-type b_{3u} orbital ($\Delta CI = 7.12$ eV; EXPT = 7.78 eV). Of the next two bands, the low-energy ~ 10 eV component corresponds to a π ionization from a $1b_{1g}$ orbital ($\Delta CI = 9.27$ eV) and the higher-energy 11 eV component to a σ ionization from the $4b_{3g}$ orbital ($\Delta CI = 11.68$ eV). The remaining two components represent the first[53] and second non-Koopmans states of PBQ. The *ab initio* CI results indicate clearly that the high-energy, low-intensity flanks of the second and third PES bands are best ascribed to shake-up ionizations. Thus, the PES problem for **1** is resolved, much as for PBQ.

VIII. THE *o*-QUINONOIDS

The PES of the *o*-quinonoids are simple and readily interpretable. The reasons are:

(1) The spectra of the *o*-quinones are closely related to those of the unsaturated α-diketones: the dicarbonyl and conjugated hydrocarbon moieties behave almost additively and interact little if at all.

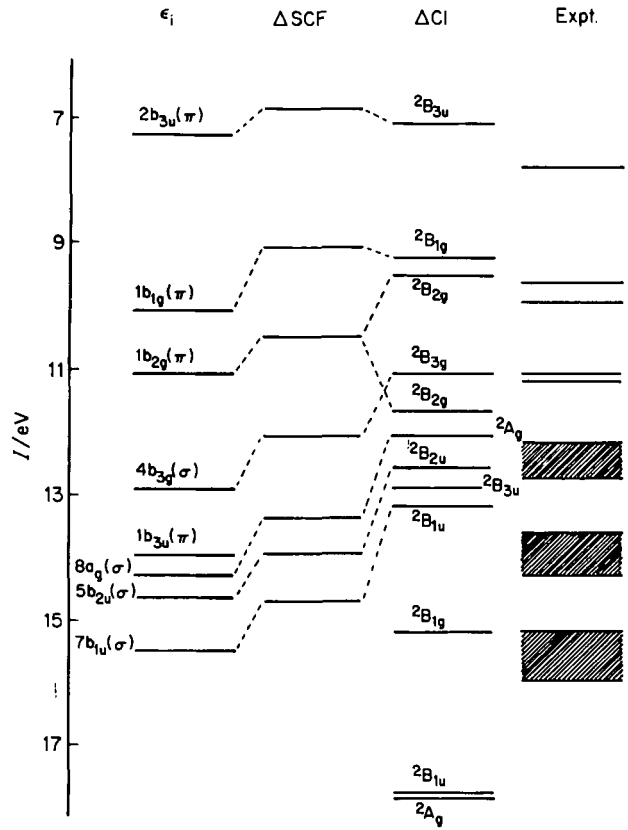


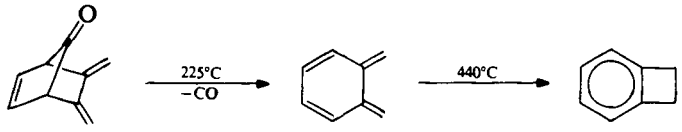
FIGURE 13. Comparison of experiment (EXPT) with the calculated ionization energies, where the ϵ_i are orbital energies, the ΔSCF are the energy differences between the SCF ground and cationic states, and the ΔCI are energy differences between the configurationally interacted ground and cationic states[76]

(2) A vast PES literature for α-dicarbonyls, saturated and unsaturated, has been amassed during the last decade[77] and the spectra are well understood.

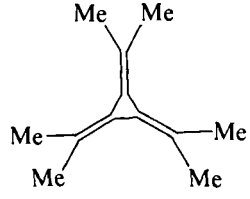
(3) Most PES for *o*-quinonoids were recorded latterly, at a time when the occurrence of non-Koopmans transitions was already widely known. That is, the *o*-quinonoids—being unstable, highly reactive or transient species in thermal and photochemical reactions—required special synthetic, handling and recording techniques prior to PES measurements.

Three research groups have been heavily involved in the study of *o*-quinonoids: those of Professors Koenig (Eugene), Gleiter (Heidelberg) and Schweig (Marburg). Each of these groups have developed sophisticated methods for the preparation and measurement of such compounds, among them vacuum flash pyrolysis[78] and variable temperature spectroscopy (VTPES)[79]. However, the first PES report for an *o*-quinonoid was the study of the orbital sequence in fulvene and 3,4-dimethylcyclobutene by Heilbronner and coworkers[80]. Clark and coworkers[81] also reported the PES of benzo(c) thiophene, 2,1,3-benzothiadiazole and benzofurazan.

Flynn and Michl[82a] were the first to prepare *o*-xylylene. Although they did not make PES measurements, their synthesis, calculations and electronic spectroscopic data were important to all the later work on *o*-quinonoids. The PES spectrum of *o*-xylylene was not reported until 1984 by Schweig's group[82b] since earlier attempts to generate and detect it by VTPES produced benzocyclobutene; the problem of the fast unimolecular consecutive reaction to this end product was solved by using 5,6-dimethylene bicyclo[2.2.1]hept-2-en-7-one as the precursor compound.



Tri*iso*propylidenecyclopropane (**2**) may be supposed to be a multiple *o*-quinonoid. Its PES was recorded, discussed and compared with the MO data for the parent unsubstituted 3-radialene by Bally and Haselbach[83].



(**2**)

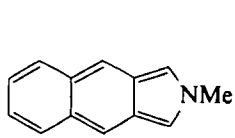
Palmer and Kennedy[84] reported PES data for benzo(c)furan (**4**), benzo(c)thiophene (**5**), and *N*-methyl*iso*indole (**6**), which are the quinonoid isomers of the benzo derivatives of five-membered ring heterocycles related to naphthalene (**3**):

(**3**) (**4**) (**5**) (**6**)

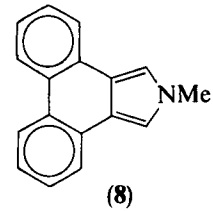
Correlation with the PES of naphthalene led to assignment of the first three π ionizations in **3**–**6** as

$$I_1(\mathbf{6}) < I_1(\mathbf{5}) < I_1(\mathbf{4}) < I_1(\mathbf{3}) < I_2(\mathbf{6}) < I_2(\mathbf{3}) = I_2(\mathbf{5}) < I_3(\mathbf{6}) = I_2(\mathbf{4}) < I_3(\mathbf{5}) = I_3(\mathbf{3}) < I_3(\mathbf{4})$$

Rettig and Wirz[85] investigated the PES of **6** and its higher analogs **7** and **8**:

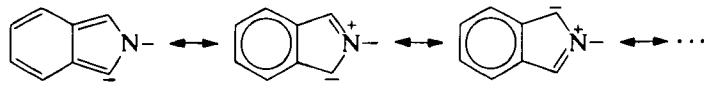


(7)



(8)

They concluded that any description based on a single *o*-quinoid structure was inadequate and that the inclusion of zwitterionic structures such as



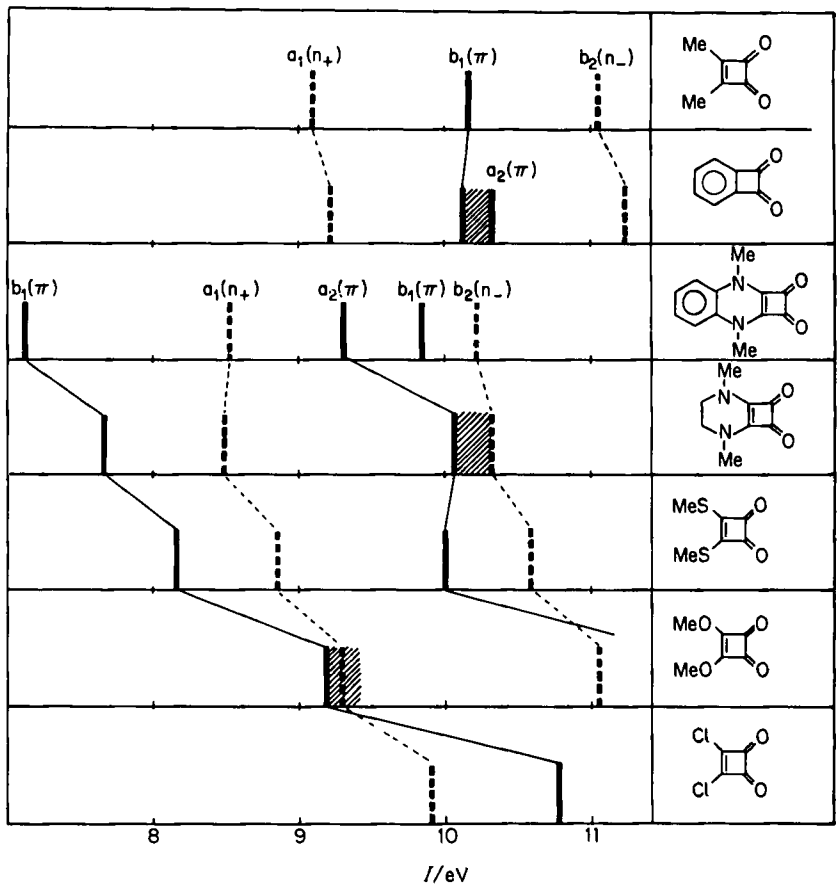
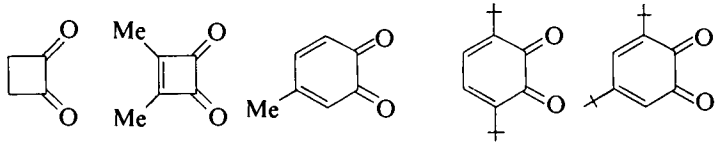


FIGURE 14. The assignment for and correlation diagram of some cyclobutene-1,2-dione derivatives[91]

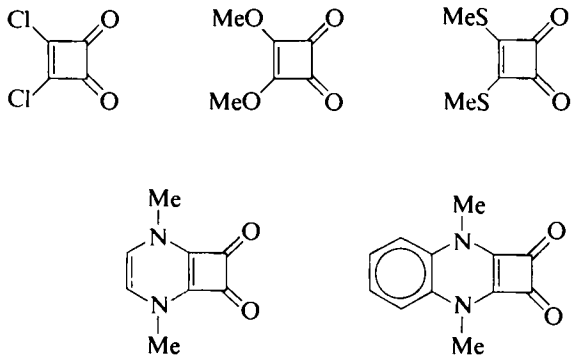
was mandatory.

The PES of *o*-benzoquinone (OBQ), first reported by Koenig and coworkers[86] was later studied by Eck and coworkers[87] and by Schang and coworkers[88]. The assignment, using MNDO(PERTCI) and MINDO/3 calculations, yields the order[87,88]: $I(n_+) < I(\pi) < I(n_-) < I(\pi)$.

Schang and coworkers[88] also reported the PES of cyclobutene-1,2-dione (CBD), some of its derivatives and certain OBQ derivatives:

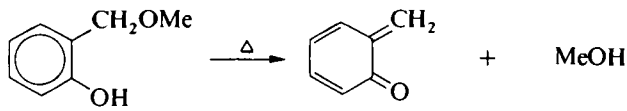


The assignments[89,90] of some of these PES data are shown in Figure 14. Gleiter and coworkers[91] also reported PES data for several squaric acid derivatives:



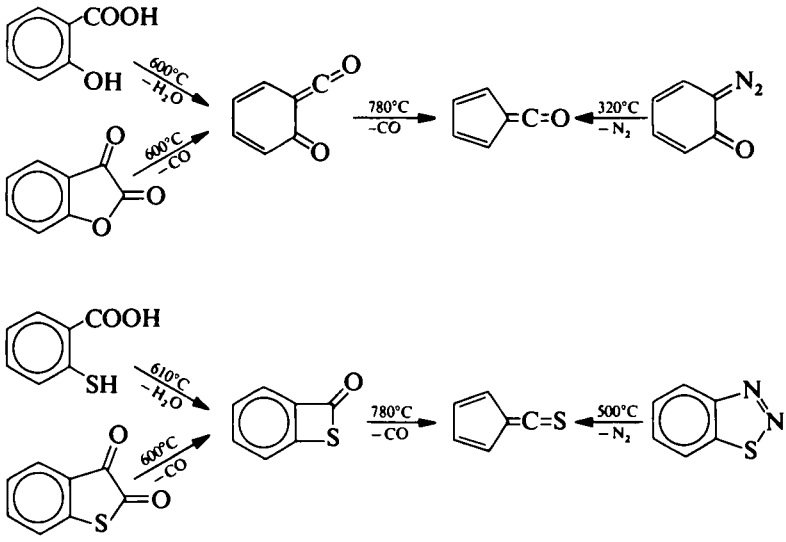
as well as that of benzocyclobutenedione and CBD. The interpretation of these[89,91] is also shown in Figure 14.

Eck and coworkers[92] reported the PES of *o*-benzoquinone methide generated by pyrolysis of 2-hydroxybenzyl methyl ether in a heated and temperature-controlled target chamber:

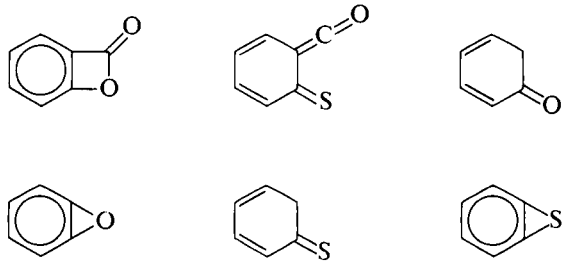


The spectra of the pyrolysis products, recorded over the range 100–600 °C, led, at 500 °C, to a new spectrum with bands at 8.80(π), 9.37(π), 10.63(π) and 12.02(π) eV.

Schulz and Schweig[93] carried out the following reactions in the PES mode:

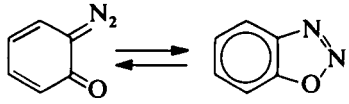


The spectra of the reaction products were recorded and their structure confirmed using computed[94] MNDO-optimized structures and large configuration interaction (PERTCI) calculations based on CNDO/S wave functions. The possible reaction products

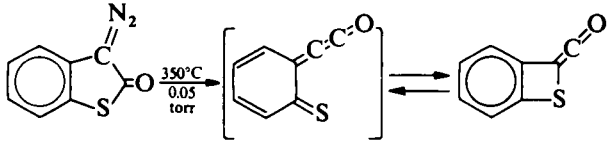


were excluded on the basis of disagreements between the calculated and observed spectral patterns.

Schweig and coworkers investigated the reactions:



Ref. 95



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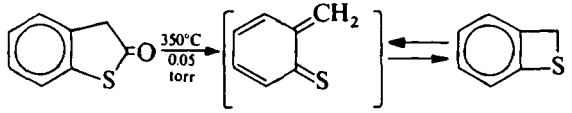

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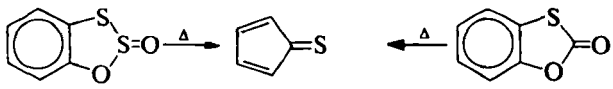
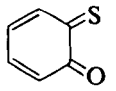
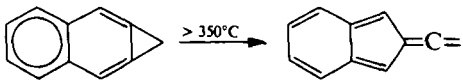


Ref. 97

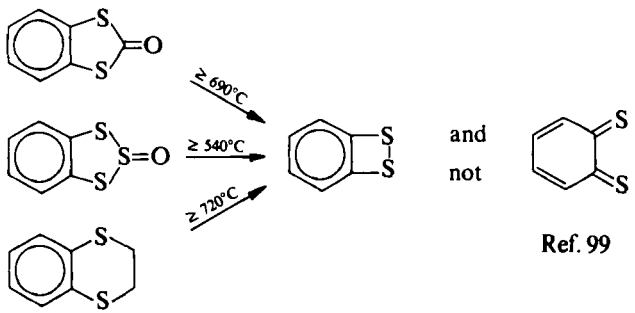
with



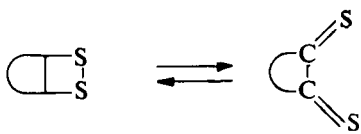
as a postulated reactive intermediate[97]. They also investigated the processes



Ref. 98



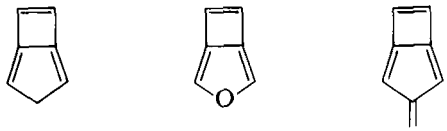
Ref. 99



Ref. 100

The formation of an *o*-quinonoid compound was generally observed for quinones and quinone methides whereas formation of a four-membered ring was preferred when a sulfur atom was present.

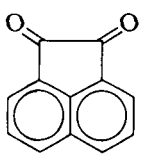
Schweig and coworkers investigated the PES of the *o*-quinonoids: bicyclo[3.2.0]hepta-1,4,6-triene (BHT), its analog furocyclobutadiene (FCB)[101] and *iso*benzofulvene (IBF)[102]. The PES of these and a large number (> 100) of other molecules have recently[103] been calculated using the semiempirical methods: MNDO, MNDO PERTCI, CNDO/S, CNDO/S PERTCI, LNDO/S and LNDO/S PERTCI; and the results have been correlated with the experimental data.



BHT FCB IBF

Gleiter and coworkers[25a,b] measured the PES of cyclopentene-1,2,3-trione, *o*-tropoquinone and *p*-tropoquinone. By comparison with related molecules and MINDO/S calculations, the low-energy ionization events in these compounds were assigned. These assignments are given in Figure 15. They provide an interesting insight into the distinct relatedness of the electronic structures of the benzoquinones and tropoquinones. Gleiter and coworkers[104-107] have also discussed the PES of several other quinonoid molecules.

Very little research has been invested in higher 'classical' quinones, ones such as those that would be generated by the oxidation of polycyclic aromatic hydrocarbons (PAHs). This, perhaps, is not too surprising. Most of these compounds are thought to be potent carcinogens and, in addition, their melting points may be too high to permit easy PES measurements. One such rare investigation is the work of Bigotto and coworkers[108] on acenaphthenequinone (ANQ) and naphthalic acid (i.e. naphthalene-1,8-dicarboxylic acid) derivatives, namely naphthalic anhydride, naphthalimide and *N*-methylnaphthalimide. The lowest-energy π-ionization events in these compounds were assigned using a Pariser–Parr–Pople SCF approach. The assignment of the two n ionizations then followed from band intensity and band shape data and by reference to results for phthalic anhydride, phthalimide and various cyclic 1,2- and 1,3-dicarbonyl compounds. For ANQ, the following results were obtained.



ANQ

Expt/eV	Calc/eV	Assignment
8.77	8.69	$\pi(a_2)$
8.77		n_+
9.53	9.48	$\pi(b_1)$
10.60	10.44	$\pi(b_1)$
10.60		n_-
11.48	11.40	$\pi(a_2)$

IX. CONCLUSION

Although much work has been invested in the photoelectron spectroscopy of quinonoids, one retains the impression that the task is grossly incomplete and heavily concentrated on but a few topics (e.g. *p*-benzoquinone and *p*-(benzo)quinodimethane and their derivatives; small, mostly unstable compounds or transients of quinoid structure). However, despite the paucity of XPS data, one may conclude that quinonoids behave normally. That is, their XPS spectra, for the most part, are predictable using standard computational schemas.

The more extensive parts of the UPS work has been put to some stringent tests: (1) to determine the electronic structure of a given compound; (2) to test calculation methods; and (3) to identify new (unknown) molecules and their structure from PES spectra. While good success has been achieved with (3) and moderate success with (2), topic (1) has proven to be highly unsatisfactory. There is no doubt that *o*-quinonoids, being essentially α-diketones (or analogs of them) are easy to assign because the interactions are short-range

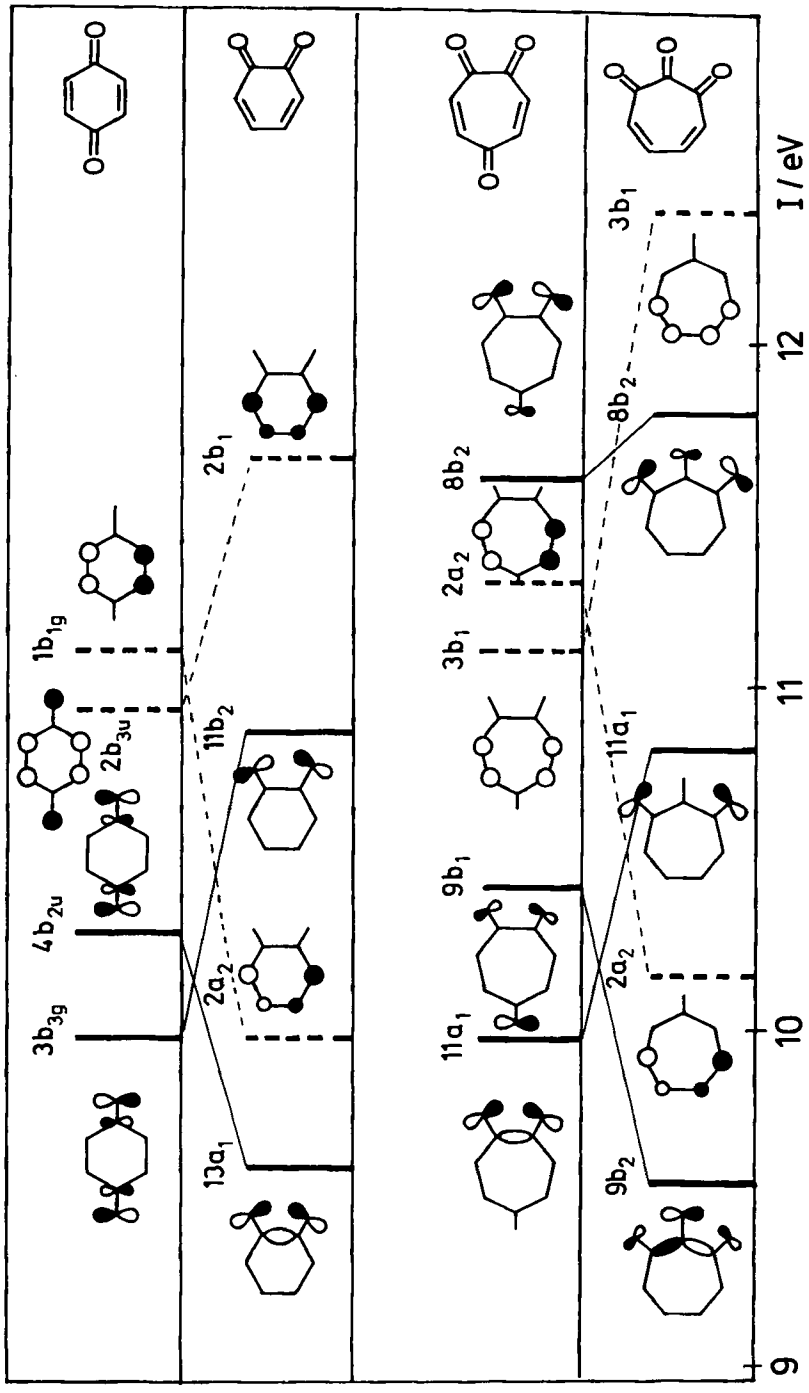
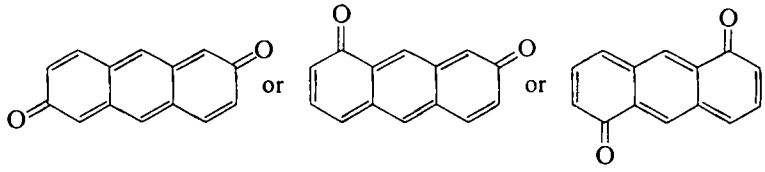


FIGURE 15. Relatedness of electronic structures of the benzoquinones and tropoquinones

and quantum chemistry knows how to handle them. However, severe problems surface in the *p*-quinonoids. So much so, that after 30 years of work on PBQ, a leading researcher feels moved to write: 'The assignment of the PE spectrum of PBQ is, however, still a matter of controversy and therefore our assignments must remain tentative'[109]. Finally, it must be stressed that the *o*- and *p*-quinonoids are but a small subdivision of this whole class of molecules and that other very interesting questions can be asked: what, for example, is the nature of the interaction of lone pairs in



and is it large or small?

PES data for steroids[109, 110] suggest that long-range interaction is strongly promoted by the localized double bonds that lie between the carbonyl groups. Indeed, there is some experimental evidence that such interactions can be promoted over numerous saturated (single) bonds[111-121]. No such work, interesting though it might be, exists for quinonoids.

A compilation of data are given in the Appendix. This compilation includes the experimental ionization data, the assignments made on the basis of various computational schemas and experimental data relating to vibrational structure (where available).

X. APPENDIX

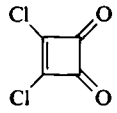
A. Compilation of Data

(in cooperation with Dr. B. Kovač, Rudjer Bošković Institute, Zagreb)

This part in the form of a table covers the data published on the subject UPS of quinonoids using the following format:

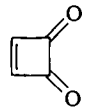
Structural formula of compound	**Sum formula**	**Symmetry**	
I/eV: ionization energy in electronvolts (*comment on experimental details*)	Reported values and assignment if given empirically	Reference number	
$-\varepsilon_i$/eV: Negative calculated MO energy in electronvolts (*basis for assignment*)	Reported values and assignment if given in the publication	Type of calculation	Reference number
ν/cm^{-1}: Observed vibrational structure in wavenumbers	Reported values of vibrational spacings		

If several entries are from same reference number this is indicated only on the first entry.



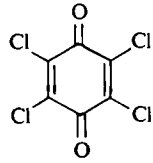
$C_4Cl_2O_2$ C_{2v}

I/eV:	9.89	10.78	12.04			91
$-\varepsilon_i$/eV:	9.65 $a_1(n_+)$	10.21 $b_1(\pi)$	10.81 $b_2(n_-)$		MINDO/3	



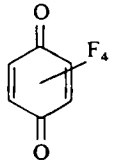
$C_4H_2O_2$ C_{2v}

I/eV:	9.79	11.55	11.87	13.61		88
$-\varepsilon_i$/eV:	9.35 $a_1(n_+)$	11.05 $b_1(\pi)$	10.71 $b_2(n_-)$	13.74 $a_2(\pi)$	MINDO/3	
	8.22 $a_1(n_+)$	8.92 $b_1(\pi)$	11.08 $b_2(n_-)$	11.88 $a_2(\pi)$	STO-3G	



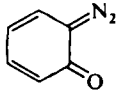
$C_6Cl_4O_2$ D_{2h}

I/eV:	9.90 $b_{3g}(n_-)$	10.1 $b_{2u}(n_+)$	10.65 b_{1g} & $b_{3u}(\pi)$	10.8	11.0	18
ν/cm^{-1}:	1300					
	(correlative study; substituent effects)					



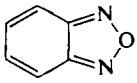
$C_6F_4O_2$ D_{2h}

I/eV:	10.72 π	11.18 π	14.82	15.0 n_u	15.96 n_g	5, 9
	(assignment based on perfluoro effect)					
I/eV:	10.96 $b_{2u}(n_+)$	11.21 $b_{3g}(n_-)$	11.31 $b_{1g}(\pi)$	11.53 $b_{3u}(\pi)$		18
ν/cm^{-1}:	1650	1350		1700		
	(correlative study; substituent effects)					
$-\varepsilon_i$/eV:	11.47 $b_{1g}(\pi)$	11.58 $b_{3u}(\pi)$	12.17 $b_{2u}(n_+)$	12.63 $b_{3g}(n_-)$	CNDO/S	19
$-\varepsilon_i$/eV:	11.1 $b_{1g}(\pi)$	11.3 $b_{3g}(n_-)$	11.3 $b_{2u}(n_+)$	11.4 $b_{3u}(\pi)$	HAM/3	22



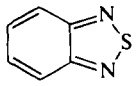
$C_6H_4N_2O$ C_s

I/eV:	8.20					95
$-\varepsilon_i$/eV:	8.10 a (π)	9.18 a' (n_-)	10.15 a (π)	11.82 a (π)	CNDO/S	
	8.50 a (π)	9.79 a' (n_-)	9.95 a (π)	11.30 a (π)	MNDO–PERT–CI	



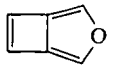
$C_6H_4N_2O$ C_{2v}

I/eV:	9.37 $a_2(\pi)$	10.44 $b_2(\pi)$	11.18 $a_1(n_+)$	11.58 $a_2(\pi)$	12.0 $b_1(n_-)$	81
	(assignment based on band shapes and semiempirical calculations)					



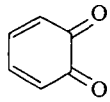
$C_6H_4N_2S$ C_{2v}

I/eV:	$8.98\,a_2(\pi)$	$9.52\,b_2(\pi)$	$10.64\,a_1(n_+)$	$11.31\,a_2(\pi)$	$11.6\,b_1(n_-)$		81
	(assignment based on band shapes and semiempirical calculations)						



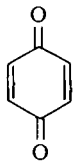
C_6H_4O C_{2v}

I/eV:	$8.05\,b_1(\pi)$	$8.95\,a_2(\pi_2)$	$11.40\,a_1(\sigma)$	11.85			101
	(based on MNDO PERTCI)						



$C_6H_4O_2$ C_{2v}

I/eV:	9.6	9.99	11.0	12.3			86
I/eV:	9.55	9.89	10.78	12.12			87
$-\varepsilon_i$/eV:	$9.72\,a_1(n)$	$10.07\,a_2(\pi)$	$11.67\,b_1(n)$	$11.95\,b_1(\pi)$		MNDO	
	$9.20\,a_1(n)$	$9.63\,a_2(\pi)$	$10.98\,b_2(n)$	$12.27\,b_1(\pi)$		CNDO/S	
I/eV:	9.60	9.98	10.88	12.16			88
$-\varepsilon_i$/eV:	$9.18\,a_1(n_+)$	$9.84\,a_2(\pi)$	$10.84\,b_1(n_-)$	$12.25\,b_1(\pi)$		MINDO/3	



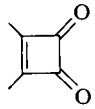
$C_6H_4O_2$ D_{2h}

I/eV:	9.67						1a
I/eV:	9.68						1c
I/eV:	$10.11\,n_g$	$10.41\,\pi_4$	$11.06\,n_u$	$11.5\,\pi_3$			9
	(assignment based on the perfluoro effect and CNDO/2)						
$-\varepsilon_i$/eV:	$9.92\,b_{1g}(n)$	$10.61\,b_{2u}(n)$	$10.91\,b_{1u}(\pi)$	$11.03\,b_{3g}(\pi)$	$14.31\,a_g(\sigma)$	CNDO–CI	10
$-\varepsilon_i$/eV:	$9.89\,b_{1g}(n)$	$10.58\,b_{2u}(n)$	$11.16\,b_{1u}(\pi)$	$11.48\,b_{3g}(\pi)$	$11.83\,a_g(\sigma)$	MINDO/2	11
$-\varepsilon_i$/eV:	$10.21\,b_{3g}(n)$	$10.51\,b_{2u}(n)$	$11.03\,b_{3u}(\pi)$	$11.12\,b_{1g}(\pi)$	$13.72b_{2g}(\pi)$	PPP	12
I/eV:	$10.01\,b_{3g}(n)$	$10.29\,b_{3u}(\pi)$	$10.96\,b_{2u}(n)$	$11.16\,b_{1g}(\pi)$		CNDO/2	13
	(assignment based on CNDO/2)						
I/eV:	10.11	10.41	11.06	11.25			14
$-\varepsilon_i$/eV:	$10.51\,b_{3u}(\pi_1)$	$10.60\,b_{3g}(n_-)$	$11.03\,b_{2u}(n_+)$	$11.08\,b_{1g}(\pi_2)$		CNDO/S	
$-\varepsilon_i$/eV:	$9.36\,b_{3g}(n_-)$	$9.67\,b_{2u}(n_+)$	$10.22\,b_{3u}(\pi_1)$	$10.89\,b_{1g}(\pi_2)$		CNDO/S-CI	
$-\varepsilon_i$/eV:	$10.91\,b_{1u}$	$11.37\,b_{2g}$	$11.75\,b_{1g}$	$12.35\,b_{3u}$	$14.91\,b_{3g}$	*ab initio*	15a
	$10.42\,b_{1u}$	$10.53\,b_{2g}$	$11.04\,b_{1g}$	$11.23\,b_{3u}$	$14.20\,b_{3g}$	ΔSCF–D_{2h}	
	$8.60\,b_1$	$8.60\,a_2$	$10.06\,a_1$	$10.06\,b_1$	$13.40\,a_1$	ΔSCF–C_{2v}	
$-\varepsilon_i$/eV:	$8.30\,b_{1u}$	$9.23\,b_{1g}$	$9.67\,b_{2g}$	$9.95\,b_{3u}$		*ab initio*	15b
$-\varepsilon_i$/eV:	$11.62\,b_{3g}(\pi)$	$11.90\,b_{3g}(n_-)$	$12.17\,b_{2u}(n_+)$	$12.50\,b_{1g}(\pi)$	$15.58\,b_{3g}(\sigma)$	CNDO/2	16
I/eV:	$9.99\,b_{3g}(n_-)$	$10.29\,b_{2u}(n_+)$	$10.93\,b_{3u}(\pi)$	$11.1\,b_{1g}(\pi)$			18
ν/cm^{-1}:	725	700	1600				
	1500						
	(correlative study; substituent effects)						

$-\varepsilon_i$/eV:	$11.17\,b_{3g}(n_-)$	$11.17\,b_{3u}(\pi)$	$11.20\,b_{1g}(\pi)$	$11.76\,b_{2u}(n_+)$	$14.35\,a_g(\sigma)$	CNDO/S	19
I/eV:	9.99	10.29	10.93	11.0	13.5		22
	14.3	14.8	14.9	15.0	15.5		
	16.2	16.7	17.0	19.5	20.1		
	(He(I) and He(II) values)						
$-\varepsilon_i$/eV:	$10.04\,b_{3g}(n_-)$	$10.50\,b_{2u}(n_+)$	$10.95\,b_{1g}(\pi)$	$11.01\,b_{3u}(\pi)$	$13.53\,b_{3g}(\sigma)$	HAM/3	
$-\varepsilon_i$/eV:	$11.14\,b_{3u}(\pi)$	$11.40\,b_{1g}(\pi)$	$11.90\,b_{3g}(n_-)$	$12.58\,b_{2u}(n_+)$	$14.06\,b_{2g}(\pi)$	opt. CNDO/S	24
$-\varepsilon_i$/eV:	$10.9\,n_-$	$11.0\,\pi_1$	$11.2\,\pi_2$	$11.6\,n_+$	$14.5\,\pi_3$	MNDO	26
$-\varepsilon_i$/eV:	$10.64\,b_{1g}(\pi)$	$10.67\,b_{3u}(\pi)$	$11.44\,b_{3g}(n_g)$	$11.67\,b_{2u}(n_u)$		ΔE(SCF)	27
	$9.59\,b_{3g}(n_g)$	$9.85\,b_{2u}(n_u)$	$10.35\,b_{3u}(\pi)$	$10.55\,b_{1g}(\pi)$		ΔE(CI)	
	$9.84\,b_{3g}(n_g)$	$10.10\,b_{2u}(n_u)$	$10.32\,b_{3u}(\pi)$	$10.50\,b_{1g}(\pi)$		ΔE(CI′)	
	$9.06\,b_{3g}(n_g)$	$9.26\,b_{2u}(n_u)$	$10.35\,b_{3u}(\pi)$	$10.50\,b_{1g}(\pi)$		ΔE(CI″)	

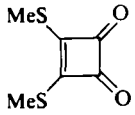
C_6H_6 C_{2v}

I/eV:	8.8	9.44	11.5	12.3	13.3	14.1	80
$-\varepsilon_i$/eV:	$11.02\,b_1(\pi)$	$11.66\,a_2(\pi)$	$14.86\,a_1(\sigma)$	$15.56\,b_2(\sigma)$	$16.41\,b_1(\pi)$	SCF-LCAO-MO	



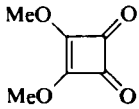
$C_6H_6O_2$ C_{2v}

I/eV:	9.10	10.18	11.05	13.08			88.91
$-\varepsilon_i$/eV:	$9.11\,a_1(n_+)$	$10.11\,b_1(\pi)$	$10.24\,b_2(n_-)$	$13.49\,a_2(\pi)$		MINDO/3	
	$7.78\,a_1(n_+)$	$7.87\,b_1(\pi)$	$10.59\,b_2(n_-)$	$11.56\,a_2(\pi)$		STO-3G	



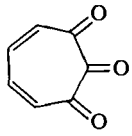
$C_6H_6O_2S_2$ C_{2v}

I/eV:	8.18	8.87	10.02	10.60			91
$-\varepsilon_i$/eV:	$8.91\,b_1(\pi)$	$8.91\,a_1(n_+)$	$10.04\,a_2(\pi)$	$9.48\,b_2(n_-)$		MINDO/3	



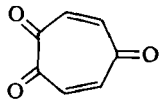
$C_6H_6O_4$ C_{2v}

I/eV:	9.20	9.30	11.05				91
$-\varepsilon_i$/eV:	$8.80\,b_1(\pi)$	$9.02\,a_1(n_+)$	$10.48\,b_2(n_-)$			MINDO/3	



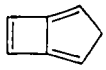
$C_7H_4O_3$ C_{2v}

I/eV:	9.55	10.16	10.82	11.8	12.4		25a, b
$-\varepsilon_i$/eV:	9.21 b_2(n)	10.07 $a_2(\pi)$	10.67 a_1(n)	11.59 b_2(n)	12.43 $b_1(\pi)$	MINDO/3	



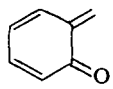
$C_7H_4O_3$ C_{2v}

I/eV:	9.98	10.42	11.1	11.3	11.6		25a, b
$-\varepsilon_i$/eV:	9.67 a_1(n)	10.24 b_2(n)	11.12 $b_1(\pi)$	11.16 $a_2(\pi)$	11.31 b_2(n)	MINDO/3	



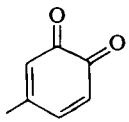
C_7H_6 C_{2v}

I/eV:	8.41 $b_1(\pi_1)$	8.93 $a_2(\pi_2)$	10.75 $a_1(\sigma)$	> 12.0			101



C_7H_6O C_s

I/eV:	8.80	9.37	10.63	12.02			92
$-\varepsilon_i$/eV:	8.56 π	9.40 n	10.78 π	11.85 π		PERTCI(CNDO/S)	

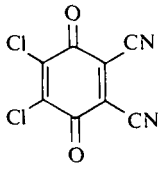


$C_7H_6O_2$ C_s

I/eV:	9.78 n	10.17 n	10.37 π	10.85 π	13.1		13
	(based on correlation with PBQ and 2,5-dimethyl-PBQ)						
$-\varepsilon_i$/eV:	9.8 $b_{3g}(n_-)$	10.3 $b_{2u}(n_+)$	10.4 $b_{1g}(\pi)$	10.8 $b_{3u}(\pi)$		HAM/3	22
	(symmetry of PBQ)						
I/eV:	9.40	9.72	10.70	11.65			88
$-\varepsilon_i$/eV:	9.12a' (n+)	9.72a" (π)	10.76a' (n−)	11.60a" (π)		MINDO/3	

C_7H_8 C_s

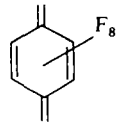
I/eV:	8.34a" (π)	9.12a" (π)	11.1				104
	(supported by the results of MINDO/3)						



$C_8Cl_2N_2O_2$ C_{2v}

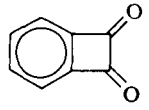
I/eV:	10.58 $b_2(n_-)$	10.76 $a_1(n_+)$	11.20 $b_1(\pi)$	11.4 $b_1(\pi)$	11.58	12.4	18
ν/cm^{-1}:	1200/1450	1200			1350, 1750		

(correlative study; substituent effects)



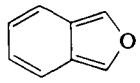
C_8F_8 D_{2h}

$-\varepsilon_i$/eV:	9.0 $b_{3u}(\pi)$	10.3 $b_{1g}(\pi)$	12.0 $b_{2g}(\pi)$	12.4 (π)	13.6 (σ)	ΔE_{CI}	69



$C_8H_4O_2$ C_{2v}

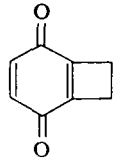
I/eV:	9.23	10.14	10.43	11.23		91
$-\varepsilon_i$/eV:	9.03 $a_1(n_+)$	9.77 $b_1(\pi)$	9.93 $a_2(\pi)$	10.25 $b_2(n_-)$	MINDO/3	



C_8H_6O C_{2v}

$-\varepsilon_i$/eV:	8.06 $a_2(\pi)$	10.89 $b_1(\pi)$	11.53 $a_2(\pi)$	14.58 $b_1(\pi)$	14.71 $b_2(\sigma)$	*ab initio*	84

(also given PE spectrum without values)

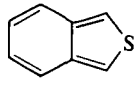


$C_8H_6O_2$ D_{2h}

I/eV:	9.64 n_-	9.9 n_+	10.1 π	10.78 π		107

(assignment based on correlation with PBQ and duroquinone)

$-\varepsilon_i$/eV:	9.30 $b_2(n_-)$	9.81 $a_1(n_+)$	10.05 $b_1(\pi)$	10.86 $b_1(\pi)$	MINDO/3	



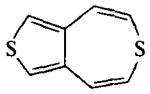
C_8H_6S C_{2v}

I/eV:	7.75 $a_2(\pi)$	8.9 $b_2(\pi)$	9.9 $a_2(\pi)$	11.33 $a_1(\sigma)$		81

(assignment based on band shapes and semiempirical calculations)

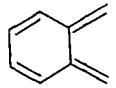
$-\varepsilon_i$/eV:	7.84 $a_2(\pi)$	9.69 $b_1(\pi)$	11.29 $a_2(\pi)$	13.16 $b_1(\pi)$	*ab initio*	84

(also given PE spectrum without values)



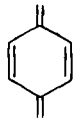
$C_8H_6S_2$ **C_{2v}**

I/eV:	7.42	8.52	9.75	10.7			105
$-\varepsilon_i$/eV:	7.48 $b_1(\pi)$	8.43 $a_2(\pi)$	10.16 $b_1(\pi)$	11.07 $a_2(\pi)$		HMO	
	8.58 $b_1(\pi)$	9.30 $a_2(\pi)$	10.69 $b_1(\pi)$	11.39 $a_2(\pi)$		MNDO	
	7.84 $b_1(\pi)$	8.51 $a_2(\pi)$	9.64 $b_1(\pi)$	11.13 $a_2(\pi)$		MINDO/3	



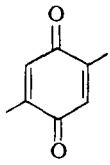
C_8H_8 **C_{2v}**

I/eV:	7.70 $a_2(\pi)$	9.6 $b_1(\pi)$	10.05 $a_2(\pi)$	10.49 $b_1(\pi)$	11.44 $a_1(\sigma)$		82b
	(assignment according to the PERTCI calculation)						82c



C_8H_8 **D_{2h}**

I/eV:	7.87	9.7, 9.8	(12.5?)				53, 56, 66
$-\varepsilon_i$/eV:	7.98 $^2B_{3u}(\pi)$	$-9.7\ ^2B_{1g}$ & $^2B_{2g}(\pi)$		10.2–10.5 $^2B_{2g}(\pi)$		SR	53
$-\varepsilon_i$/eV:	7.94 $b_{1u}(\pi)$	9.8 $b_{3g}(\pi)$	10.0 $b_{2g}(\pi)$	12.86 b_{1u}		LCBO	56
I/eV:	7.87	9.7	11.1	12.2–12.8	13.6–14.3		67
$-\varepsilon_i$/eV:	8.18 $b_{1u}(\pi)$	9.94 $b_{3g}(\pi)$	10.73 $b_{2g}(\pi)$	11.76 $b_{1g}(\pi)$	12.70 $b_{1u}(\pi)$	MNDO	
$-\varepsilon_i$/eV:	7.85 $b_{3u}(\pi)$	9.51 $b_{1g}(\pi)$	10.30 $b_{2g}(\pi)$	10.41 $b_{2g}(\pi)$	11.58 (σ)	HAM/3	69
	7.92 $b_{3u}(\pi)$	9.41 $b_{1g}(\pi)$	9.70 $b_{2g}(\pi)$	11.02 $b_{2g}(\pi)$	11.37	ΔE_{CI}	
$-\varepsilon_i$/eV:	9.02 $b_{3u}(\pi)$	11.58 $b_{1g}(\pi)$	12.74 $b_{2g}(\pi)$	13.10 $b_{3g}(\sigma)$	13.28 $a_g(\sigma)$	CNDO/S	70
	7.90 $b_{3u}(\pi)^{-1}$	9.92 $b_{1g}(\pi)^{-1}$	9.96 $b_{2g}(\pi)^{-1}$	11.19 $b_{3g}(\sigma)^{-1}$	11.33 $a_g(\sigma)^{-1}$	CNDO/S–CI	
$-\varepsilon_i$/eV:	8.18 $b_{3u}(\pi)$	10.54 $b_{1g}(\pi)$	11.74 $b_{2g}(\pi)$	12.11 $b_{3g}(\pi)$	12.28 $a_{1g}(\pi)$	CNDO/S	71
I/eV:	7.87	9.70	−9.8	11.10	−12.5		57, 72
$-\varepsilon_i$/eV:	7.87 $b_{3u}(\pi)$	9.89 $b_{1g}(\pi)$	9.93 $b_{2g}(\pi)$	11.16 $b_{3g}(\sigma)$		CNDO/S	72
$-\varepsilon_i$/eV:	7.12 $b_{3u}(\pi)$	9.27 $b_{1g}(\pi)$	9.50 $b_{2g}(\pi)$	11.00 $b_{3g}(\sigma)$	12.0 a_g	ΔE-CI	76
	7.35 $b_{3u}(\pi)$	10.10 $b_{1g}(\pi)$	11.12 $b_{1g}(\pi)$	12.93 $b_{3g}(\sigma)$	14.28 a_g	*ab initio*	
	6.78 $b_{3u}(\pi)$	9.10 $b_{1g}(\pi)$	10.51 $b_{2g}(\pi)$	12.08 $b_{3g}(\sigma)$	13.4 a_g	ΔE-SCF	

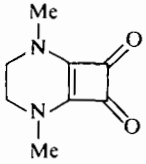


$C_8H_8O_2$ **C_{2h}**

I/eV:	9.60 $a_g(n_-)$	10.05 $b_g(\pi)$, $b_u(n_+)$		10.51 $a_u(\pi)$		18
ν/cm^{-1}:	1500			1600		
	(correlative study; substituent effects)					
I/eV:	9.58 n	10.06 n	10.58 π	13.0 π		22
$-\varepsilon_i$/eV:	9.7 $b_{3g}(n_-)$	10.2 $b_{2u}(n_+)$	10.1 $b_{1g}(\pi)$	10.4 $b_{3u}(\pi)$	HAM/3	
	(symmetry of PBQ)					

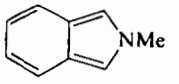
C_8H_{10} C_{2v}

I/eV: 8.05 $b_1(\pi)$ 8.87 $a_2(\pi)$ 10.75 — 104
(supported by the results of MINDO/3)



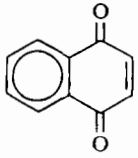
$C_8H_{10}N_2O_2$ C_{2v}

I/eV:	7.68	8.48	10.33	11.08			91
$-\varepsilon_i$/eV:	7.64 $b_1(\pi)$	9.07 $a_1(n_+)$	10.49 $b_2(n_-)$	10.21 $a_2(\pi)$		MINDO/3	



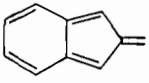
C_9H_9N C_s

$-\varepsilon_i$/eV:	7.14 a″ (π)	9.26 a″ (π)	10.55 a″ (π)	12.71 a′ (σ)	13.16 a″ (π)	*ab initio*	84
	(also given PE spectrum without values)						
I/eV:	7.12 $a_2(\pi)$	8.35 $b_1(\pi)$	9.42 $a_2(\pi)$	11.0 (σ)			85
	(assignment based on HMO and PPP-SCF-CI)						



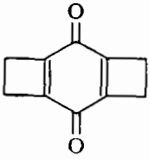
$C_{10}H_6O_2$ C_{2v}

I/eV:	9.49	9.62	9.82	10.53			14
$-\varepsilon_i$/eV:	**9.94 $a_2(\pi_1)$**	**9.98 $b_1(\pi_2)$**	**10.25 $b_2(n_-)$**	**10.65 $b_1(\pi_3)$**	10.83 $a_1(n_+)$	CNDO/S	
	9.21 $b_2(n_-)$	9.48 $a_2(\pi_1)$	9.62 $b_1(\pi_2)$	9.73 $a_1(n_+)$	**10.42 $b_1(\pi_3)$**	CNDO/S–CI	



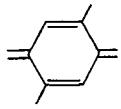
$C_{10}H_8$ C_{2v}

I/eV: 7.32 $a_2(\pi)$ 9.10 $b_1(\pi)$ 9.90 $a_2(\pi)$ — 102
(based on LNDO/S–PERTCI)



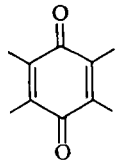
$C_{10}H_8O_2$ D_{2h}

I/eV:	9.4 n_-	9.5 π	9.7 n_+	10.3 π	10.5		107
	(assignment based on correlation with PBQ and duroquinone)						
$-\varepsilon_i$/eV:	9.01 $b_{3g}(n_-)$	9.54 $b_{2u}(n_+)$	9.84 $b_{1g}(\pi)$	10.15 $b_{3u}(\pi)$		MINDO/3	



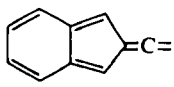
$C_{10}H_{12}$ C_{2h}

I/eV:	$7.58\,a_u(\pi)$	$8.97\,b_g(\pi)$	$9.80\,b_g(\pi)$	$10.91\,a_u(\pi)$	-12		66
	(assignment based on SR method)						
I/eV:	7.58	8.97 (9.80)	10.70	11.7–12.5	13–14		67
$-\varepsilon_i$/eV:	$8.18\,a_2(\pi)$	$9.76\,b_2(\pi)$	$10.69\,b_2(\pi)$	$11.71\,a_1(\sigma)$	$12.27\,a_2(\pi)$	MNDO	
$-\varepsilon_i$/eV:	7.77	8.91	9.62	10.78	11.09	ΔE_{CI}	69
I/eV:	7.58	8.97	9.80	10.91			72
$-\varepsilon_i$/eV:	$7.58\,a_2(\pi)$	$9.17\,b_2(\pi)$	$9.57\,b_2(\pi)$	$10.6\,a_1(\sigma)$	11.15	CNDO/S–CI	



$C_{10}H_{12}O_2$ D_{2h}

I/eV:	$9.25\,b_{3g}(n_-)$	$9.50\,b_{1g}(\pi)$	$9.75\,b_{2u}(n_+)$	$10.02\,b_{3u}(\pi)$			18
ν/cm^{-1}:				1600			
	(correlative study; substituent effects)						
$-\varepsilon_i$/eV:	$9.5\,b_{3g}(n_-)$	$9.7\,b_{1g}(\pi)$	$10.0\,b_{2u}(n_+)$	$10.0\,b_{3u}(\pi)$		HAM/3	22
$-\varepsilon_i$/eV:	9.35 (n_-)	9.53 (π)	9.83 (π)	10.10 (n_+)		CNDO/F	23

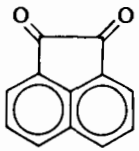


$C_{11}H_8$ C_{2v}

I/eV:	$7.25\,a_2(\pi)$	$8.83\,b_1(\pi)$	9.63–9.89 $b_2(\pi)$, $a_2(\pi)$		$11.02\,a_1(\sigma)$		98
	(based on CNDO/S PERTCI)						

$C_{12}H_4N_4$ D_{2h}

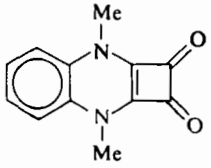
I/eV:	9.61	10–12	12.41	12.68	12.90		57, 58
$-\varepsilon_i$/eV:	$9.01\,b_{1u}(\pi)$	$10.44\,b_{3g}(\pi)$	$11.0\,b_{2g}(\pi)$	$11.85\,b_{1g}(\sigma)$	$11.95\,b_{2u}(\sigma)$	HAM/3	57
$-\varepsilon_i$/eV:	$9.95\,b_{1u}(\pi)$	$15.31\,b_{3g}(\pi)$	$15.86\,b_{3u}(\sigma)$	$15.88\,b_{2u}(\pi)$	$16.05\,b_{2g}(\pi)$	CNDO/2	58
$-\varepsilon_i$/eV:	$8.94\,b_{1u}(\pi)$	$11.69\,b_{3g}(\pi)$	$12.14\,b_{2g}(\pi)$	$13.66\,b_{2u}(\pi)$	$13.65\,b_{1g}(\pi)$	*ab initio*	60
$-\varepsilon_i$/eV:	$9.30\,b_{1u}(\pi)$	$9.7\,b_{3g}(\pi)$	$11.2\,b_{2g}(\pi)$	$12.4\,b_{1u}(\pi)$	$12.8\,b_{1g}(\sigma)$	X_α	61
$-\varepsilon_i$/eV:	$10.06\,b_{1u}(\pi)$	$13.90\,b_{1g}(\sigma)$	$14.82\,a_g(\sigma)$	$15.37\,b_{2g}(\pi)$	$15.89\,b_{2u}(\sigma)$	CNDO/2	62
	$9.26\,b_{1u}(\pi)$	$10.44\,b_{1g}(\sigma)$	$10.75\,b_{2u}(\sigma)$	$10.81\,a_g(\sigma)$	$11.22\,b_{3u}(\sigma)$	MINDO/2	62
$-\varepsilon_i$/eV:	$9.52\,b_{1u}(\pi)$	$12.06\,b_{3g}(\pi)$	$12.53\,b_{2g}(\pi)$	$14.11\,b_{1g}(\sigma)$	$14.14\,b_{2u}(\sigma)$	*ab initio*	63
	$8.90\,b_{1u}$	$10.81\,b_{3g}$	$12.04\,b_{2g}$	$13.73\,b_{1g}$	$13.74\,b_{2u}$	ΔSCF	
$-\varepsilon_i$/eV:	$7.85\,b_{1u}(\pi)$	$10.32\,b_{3g}(\pi)$	$10.51\,b_{2g}(\pi)$	$11.12\,b_{1g}(\sigma)$	$11.33\,b_{2u}(\sigma)$	INDO/S	65
	$9.54\,b_{1u}(\pi)$	$11.80\,b_{3g}(\pi)$	$11.88\,b_{2g}(\pi)$	$13.03\,b_{1g}(\sigma)$	$13.40\,a_g(\sigma)$	CNDO/S2	64
	$9.65\,b_{1u}(\pi)$	$13.28\,b_{1g}(\pi)$	$14.14\,a_g(\sigma)$	$14.49\,b_{2u}(\sigma)$	$14.95\,b_{2g}(\pi)$	INDO	65
I/eV:	9.75	11.4	11.4	> 12.50			72
	$9.75\,b_{3u}(\pi)$	$11.44\,b_{2g}(\pi)$	$11.77\,b_{1g}(\pi)$	$12.66\,b_{3g}(\sigma)$	$12.84\,b_{2g}(\pi)$	CNDO/S	



$C_{12}H_6O_2$ C_{2v}

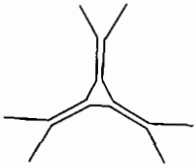
I/eV:	8.77	9.53	10.60	11.48			108
$-\varepsilon_i$/eV:	8.69 $a_2(\pi)$ & n_+	9.48 $b_1(\pi)$	10.44 $b_1(\pi)$&n_-			PPP	

(assignment of n ionizations based on correlation with α-dicarbonyls)



$C_{12}H_{10}N_2O_2$ C_{2v}

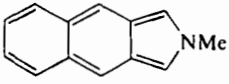
I/eV:	7.13	8.53	9.31	9.86	10.23		91
$-\varepsilon_i$/eV:	7.02 $b_1(\pi)$	9.06 $a_1(n_+)$	9.22 $a_2(\pi)$	9.76 $b_1(\pi)$	10.16 $b_2(n_-)$	MINDO/3	



$C_{12}H_{18}$ D_{3h}

I/eV:	7.49 e″ (π)	9.71, 10.45 e′ (Walsh)	11.50 a_2'' (π)		83

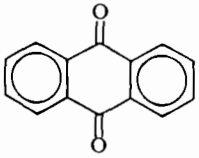
(assignment based on MINDO/3)



$C_{13}H_{11}N$ C_{2v}

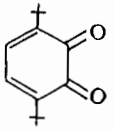
I/eV:	6.57 $a_2(\pi)$	8.13 $b_1(\pi)$	8.55 $a_2(\pi)$	9.74 $a_2(\pi)$	10.2 $b_1(\pi)$	85

(assignment based on HMO and PPP SCF CI)



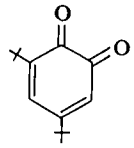
$C_{14}H_8O_2$ D_{2h}

I/eV:	9.34						Ic
I/eV:	9.25				9.63		14
$-\varepsilon_i$/eV:	9.81 ($b_{2g}(\pi_1)$:	$a_u(\pi_2)$:	$b_{3u}(\pi_3)$:	$b_{3g}(n_-)$:	$b_{1g}(\pi_4)$)	10.63 $b_{2u}(n_+)$	CNDO/S
	9.19 ($b_{3g}(n_-)$:	$b_{2u}(n_+)$:	$b_{2g}(\pi_1)$:	$a_u(\pi_2)$)	9.76 ($b_{1g}(\pi_4)$:	$b_{3u}(\pi_3)$)	CNDO/S–CI



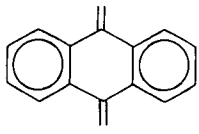
$C_{14}H_{20}O_2$ C_{2v}

I/eV:	8.71	8.93	10.03	11.34		88
$-\varepsilon_i$/eV:	8.93 $a_1(n_+)$	9.33 $a_2(\pi)$	10.69 $b_2(n_-)$	11.66 $b_1(\pi)$	MINDO/3	



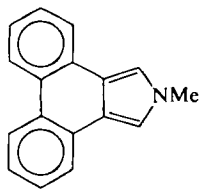
$C_{14}H_{20}O_2$ C_s

I/eV:	8.81	9.02	10.01	11.03			88
$-\varepsilon_i$/eV:	8.97 a′ (n_+)	9.47 a″ (π)	10.61 a′ (n_-)	11.50 a″ (π)		MINDO/3	



$C_{16}H_{12}$ D_{2h}

I/eV:	7.95	8.66	9.1		10.7		56
	7.87 $b_{1u}(\pi)$	8.62 $b_{2g}(\pi)$	8.99 $b_{3g}(\pi)$	9.17 $a_u(\pi)$	10.69 $b_{1u}(\pi)$		
I/eV:	8.0	8.7	9.1	10.7			67
	planar						
$-\varepsilon_i$/eV:	8.27 $b_{1u}(\pi)$	9.0 $b_{2g}(\pi)$	9.28 $b_{3g}(\pi)$	9.46 $a_{1u}(\pi)$	10.91 $b_{1u}(\pi)$	MNDO	
	non-planar						
	8.44 $b_{1u}(\pi)$	9.05 $b_{2g}(\pi)$	9.29 $b_{3g}(\pi)$	9.38 $a_{1u}(\pi)$	10.81 $b_{1u}(\pi)$	MNDO	



$C_{17}H_{13}N$ C_{2v}

I/eV:	7.15 $a_2(\pi)$	7.61 $b_1(\pi)$	8.14 $a_2(\pi)$	9.20 $a_2(\pi)$	9.35 $b_1(\pi)$		85
	(assignment based on HMO and PPP-SCF-CI)						

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CHAPTER 6

Photochromism and thermochromism in bianthrones and bianthrylidenes*

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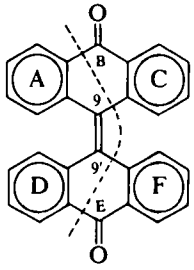
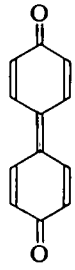
*Dedicated to Professor Ernst Fischer, on the occasion of his 65th birthday, as a token of personal friendship and of admiration for his contributions to our understanding of reversible photochromic molecular transformations.

I. INTRODUCTION

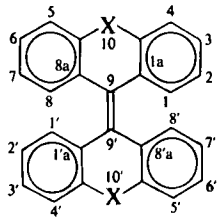
Several striking colour phenomena are associated with bianthrone (**1**), the tetra benzo-annelated diphenoquinone (**1a**), and with several bianthrylidene (**2**, X = CH) related systems (e.g., X = CH_2, CHOH, O, S, and *N*-Me). These colour phenomena are largely



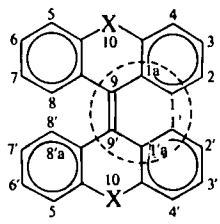
(**1**)



(**1a**)



(**2**) (*E*, D_2)



(**2**) (*Z*, C_2)

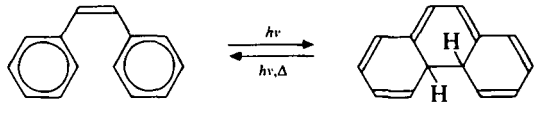
reversible, and can be induced by a variety of physical agents providing for different means of molecular excitation: light[1], exposure to higher temperature[2], application of high pressure[2] and ionizing radiation[3]. The first three of these effects are widely known as photochromism[1], thermochromism[2] and piezochromism[2], respectively, and form the subject of this chapter.

The explanation of these colour changes in terms of well accepted classical molecular structures has been a matter of considerable scientific challenge and much debate over a long period, since the original description of thermochromism and of piezochromism of bianthrone by Meyer in 1909[2]. Only in the last decade, after the advent of new and powerful methods of structure determination could significant progress be made in the definitive elucidation of the molecular structures responsible for these colour changes[4,5]. Photochromism and thermochromism, the two principal reversible colour changes, have been presently associated with definite but nevertheless labile molecular modifications formed in chemically reversible processes[5]. All these labile modifications have singlet electronic ground states[6].

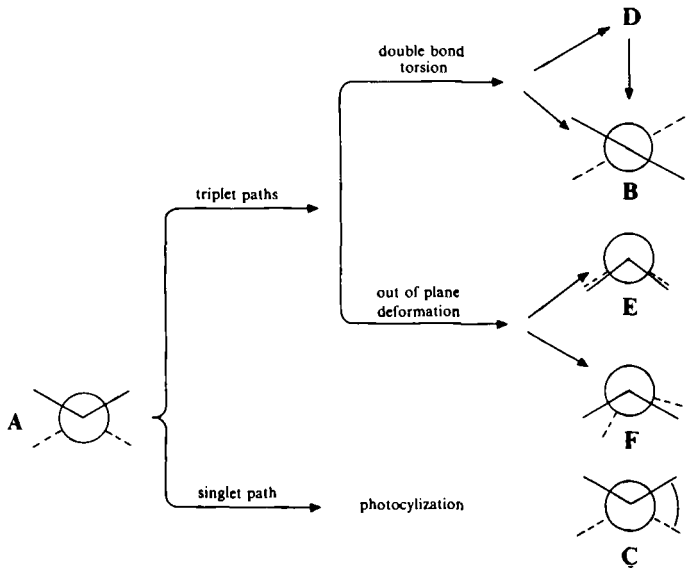
As we shall have ample opportunity to see later in detail, many of the unusual physical, chemical and photochemical characteristics of bianthrones and of all the other members of the bianthrylidene series can be traced to their fundamental structural unit, the central 9,9' double bond. Obviously this bond is very much different from the isolated double bond of ethylene, as it is significantly perturbed by the surrounding atomic network. In addition, the central double bond is part of a smaller *cis*-1,2-diphenyl ethylene unit (i.e. ring A, 9–9' double bond, ring D) as shown in **1**, itself containing as subunit the appropriately substituted hexatriene (e.g., carbon atoms 1, 1a, 9, 9', 1'a and 1', as shown in **2**). In addition several of the physically realizable conformations of the 9,9' double bond of these molecules can be and also are effectively constrained and stabilized by the molecular skeleton and by its internal non-bonded interactions, as we shall see below.

There are three main molecular transformations (see Scheme 1) giving rise to labile modifications in the bianthrylidene series. (The designation of the stable modifications as **A**, of the thermochromic as **B**, and of the photolabile as **C** is due to Kortüm[7,8].)

(1) Concerted photocyclization similar to that of *cis*-stilbene (**3**), to give 4a,4b-dihydrophenanthrene (**4**)[9,10], yielding the **C** photochromic modification (between centres 1–1' or 1–8' in **2** or **2'**)[7,8]. The absorption spectrum of one such photointermediate, the **C** modification of 1,1',3,3'-tetramethylbianthrone is shown in Figure 1.



(3) (4)



SCHEME 1: Reversible photoproducts of bianthrones and of related bianthrylidene-derived systems. Conformations (Newman projections along 9,9′ double bond) and photochemical paths. **A**, fundamental conformation; **B**, double bond twisted photo and thermo conformer; **D**, labile precursor of **B**; **E**, out of plane deformed photoconformer; **F**, same as **E**, but with double bond twist; **C**, 1,1′ or 1,8′-photocyclization product, photolabile

(2) Torsion about the central 9,9′ double bond, to give double bond conformers, as in the photochromic and thermochromic **B** modification, and its labile precursor **D**[5, 11, 12]. The absorption spectra of two such intermediates, the **B** and **D** modifications of 2,2′,4,4′-tetramethylbixanthylene[11] are given in Figure 2.

(3) Out of plane deformations about the four central single bonds between atom 9 and atoms 1a and 8a and between atom 9′ and atoms 1′a and 8′a (see e.g., **2** and **2′**) to give single bond conformers, as in the photochromic **E** and **F** modifications[12, 13]. Absorption spectra of such forms in 10,10′-dimethylbiacridan and in 1,1′,10,10′-tetramethylbiacridan are shown in Figure 3.

The bianthrylidene atomic network (see, e.g., Figures 4 and 5) possesses a highly successful built-in molecular mechanism ensuring the freezing-in of labile (metastable) conformers reached thermally or photochemically. This is the strong 1–8′ and 1′–8 (in D_2 symmetry species; or 1–1′ and 8–8′ in C_2 species, cf. **2′** (*E*) and **2** (*Z*); here we shall limit ourselves to the D_2 case) non-bonded interaction coming into effect in all molecular

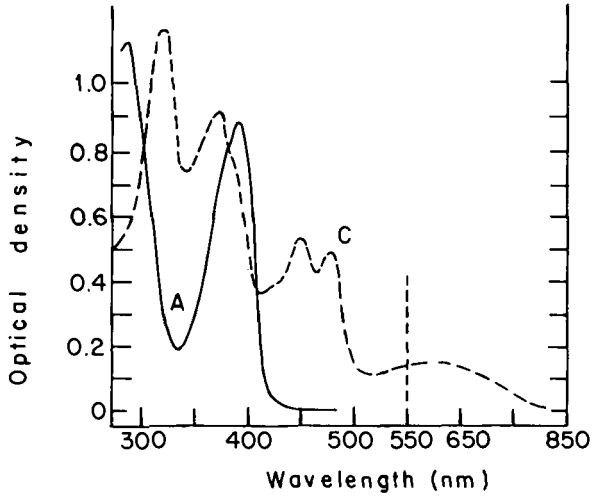


FIGURE 1. Absorption spectra of 1,1',3,3'-tetramethylbianthrone in 2-methyltetrahydrofuran solution at 183 K[6]. Full curve A form; broken line, C form, obtained by 405 nm irradiation. This is a computed spectrum, as only partial conversion of A into C is realizable in practice. Reproduced by permission of the Weizmann Science Press of Israel from Ref. 6

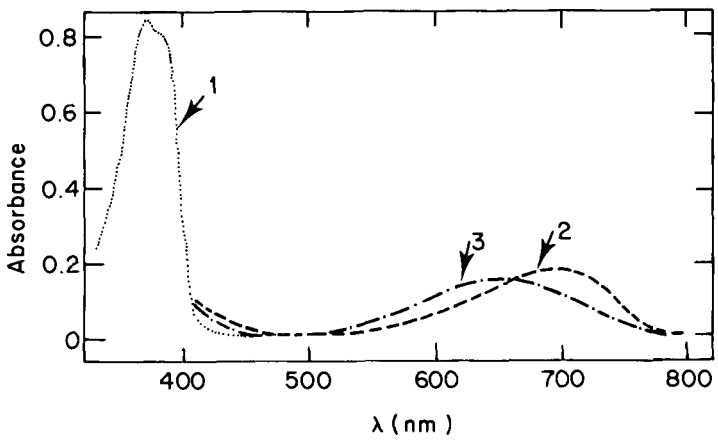


FIGURE 2. 2,2',4,4'-Tetramethylbixanthylene in methylcyclohexane/2-methylpentane 1 : 1 solution, at 83 K[11]. Curve 1, A form; curve 2, D form, obtained by 365 nm irradiation. Curve 3, B modification, formed by thermal decay of D form. Reproduced by permission of Elsevier Sequoia SA from Ref. 11

structures in which coplanarity of the two anthryl units is attempted. This interaction forms the steep walls of the potential well which oppose the various vibrations of the 9–9' bond along the reaction coordinates of the reversal processes leading to the fundamental modification (see Scheme 1). In addition to this kinetic factor, the 1–8' and 1'–8 non-bonded interactions determine also the thermodynamics of the various conformers. Thus the exact structure of each form (for definition see caption to Scheme 1) is due to a delicate

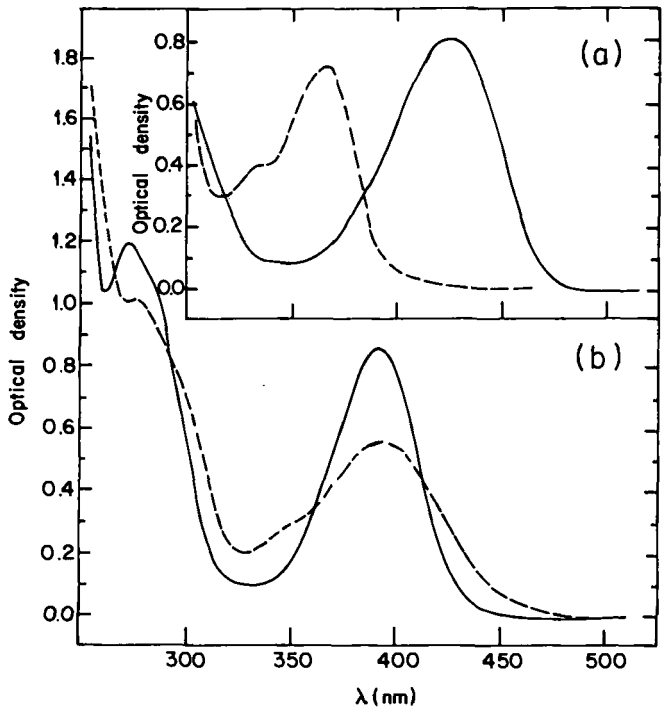


FIGURE 3. Absorption spectra of 10,10′-dimethylbiacridan (a) and of 1,1′,10,10′-tetramethylbiacridan (b), in methylcyclohexane-3-methylpentane 1 : 1 solution at 93 K. (a) Full curve, A form; broken line, E form. (b) Full curve, A form; broken line, F form[13]. Reproduced by permission of the Royal Society of Chemistry from Ref. 13

interplay of opposing energy contributions operating within the constraints imposed by the rigid molecular skeleton.

These considerations (kinetic and thermodynamic) determine not only the existence of conformations of isocovalent modifications but also play a decisive role in explaining kinetics and thermodynamics of covalent photoisomers such as the **C** forms. In these the potential barriers preventing thermal decay to the fundamental modification contain additional contributions, from the antibonding interactions of a forbidden conrotatory ground state electrocyclic process in a hexaene-derived system[9,66–68].

To illustrate the operation of the thermodynamic factors let us consider the case of the **B** forms. Here the non-bonded interaction between the atoms at the 1 and 8′ (and 8–1′) positions is minimized by the 9–9′ double bond torsion. This deformation acts however to destabilize the ground state, decreasing all stabilizing interactions such as the bonding π-system interaction[5].

The double bond twisted **B** modifications of bianthrones and bianthrylidene-related systems provide spectroscopists and chemists alike with the unique opportunity of studying a twisted essential double bond. The MO theoretical analysis of the spectral consequences of this unusual deformation have been predicted in the earlier work of Coulson and Longuet-Higgins[14].

The diphenoquinone moiety (**1a**) does not play a cardinal role in determining the existence of photo- or thermochromism, for these phenomena are observable in other

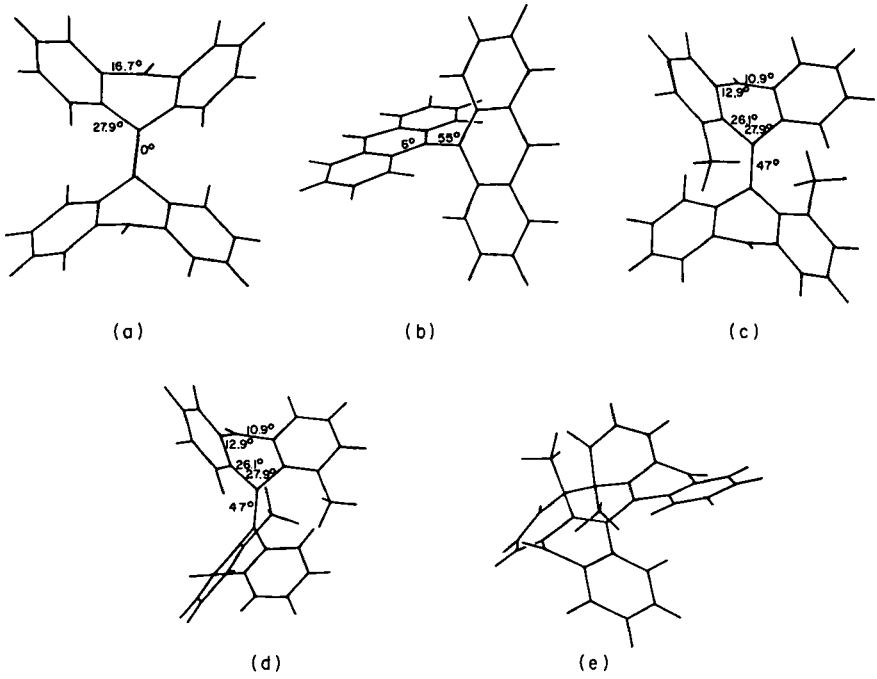


FIGURE 4. Space models built from computed minimum energy geometries of the modifications of bianthrylidene-type systems. (a) Fundamental form, A; (b) 9–9′ bond twisted thermochromic and photochromic **B** form, in systems unsubstituted at 1, 1′, 8 and 8′ positions; (c) and (d) **B** form in 1- and 8′-disubstituted bianthrylidenes; (e) **C** form (4a,4b-dihydrophenanthrene-like) in 1,1′-disubstituted bianthrylidenes. Reproduced with permission from Korenstein, Muszkat and Sharaly-Ozeri, *J. Am. Chem. Soc.*, **95**, 6177–81. © (1973) American Chemical Society

dianthrylidene-derived systems (**2**, X = CH_2, CHOH, O, S, and N–Me[11, 13, 15–22]). Nevertheless the irreversible processes accompanying photocyclization[23] and probably thermal cyclization in bianthrone proper and in bianthrones not substituted at the 1 and 8′ positions depend on this structural element, as also does the efficient singlet to triplet intersystem crossing process of all bianthrones[13, 21].

As far as the interesting history of the effects is concerned, thermochromism in bianthrone was first described by Meyer in 1902[2]. The range of known systems was much enlarged by Schönberg[24, 26] and by Bergmann[27, 28]. It was he who introduced these topics to Rehovot[29] and later, to Jerusalem. The modern phase of experimental research on thermochromism starts undoubtedly with the important works of Grubb and Kistiakowsky[30] and of Theilacker and coworkers[31]. Photochromism was first described by Hirshberg in 1950[1]. In the fifties, significant progress was made, in the parallel investigations conducted by Hirshberg in Rehovot[32–34], and by Kortüm and collaborators in Tübingen[35]. This situation led to a bitter and very regrettable personal controversy[35–37]. These studies resulted, however, in the clear distinction, between the photostable **B** modification, and the photolabile **C** modification, on both spectrophotometric and photochemical grounds[7, 8, 33, 34].

Our own research on the reversible photochromism and thermochromism of bianthrones and of related systems was started in 1968[6, 15]. At that time our interest in this field was motivated by the emergence of clear possibilities for achieving significant

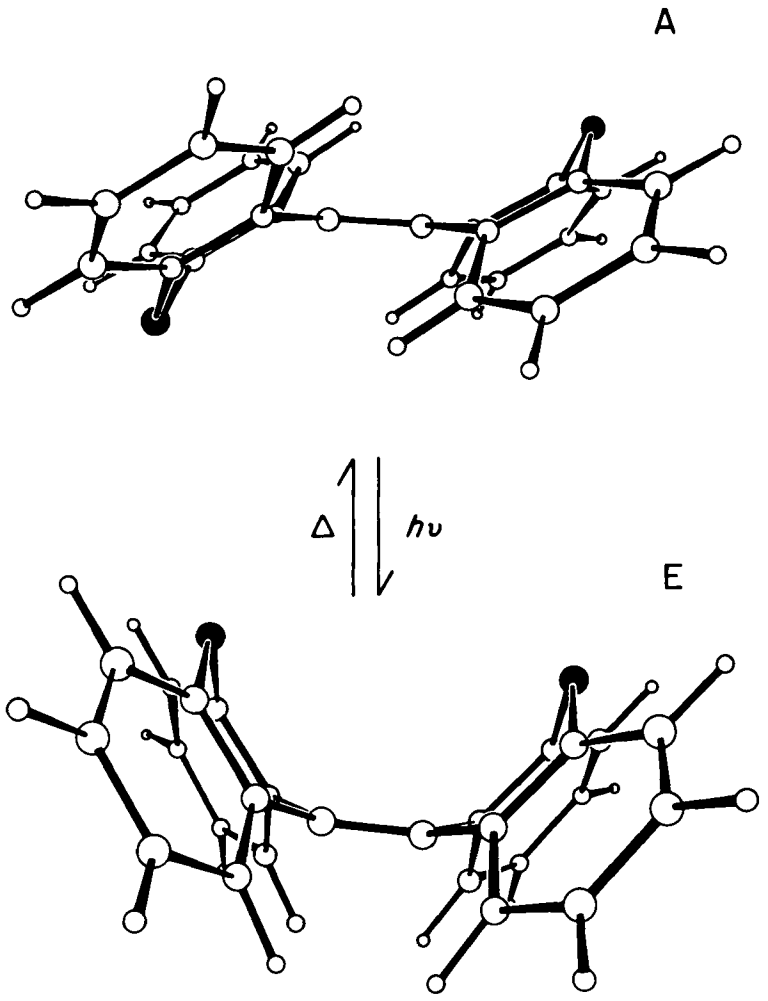


FIGURE 5. Molecular conformations of A and E forms (e.g. in bixanthylidenes, bithioxanthylidenes, biacridans and 10,10'-di-H-bianthrylidenes). Reproduced by permission of Elsevier Sequoia SA from Ref. 21

progress as indicated by the just previously completed work on the 4a,4b-dihydrophenanthrenes[9, 10]. The approach adopted in that work consisted of:

(1) development of suitable molecular architecture to achieve the highest stability and chemical inertness[10, 38].
(2) application of NMR measurements to determine molecular structure.
(3) application of MO theory and related theoretical procedures to the study and correlation of the electronic spectra of the labile intermediates. In particular, the Exciton Theory of molecular electronic spectra of conjugated polyenes proved to be very useful for the analysis of the spectra of the 4a,4b-dihydrophenanthrenes[39]. This method was later supplemented by the π-electron MO computational analyses.

Several new factors proved to be of particular importance in our investigations of bianthrones and of related systems. First and foremost proved to be the possibility of securing separate existence of each photochromic intermediate by taking advantage of effects such as differences in thermal stability or photolability[5] and differences in solvent or temperature dependences of photoformation or photocleavage quantum yields.

Such differences lead to what can be termed variously as kinetic, thermal, or photochemical isolation[5,19,20] of a desired labile intermediate[11].

Another new factor was the observation of substantial differences in the NMR diamagnetic shielding effects on the ring methyl protons of the various modifications[5,13,20,21]. The numerical analysis of such effects proved to be a rich source of information on the molecular conformation of photointermediates. Such experimentally derived geometry could be, and was, compared with theoretically computed geometries generated first[5] using our strain energy minimalization program CONFI[40], and then also[11] with geometries computed by the Consistent-Force-Field-π-electron model of Warshel and Karplus[41].

Finally, we should mention that the theoretical analysis of the energy levels of the twisted double bond formed the essential basis for our understanding of the electronic spectra of the **B** modifications[5].

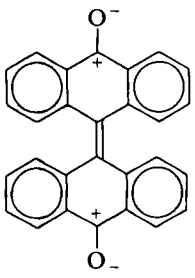
While the study of labile photochromic modifications and of their electronic spectra might seem at first glance to be a frankly esoteric subject, it has nevertheless considerable importance as a model for one molecular geometry change which could result in spectral changes similar to those observed in the vision cycle of rhodopsin[19]. Much support was obtained in recent years for a process of reversible proton transfer in a protonated retinal Schiff base as a mechanism responsible for the geometry change of rhodopsin in the vision cycle (see, e.g. Ref. 42). However, the possibility of double bond torsion in the retinal moiety of rhodopsin, much similar to the transition to the B form of bianthrone, is an interesting alternative source of large scale molecular geometry changes producing strong bathochromic effects[19].

Thermochromism and photochromism of bianthrones and of related systems have been the subject of numerous reviews, as befits this intriguing and rather mysterious chapter of chemical science. The most recent (1984) is the review of E. Fischer[43]. The PhD thesis of R. Korenstein gives a complete account of our studies of the photochromism in the bianthrylidene-related systems[44]. The introductions to the papers by Agranat and Tapuhi[45] provide up to date reviews on thermochromism. The earlier literature on this subject is referred to in the general review of Day[46].

Our companion review[9] on the 4a,4b-dihydrophenanthrenes deals exhaustively with that aspect of the photochemistry of bianthrone-related systems. Our 1970 report on bianthrone photochromism[15], the paper by Becker and Earhart[47], as well as Kortüm's definitive account of his work[48] provide descriptions of the development of this field just at the inception of the NMR period. A survey of Schönberg's contributions is to be found in his 1946 paper[49].

Many different hypotheses have been advanced over the years to explain the molecular structures of the thermochromic and of the photochromic modifications of bianthrones and of the related bianthrylidene systems. Up to the late 1960s, the experimental means available to prove or disprove these hypotheses were as a rule far too short for such ambitious attempts.

The first hypothesis concerning thermochromism was put forward in 1910 by Padova[50] who suggested a depolymerization process. Wizinger, in 1927[51] suggested a zwitterion (**5a**) as the thermochromic form. Schönberg[25] and later Bergmann and Engel[27] and Bergmann and Corte[28] all suggested a biradical structure, **5b**. Grubb and Kistiakowsky[30] proposed a double bond twisted structure, with one anthrone moiety perpendicular to the other. Its ground state would be a triplet. Matlow carried out π-electron–LCAO–MO computations



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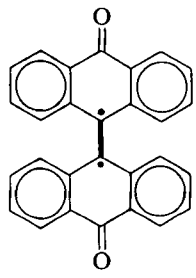

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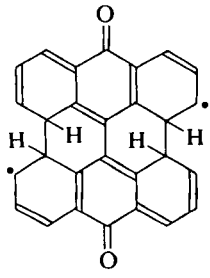

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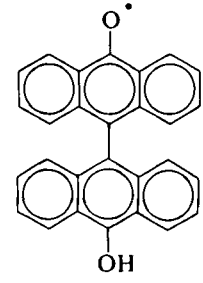
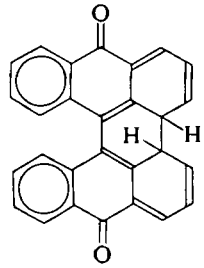


(5d)

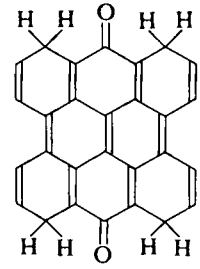
for the planar ground state, the planar triplet and the perpendicular triplet and concluded in support of Grubb and Kistiakowsky that the thermochromic form had the perpendicular triplet structure[52]. In fact, several ESR studies of thermochromism from that period (Nielsen and Fraenkel[53], Wasserman and Woodward[54]) attempted to attribute it to paramagnetic species, e.g. such as **5c**.

However, later studies by Hirshberg and Weissman, by Harrah and Becker and by Kortüm and Koch have clearly shown that the **B** form is diamagnetic[55-57]. We could fully confirm such observations for **B** forms obtained either photochemically or thermally[4]. Nevertheless the formation of paramagnetic species upon heating solutions of bianthrone or of bixanthylidene (**2**, X = O) is a genuine observation. However, this free radical is formed in an irreversible reaction, and is not involved in the reversible thermochromism. Agranat's group have identified this free radical as the phenoxyl species **5d**[58].

In juxtaposition to the hypotheses on paramagnetic structures, several cyclic diamagnetic structures were variously assigned to the thermochromic modifications. The cyclic structure **6a** (now undoubtedly known to be that of the photochromic **C** isomer) has



(6a)



(6b)

been tentatively assigned by Lorentz and coworkers[59] to the **B** form. Similarly, Philips and Schug[60] suggested a double cyclization to the quinonoid structure, **6b**. The presently available experimental evidence concerning **B** (NMR measurements as well as chemical and photochemical inertness) speaks clearly against these two possibilities.

Torsion about the 9–9′ double bond, but in the reversed sense to what we accept as correct today, has been invoked by Heller[61]. On the basis of his computations he suggested that the fundamental form (**A**) is twisted by 76 degrees, while the thermochromic form (**B**) is twisted only by 14 degrees.

Very interestingly, Bergmann in 1948 (quoted in the 1951 note)[29] has arrived at the 9,9′ double bond twisted structure. It seems he meant a partially twisted structure, his ideas much resembling our actual concepts.

However, our present day notions about the structure of the **B** modification should be clearly traced to the specific suggestion of Harnik[62a] that the thermochromic form is twisted by some 60 degrees about the central double bond. This conclusion was reached by assuming the same closest approach non-bonded distances of the 1–8′ atoms in the A and B modifications. Important support for Harnik's idea was provided by Grabowski and coworkers[63] from the conclusions of their polarographic and voltammetric studies of electrode processes of bianthrone. The type of isomerism existing among the then known modifications of bianthrone has been very appropriately termed by Harnik as 'chromic isomerism'[62a].

Before concluding this introduction we would like to mention some points about the nomenclature of the molecules and of the effects. In addition to the common ring atom numbering system (see e.g., **2** and **2′**) there is another numbering system used, e.g. by Becker and coworkers[47, 56] and by Strong and coworkers[64], in which the numbering of positions 1 and 4 is interchanged. Great care is needed to avoid confusion, as the numbering convention used is never self-evident.

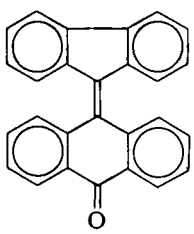
In the typical photochromic or thermochromic systems the labile isomers absorb at longer wavelengths than the parent, usually a colourless molecule. These are the bathochromic effects observed in the **B**, **C** and **D** modifications. However, the reverse change, i.e. the disappearance of a strong absorption band because of photochromic or thermochromic effects, is not uncommon. In photochromic bianthrylidene-related systems this situation is observed with the **E** and **F** modifications[11, 13, 22, 23]. In some thermochromic systems a reversed effect is also possible, as in the rhodamine lactone–zwitterion system where the low temperature form is deeply coloured[65]. Obviously the decisive factors defining the spectral effects of both thermochromism and photochromism are the exact molecular structures which determine the effect on the energy and intensity of the electronic transition.

II. THERMOCHROMISM AND THERMOCHROMIC SYSTEMS IN THE BIANTHRYLIDENE SERIES

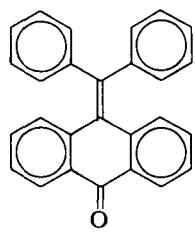
Bianthrylidene-derived systems (**2**, X=CO and O) are as a rule thermochromic. Thermochromism is prevented by bulky substituents at the 1, 1′, 8 and 8′ positions[1b, 62b]. For reasons of molecular mechanics it is not observed in dithioxanthylidene or in 10,10′-dimethylbiacridan[31, 69]. Substitution by fluorine at position 1 does not prevent thermochromism[1b, 62b]. The absence of thermochromism in the 1 (and 1′, 8 and 8′) as well as otherwise substituted derivatives is not an indication that the **B** form should be incapable of existence. Quite to the contrary, this form is readily obtained by the photochemical route. However, the thermal path leading to it requires surmounting too high potential barriers due to the strong non-bonding 1–8′ interactions and is therefore unobservable.

In addition to the symmetric thermochromic systems in which the groups at the 10 and 10′ positions are identical, several mixed thermochromic bianthrylidenes have been reported, e.g. 9,9′-fluorenylidene anthrone, **7a**[70], 9,9′-diphenylmethylene anthrone, **7b**, and its substituted derivatives; xanthylidene anthrone, **7c**, and diphenyl methylene xanthene, **7d**[49].

Solutions of difluorenylidene, **8a**, and of its benzo-annelated derivatives, e.g. [*a*,*a*′]-dibenzo, [*b*,*b*′]-dibenzo and [*a*,*f*]-dibenzo, as well as [*a*,*a*′,*f*,*f*′]-tetrabenzo difluorenylidene, are deeply coloured at room temperatures[71]. Here the fundamental modifi-



(7a)



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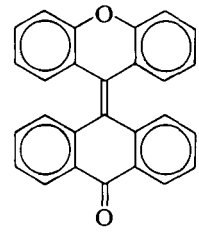

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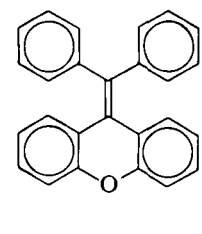
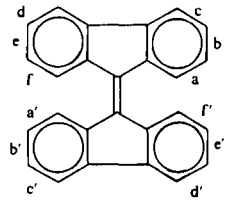


(7d)

cation seems to be already twisted significantly about the 9,9′-double bond, resembling in this sense the **B** conformers of bianthrylidenes.



(8a)

From the change (increase) of the equilibrium constant $K = [\mathbf{B}]/[\mathbf{A}]$ with temperature it is seen that the thermal conversion **A** → **B** is slightly endothermic. Values of this enthalpy change falling within the range of 2–4 kcal mol^{-1} can be variously estimated[15, 30, 31, 45f, 48]. This narrow range, little affected by substitution pattern (for the less sterically hindered molecules) certainly merits some special attention. Conversion extents of up to 0.1 are obtained at atmospheric pressure. The higher conversion extents (0.05–0.1) are observed at temperatures around 500 K in the not excessively sterically hindered bianthrones, e.g. the parent molecule[31] and 3,3′-dicarboxybianthrone[48]. The conversion extents obtained in the 2,2′-dimethylbianthrone are much lower, 0.0013 at 330 K and 0.008 at 490 K[45f], because of additional non-bonded interactions of intermediate magnitude. Such values are estimated by assuming either that the ε_A and ε_B extinction coefficients at the respective maxima of **A** at 380 nm and of **B** at around 700 nm are approximately equal, or from the ε_B values deduced under conditions of complete photoconversion to **B**, $\varepsilon_B = 15\,500$[45f]. The thermochromic **B** form can be also obtained by sublimation, e.g. by condensing bianthrone vapour (at ca. 0.001 mmHg pressure) on a surface cooled to 90 K[72].

III. PIEZOCHROMISM

Pressure and strong shearing such as grinding result in the formation of the coloured form (now known to be the **B** form) identical with the photo- and thermochromic forms[2, 49]. Piezochromism is temperature dependent, being stopped by cooling to 90 K[73]. Schönberg's conclusion[73] that such temperature dependence is an indication that piezochromism is to be attributed to thermochromism seems, however, unwarranted. In fact much insight into the nature of the piezochromic transition of bianthrones has been obtained in high pressure studies[74]. Such studies on bianthrone and its substituted derivatives, embedded in polymethyl methacrylate, show very significant extents of

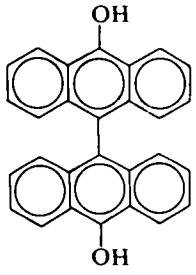
conversion into the **B** modification. At 120 kbar, the observed conversion extent amounts to 0.3 in bianthrone, 0.13 in 3,3′-dimethylbianthrone, 0.16 in 3,3′-dibromobianthrone, and 0.08 in the more strongly hindered 1,1′-dimethylbianthrone. The energy difference $\Delta H_A - \Delta H_B$ is pressure dependent decreasing three- to fourfold over the range of 0–120 kbar. The partial molar volume difference for the **A** → **B** process amounts to ca. −0.90 ml for bianthrone at 60 kbar and drops to −0.50 ml at 120 kbar. That the partial molar volume of **A** is larger than of **B** is the obvious macroscopic origin for the pressure-dependence effect. The molecular interpretation of this difference seems to rest on the number and magnitude of the various non-bonded interactions in the region of closest non-bonded approach. Apparently similar differences have been previously invoked in other photoconformers, such as in the *cis* and *trans* isomers of stilbenes. There steric hindrance is the origin of the 1–α single bond torsion[75–77] as it is of the 9–9′ double bond torsion in the **B** conformer.

IV. CHEMICAL AND ELECTROCHEMICAL PATHS LEADING TO THE *B* MODIFICATION

We have already mentioned the paths to the **B** form involving the thermal, high pressure, ionizing radiation, photochemical and sublimation processes. The crystallization (precipitation) step in the chemical synthesis of bianthrone has already been reported by Meyer[2] to lead to crystals of the metastable green coloured modifications (presumably the **B** form, cf. also Ref. 7). Two other paths leading to the **B** form, one involving a chemical process[7], the other an electrochemical process[63], have been carefully studied. The chemical process[7] consists of the low temperature (183 K) hydrolysis of the (diprotonated) adduct of 1,3,1′3′-tetramethylbianthrone (= 1,3,6′,8′-tetramethylbianthrone) with sulphuric acid in an ethanol–water mixture. The absorption spectrum clearly shows[7] efficient (but partial) conversion into the **B** form. Oxidation of the corresponding 1,1′-dimethyl dianthranols leads also to the **B** forms[7], observable as metastable products[48]. Good evidence connecting the green form **B** to the 9,9′-double bond twisted conformer is provided by the electrochemical results of Grabowski and coworkers[63a, b] and of Peover[78]. The principle governing the electrochemical reactivity of two species K and L converted one into the other by an electrode process is the least structural change rule[63]. Their rule states that the overall rate of an electrode process is high provided the structure difference between K and L is minimal. Thus bianthranol (**9**) is reversibly converted into the **B** form by anodic oxidation on a frozen mercury drop electrode at 188 K. The rate of the thermal process **B** → **A** is sufficiently slowed down at this temperature so that in the oxidation stage of the cyclic voltammetry experiment the **B** form will accumulate in the vicinity of the electrode.

The reduction of the A form (reduction potential $E_{1/2} = -1.25$ V against saturated Hg sulphate electrode) to bianthranol is a diffusion-limited irreversible process. The reduction of the **B** form to bianthranol takes place at a much less negative potential, $E_{1/2} = -0.55$ V. This reduction is kinetically controlled. The reduction current for this process is temperature dependent, increasing strongly upon going up from 288 to 333 K. This current is kinetically limited by the **A** → **B** equilibrium (which is heavily in favour of **A** at these temperatures). To conclude, the electrode reduction of **B** and the oxidation of bianthranol form a reversible redox system. Thus according to the least structural change rule we can deduce that the **B** form and the necessarily twisted (about 9,9′ bond) bianthranol have similar nuclear conformations.

These findings of Grabowski and coworkers and of Peover have been amply confirmed in the recent comprehensive studies of Evans and coworkers on electrode processes of bianthrones in non-aqueous solvents[79, 80].



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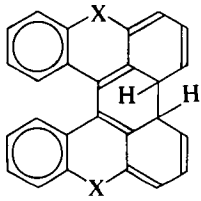

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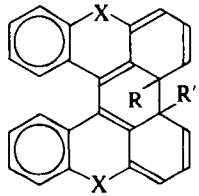


(10a)

V. INTERCONVERSIONS AND EQUILIBRIA BETWEEN *A* AND *B* MODIFICATIONS IN IONS OR RADICALS

We have already mentioned that the bond order (and electronic density) of the unique 9–9′ double bond and the electronic densities at the 9 and 9′ atoms are of prime importance in determining both the interconversion kinetics of the **A** and **B** forms and their relative thermodynamics as well. For this reason it is to be expected that the relative energetics and the interconversion rates and barriers would be deeply affected by electronic processes and reactions which change the electronic density at the 9–9′ bond: ionization (or oxidation) to form the molecular cation $\mathbf{A}^{+\cdot}$; reduction to give the anion radical $\mathbf{A}^{-\cdot}$ or its protonated counterpart $\mathbf{AH}^{\cdot}$ and twofold reduction to give the dianion $\mathbf{A}^{2-}$; protonation at the O atoms to give successively $\mathbf{AH}^{+}$ and $\mathbf{AH}_2^{2+}$; and undoubtedly excitation to give the excited singlet and the excited triplet, either by intersystem crossing or by triplet sensitization. These processes are likely to weaken this double bond either by removing an electron from the bonding HOMO; by inserting one or two electrons into the mirror symmetry antibonding LUMO; by promoting an electron from a HOMO into a LUMO; and by perturbing the nuclear core topology (by positive charges as in the diprotonated dication $\mathbf{AH}_2^{2+}$). We have already seen how many of these processes (e.g. excitation, diprotonation and oxidation) worked in practice, and in subsequent sections we shall consider the effects of some of the other processes. In general, as the interconversion $\mathbf{A} \rightarrow \mathbf{B}$ for the neutral ground state configuration is only weakly exothermic, $\Delta H = 2$–5 kcal, we expect any weakening of the 9,9′ C=C bond to result in further molecular deformation to allow better reduction of the 1–1′ and 8–8′ (or 1–8′ and 1′–8) non-bonded repulsions. This situation should give rise to further preference for the **B** form. In addition to the above-mentioned results, information on some processes has become available from pulse radiolysis and cyclic voltametry experiments [79–81]. The pulse radiolysis experiments in 2-propanol solution involve the radiolytic preparation of the acetone ketyl radical, $Me_2C^{\cdot}OH$, and the study of its subsequent reaction with the **A** modification to give within 4–5 μs the anion radical $\mathbf{A}^{-\cdot}$ which is converted into $\mathbf{B}^{-\cdot}$ within the next 25–30 μs[81]. The interpretation of these experiments rests on the assumption that the absorption maximum of $\mathbf{A}^{-\cdot}$ is at 560 nm and that of $\mathbf{B}^{-\cdot}$ is at 460 nm and on other assumptions as well. For the $\mathbf{A}^{-\cdot} \rightarrow \mathbf{B}^{-\cdot}$ step in bianthrone they obtain a rate constant $k_{AB^{-\cdot}} = 7 \times 10^4\ s^{-1}$. In 1,1′-dimethylbianthrone they get $k_{AB^{-\cdot}} = 1.1 \times 10^3\ s^{-1}$. For the 3,3′-disubstituted bianthrones they estimate $k_{AB^{-\cdot}}$ roughly similar to those for bianthrone (for the dimethyl compound, $k_{AB^{-\cdot}} = 1.7 \times 10^4\ s^{-1}$, for the dimethoxy compound, $k_{AB^{-\cdot}} = 7 \times 10^4\ s^{-1}$, as in bianthrone)[81]. The $k_{AB^{-\cdot}}$ values obtained from the cyclic voltametry experiments are $k_{AB^{-\cdot}} = 2 \times 10^6\ s^{-1}$ for bianthrone and $k_{AB^{-\cdot}} = 5 \times 10^4\ s^{-1}$ for 1,1′-dimethylbianthrone[79,80]. While the trend of these values is entirely reasonable, there is still the discrepancy between the two sets of

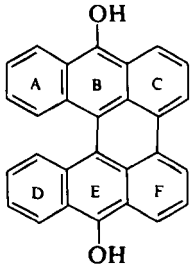
experiments to be explained. The above values for k_{AB^-} in the radical anion of bianthrone should be compared to the corresponding value of $k_{AB} = 8 \times 10^{-3}\ s^{-1}$ for ground state singlet bianthrone. This value can be deduced from the values of $K_{AB} = [B]/[A] = 2.2 \times 10^{-3}$ and the accepted value of $k_{BA} = 3.7\ s^{-1}$ [79b].

VI. IRREVERSIBLE PHOTOCHEMICAL PROCESSES OF BIANTHRONE AND OF 1,1′-UNSUBSTITUTED DERIVATIVES

A very significant aspect of the molecular transformations of the bianthrylidene series is that of high chemical reversibility, implying that transformation of one conformation or structure into the other and back can be carried out repeatedly without occurrence of side reactions which would yield stable side products, and consequently lead to depletion of the starting parent molecules. The crucial factor governing reversible behaviour in the bianthrone series is the presence or absence of at least two substituents (such as alkyl, alkoxy or benzo annelation) at the 1 and 1′ (or 8 and 8′) positions[4,6,23,48]. Such substituents determine the resistance or reactivity of the 4a,4b-dihydrophenanthrene-like C photoisomers (**10** and **10a**) in irreversible processes such as oxidation or hydrogen shift of the angular H atoms at the C centres forming the new bond[4,6,9–11,15,16,18,22].

The processes leading to and from the **D**, **B**, **E** and **F** photoisomers are highly reversible in all bianthrones and in the other bianthrylidene series (**2**, X = O, CH_2, CHOH, NMe and S). As all irreversible behaviour is to be traced to the **C** modification, high extent of chemical reversibility will be observed in all members of these series under conditions under which no **C** modification is formed, such as at very low temperatures[23]. High extent of reversibility is observed also in compounds such as **2**, X = NMe in which no **C** modification is formed at all. In the **C** modifications of bixanthylidenes and of 10,10′-di-*H* bianthrylidenes in the absence of 1 and 1′ substituents, the source of irreversibility is the oxidation of these hydrogens by molecular oxygen as in other 4a,4b-dihydrophenanthrenes[9]. However, in the **C** modifications of bianthrones (again, in the absence of 1 and 1′ substituents) other avenues of irreversible chemical reactivity are open as well: intramolecular H atom shift followed by intermolecular H shift or oxidation by molecular oxygen, and further photochemical and dark processes leading to a very complex photochemical system[4,6,23]. The products of these processes were correctly figured out in 1949 by Brockmann and Mühlmann[82]. Their conclusions about the identity of the products have withstood the test of time, though much additional information was obtained in later studies[23] of bianthrone. Here, the **B** modification is formed exclusively at temperatures below 140 K, or at higher temperatures, ca. 200 K and above, by biacetyl triplet sensitization. The **B** modification of bianthrone is chemically inert and goes reversibly into **A**. The **C** modification (**10**) can be observed at low temperatures in polar (protic or aprotic) solvents, as a short-lived transient (half lifetime of 80 ms at 200 K in 2-propanol)[23]. This intermediate undergoes an irreversible 1,5 H atom shift to give dihydrohelianthrone, **11**. Dihydrohelianthrone is highly reactive chemically. It reacts with oxygen at low temperatures to give helianthrone, **12**, and hydrogen peroxide. This reaction is not inhibited by 2,6-di-*t*-butyl-4-methylphenol[9,83–85].

The reasons for this difference could be either very fast reaction rate of **11** with oxygen or simultaneous reaction of the two 1 and 1′ hydrogens. In the absence of oxygen **11** will react by intermolecular hydrogen atom transfer with the parent molecule **2** to give one molecule each of **12** and of dianthranol **9**. These are also the products of the photolysis of **2** in non-polar solvents such as hydrocarbons or CS_2. Here no dihydrohelianthrone can be observed, probably because its reaction with bianthrone is too fast. No details are known about the molecular paths of the rearrangement of **10** to give **11**, and of the dismutation of **11** with **1** to give **11** and **12**. The *o*-quinonoid double bond topology of **11** (rings B, C, E, and F) seems to be at the origin of its unusual properties. First, the considerable reactivity



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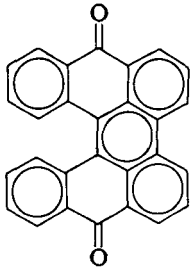

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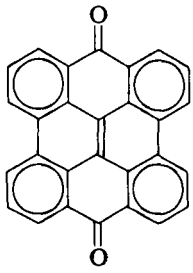

(13)

we mentioned already, and then also the blue colour of this compound, due to strong absorption maxima in the visible at 610 and 575 nm. **11** is thermally stable at room temperature in the absence of oxygen. It is also stable photochemically. Further irradiation of helianthrone **12** results in the formation of mesonaphthobianthrone, **13**. In the absence of oxygen, the two angular H atoms in the primary cyclization product preceding **13** apparently can be transferred to **12** to give **11**[82].

VII. THE PHOTOCHROMIC *C* MODIFICATION

Our initial proton NMR studies on the **C** forms of 1,8′-dimethylbianthrone and of 1,3,6′,8′-tetramethylbianthrone[4, 15] and our subsequent study of the C form of 1,4,5′,8′-tetramethylbixanthylene[11] clearly indicates that these **C** forms are photocyclization products of the 4a,4b-dihydrophenanthrene type[9, 10, 38]. In such photoisomers[9] the two groups attached at the atoms forming the new bond (i.e. R and R′ in **10a**) have been shown to be in the *trans* conformation. We assume that this is also the case for the **C** photoisomers. This is in fact the steric outcome predicted by the orbital symmetry conservation rules (see, e.g. Refs 9, 10 and 66) for the case of the concerted conrotatory first excited state photocyclizations of a hexatriene or a derived system to give a cyclohexadiene-related product[66]. Our studies[4, 11, 15] show also that in the case of 1,8′-dimethyl substitution in the educt, the new bond of the product is always formed between two methyl-bearing ring atoms (Me–C–C–Me mode, i.e. in **10a**, R = R′ = Me). None of the other possible cyclization products (H–C–C–H mode, R = R^1 = H or H–C–C–Me mode, R = H, R′ = Me) is formed. The calculated energy difference[11] for 1,8′-dimethylbianthrone between the Me–C–C–Me mode and the H–C–C–H mode amounts to 27 kcal in favour of the former. This difference is to be attributed to the much higher molecular strain imposed by the large non-bonded methyl–methyl repulsion in the H–C–C–H mode product.

All **C** modifications undergo the reverse 1–1′ bond cleavage, both thermally (dark reaction) and photochemically (excited singlet process). The photochemical conrotatory process (ring-opening) is allowed by orbital symmetry rules and takes place without requiring any activation energy[4, 9, 10, 15]. The thermal process is a forbidden conrotatory ground state ring-opening of a D_2 symmetry system related to cyclohexadiene[66, 86]. That the thermal ring-opening in 4a,4b-dihydrophenanthrenes[9, 10, 66] and in **C** photoisomers of the bianthrylidene series[4, 15] takes place quite readily is chiefly due to the significant destabilization of the ground state, a fact which decreases the potential barrier for ring-opening[66, 86]. The measured values of the ring-opening activation energies of the **C** photoisomers all fall in the very narrow range of 12–15 kcal[4, 10, 11, 15, 22]. The **C** photoisomers are less stable (towards thermal ring-opening to **A** form, in the absence of oxygen) than typical 4a,4b-dihydrophenanthrenes[9, 10]. The least stable (apart from the **C**

form of bianthrone itself) are the **C** forms of 10,10′-di*H*-bianthrylidenes (**2**, X = CHOH, or X = CH_2) where the 1 and 1′ positions are unsubstituted. In such photoisomers thermal half lifetimes τ are of the order of 0.5–2 s at 253 K. **C** forms of bianthrones with dimethyl substitution at 1 and 1′ positions have τ values of the order of 1–2 h at 215 K[22]. The **C** form of bixanthylene is however unusually stable, resembling 4a,4b-dihydrophenanthrenes. It is stable at 273 K, while at 328 K τ is 14 s[18]. Obviously not all factors governing thermal stability of the **C** photoisomers seem to be completely understood.

The **P** photoisomers of bixanthylidene[18] and of bithioxanthylidene[21] seem to be closely related to the **C** forms. Preliminary results indicate that the **P** isomers originate from the excited singlet. It is yet unclear whether the **P** forms are precursors of **C** forms. There is also a possibility that **P** and **C** photoisomers are formed concurrently. Unlike the **C** modifications, **P** forms are light stable. They were observed at temperatures in the range of 250–360 K. The **P** photoisomer of bixanthylidene has been detected in flash photolysis experiments at 293 K. Its absorption spectrum resembles that of **C**, but its first absorption band maximum at 520 nm is much more intense, and thus it is quite probable that this is an unstable conformeric isomer (and precursor) of **C**, the two differing in some conformational details. The thermal decay activation energy of **P** amounts to 14 kcal. Its thermal half lifetime value τ is ca. 11 s at 250 K.

The **A** and **C** forms constitute a photoreversible photochromic system as light converts one form into the other. The composition of such a system (concentration c_i of each isomer) at photostationary equilibrium is determined by the extinction coefficient ε_i at the irradiation wavelength, and by the quantum yield ϕ_i so that the product $\varepsilon_i \cdot \phi_i \cdot c_i$ for each isomer is constant (cf. Refs 9 and 10). Thus visible light absorbed only by **C** results in complete reversal to **A**. On the other hand short wavelength light absorbed by **A** (and so also by **C**) leads to a photostationary equilibrium. We should note however that system **A** + **C** does not constitute a perfect photoreversible system as excitation of **A** leads to the parallel formation of **C** and of the triplet product **B** which does not undergo the photoreversal reaction to give back **A**. Formation of the other triplet products **E** and **F** leads to the same consequences. Thus the time evolution of a prolonged irradiation of **A** at temperatures where both **B** and **C** are stable is characterized by the initial simultaneous formation of **C** and **B**. The concentration of **C** then passes through a maximum and decreases gradually till complete conversion into the photostable isomer is obtained[4, 11, 15, 18, 22].

However, when the photostable intermediate (**B**, **E** or **F**) is less stable thermally than the **C** form we should expect high conversion into this form and complete reversibility. This situation is achieved, e.g. with 1,1′-dimethylbianthrone in methylene chloride[4, 15]. It seems that the **C** form is the only photoisomer observed in 10,10′-dihydroxy-10,10′-di*H*-1,1′-dimethylbianthrylidene[22]. While all wavelengths absorbed by **A** are effective in producing some conversion into **C**, the highest extent of conversion (cf. Ref. 10) at photostationary equilibrium is achieved at irradiation wavelengths for which the extinction coefficient of **C** is a minimum while that for **A** is a maximum. With the excitation frequencies choice provided by the mercury arc, the highest extent of conversion is usually obtained using the 405 nm line. As in most 4a,4b-dihydrophenanthrenes[9, 10], the *photocyclization* quantum yields $\phi(\mathbf{A} \rightarrow \mathbf{C})$ of all **A** forms to give the **C** forms show a strong temperature dependence[4, 15, 18, 22]. Thus in the 10,10′-di*H*-bianthrylidenes, quite typically, these quantum yields are high, ca. 0.5, and constant, down to 150 K. They drop to zero below 110 K[22]. Obviously the excited state cyclization process requires surmounting a small potential barrier (3–4 kcal) (cf. Refs 9, 66). In 1,4,1′,4′-tetramethylbianthrone[16], $\phi(\mathbf{A} \rightarrow \mathbf{C})$ is even higher, ca. 0.9. The temperature dependence of $\phi(\mathbf{A} \rightarrow \mathbf{C})$ is a genuine temperature effect and is not due to a transmitted viscosity dependence[75, 76]. The photocyclization process shows marked solvent preferences[7, 8, 15]. For 1,3,6′,8′-tetramethylbianthrone and

1,8′-dimethylbianthrone highest initial conversions **A** → **C** (and thus probably highest quantum yields) are obtained using 2-methyltetrahydrofuran and methylene chloride as solvents[6,15].

The pronounced resemblance of the photochemical behaviour here and in the 4a,4b-dihydrophenanthrenes extends also to the *photochemical* ring-opening process **C** → **A**. Its quantum yield is high, 0.2–0.3 in the 10,10′-di*H*-bianthrylidenes[22]. It is temperature independent, to be expected of an allowed excited state conrotatory cyclohexadiene-type ring-opening[66,68]. In the **C** forms of bianthrones ϕ(**C** → **A**) is lower (0.08–0.05) and shows a weak temperature dependence at low temperatures[6,15].

The absorption spectrum of the **C** forms[4,9,15,16,18,22] resembles closely that of 4a,4b-dihydrophenanthrene and of its derivatives[9,10], both in terms of transition energies and intensities. This similarity is in fact a powerful piece of independent evidence for assigning the 4a,4b-dihydrophenanthrene structure to the **C** forms. The first long wavelength band (I) of the **C** forms has its maximum at 500–600 nm, depending on the exact system[4,15,22]. It is a low intensity band (e.g. ε = 3360 in 10,10′-di-*H*-bianthrylidene[22]). According to the exciton theory of the polyene spectra[9,10] this band is the fundamental, in-phase transition. Its low intensity is due to the partial cancellation of the unitary ethylene transition moments (M) in the vectorial summation of the unitary moment to give the molecular transition moment of a s-*cis*,s-*trans*,s-*trans*,s-*trans*,s-*cis*-hexaene. In this case the molecular transition moment $\sqrt{I}$ is $\sqrt{I_1}$ = 0.465 M. For the sake of comparison, in the all-*trans* linear polyene this transition is much stronger, $\sqrt{I_1}$ = 2.03 M. The large width of the first transition, $\Delta\nu_{1/2} \sim 4500\ cm^{-1}$, indicates a significant geometry change going from the ground to the first excited state. In some systems[9] it was possible to identify a progression in the first excited state totally symmetric stretching mode of the C=C double bonds at ca. 1200–1300 cm^{-1}[9]. The second transition (II, Ref. 9) of the **C** modifications, in the 380–480 nm range has also a number of typical features. It is much stronger than the first transition (e.g. ε = 17 700 in 10,10′-di*H*-bianthrylidene[22]. It shows a very distinct 2–3 vibrational component progression in the 1200–1300 cm^{-1} mode. The first component is the strongest, implying a small geometry change. According to the exciton model the transition moment of this transition (first harmonic band) is $\sqrt{I_2}$ = 1.30 M, i.e. much larger than for the first transition. Two shorter wavelength transitions, at 370 and 320 nm, have been observed in the **C** forms of 1,3,6′,8′-tetramethylbianthrone (in 2-methyltetrahydrofuran or methylene chloride solutions). It seems uncertain whether one of these should be identified with the second harmonic band of the hexaene system (at 237 nm in 4a,4b-dihydrophenanthrene[9,10].

VIII. THE TRIPLET STATE OF BIANTHRONES AND OF BIANTHRYLIDENE-DERIVED SYSTEMS

Several detailed studies of the bianthrylidene series have shown that photoproducts **D**, **B**, **E** and **F** are formed through the intermediacy of a distinctly observable triplet state T[13,15–22,87,88]. In fact, the bianthrylidene series is one of the rare photochemical systems in which exact information on the course of molecular events leading to photoproducts could be obtained. The common triplet state, observable by both optical and magnetic resonance methods is in all probability the first triplet state T_1 and is formed directly by activated singlet-to-second triplet intersystem crossing ($S_1 \rightarrow T_2$). In several systems (e.g. bixanthylidenes, dithioxanthylidenes and 10,10′-dimethylbiacridans) the $S_1 \rightarrow T_2$ process is incomplete, as the formation of the triplet product (**B**, **D**, **E** or **F**) can be strongly enhanced by external spin-orbit coupling enhancing agents such as molecular oxygen, alkyl halides, carbon disulphide and xenon[17–19,21,22]. The exact mechanism of this enhancement process is unclear at this moment. One possible description of this enhancement is by the

acceleration of an unactivated path to first (lower energy) triplet T_1. However, this possibility is not unique, as several theories of radiationless transitions (see, e.g. Ref. 22) predict a transition to a single triplet state showing non-activated behaviour at low temperatures but requiring activation at higher temperatures. The lifetimes and chemical evolution of bianthrylidene triplets T are all very strongly controlled by the viscosity of the medium[15-22]. Very high viscosities, as achieved in hydrocarbon glasses around 90 K, in alcohol glasses around 120 K or in triacetin glasses around 200 K will stabilize these triplets to an extent allowing time-resolved optical or ESR studies on a time scale extending from tens of microseconds to tens of milliseconds. In fluid solutions at 300 K these triplets can be observed by nanosecond flash photolysis[13, 15-22, 87-89]. The optical absorption of bianthrylidene series triplets shows a maximum at around 500 nm (e.g. 490 nm in 1,3,6′,8′-tetramethylbianthrone at 100 K, 450 nm at ~ 300 K; 540 nm in dibenzo[*a,g*] bixanthylidene, and 400–450 nm in 10,10′-dihydroxybianthrylidene). The triplet–triplet absorption spectra extend to much longer wavelengths beyond the ~ 500 nm maximum. In the 1,3,6′,8′-tetramethylbianthrone triplet a long wave absorption maximum at 890 nm was reported[90].

The ESR spectra of the bianthrylidene series triplets T_1 provide a definitive identification of the optical transients. These spectra have established positively that the optical transients are genuine triplet spin species and not free radicals (doublets) or diamagnetic transients. The crucial experimental evidence consists of the strong two quantum ESR transition $\Delta m = 2$ observable at half field, e.g. at 1525 *g* in 1,3,6′,8′-tetramethylbianthrone[15] and at 1528 *g* in dibenzo[*a,g*]bixanthylidene[16]. The rates of disappearance of the optical absorption of the triplets, the rates of formation of the triplet manifold products and finally the rates of disappearance of the ESR signal at half field are equal within experimental error.

The formation of **B**, **E** and **F** can be sensitized by triplet energy transfer from biacetyl triplet (see, e.g. Refs 13, 21 and 91). Triplet sensitization provides access to triplet products under conditions where the singlet manifold product **C** is formed preferentially by direct excitation. This is the situation observed with 1,8-dimethylbianthrone in methylene chloride at 203 K. Direct excitation leads to **C** while biacetyl triplet energy transfer results in the formation of **B**[87].

We mentioned previously that all molecular transformations and photophysical processes of the triplets of the bianthrylidene series are strongly controlled by viscosity (in the range of very high viscosities). Genuine temperature effects seem to be factors of lesser importance in this context (cf. Ref. 75 for the related phenomena in the stilbene series). This point is made clear by noting the critical temperature (t_1) for the complete reversal of the triplet ^{3}**A** to the ground state **A**, ($^3\mathbf{A} \rightarrow \mathbf{A}$) and the critical temperature (t_2) for the complete conversion of the triplet ^{3}**A** into the triplet product, $^3\mathbf{A} \rightarrow$ Product (e.g. **D**, **E** or **F**). For 1,3,6′,8′-tetramethylbianthrone t_1 is 87 K in hydrocarbon (methylcyclohexane/2-methylpentane) glass; 104 K in alcohol glass (1-propanol/2-propanol) and 195 K in a triacetin glass. Below t_1 complete reversal to **A** takes place and above t_2 some product is obtained. In the same derivative, t_2 is 100 K for the hydrocarbon glass, 119 K in an alcohol glass and 213 K in the triacetin glass. Above t_2 the extent (e.g. quantum yield) of photoproduct formation from ^{3}**A** is maximal.

The stability of the triplet manifold metastable products, such as **D** forms, which convert into the **B** forms[15, 16] is also completely controlled by the viscosity of the medium. In fact the apparent activation energies E_c for the process $^3\mathbf{A} \rightarrow \mathbf{D}$ and for the process $\mathbf{D} \rightarrow \mathbf{B}$ seem to be sensibly equal and very similar to the apparent value of the potential barrier for the viscosity determining diffusion process, E_v. Thus in the same bianthrone derivative, in a triacetin glass medium at 214 K, E_c for the $^3\mathbf{A} \rightarrow \mathbf{D}$ process amounts to 36 kcal, E_c for the $\mathbf{D} \rightarrow \mathbf{B}$ process amounts to 46 kcal, and E_v amounts to 46 kcal (at 214 K). The viscosity of this medium at this temperature is 6×10^8 cp. For comparison, the approximately

viscosity-independent $^3\mathbf{A} \rightarrow \mathbf{A}$ process has under the same conditions an activation energy E_c of 5 kcal[15]. These results are of great importance as they provide as yet the only approach of arriving at an educated guess about the conformations of the metastable $^3\mathbf{A}$ and **D** intermediates. To explain the differences in the viscosity effects on $^3\mathbf{A} \rightarrow \mathbf{A}$, $^3\mathbf{A} \rightarrow \mathbf{D}$ and on $\mathbf{D} \rightarrow \mathbf{B}$ in terms of molecular geometry changes we should note first that at such high viscosities any large scale internal motions of our molecules are severely restricted, even more than are the internal motions of the solvent molecules. First we can conclude that the $^3\mathbf{A} \rightarrow \mathbf{A}$ process involves only minor geometry change. Thus the triplet and ground state of these molecules should have roughly similar conformations. This is indeed a surprising but none the less rigorous conclusion as the perpendicular conformation is usually assumed for the bianthrone triplet. The opposite applies to **D** and **B**. These two when taken together, as well as **A**, have all different conformations. We know already that this conclusion applies to **A** and **B** when taken together. However, the present results imply also that **D** and **B** have significantly different conformations. While that of **B** seems to be quite well established[5], that of its metastable form **D** is as yet known only in general terms. Like **B**, it should involve some large scale twisting about the 9–9′ double bond. However, considering its origin from the **A** form we anticipate a lesser extent of folding about the 9–10 and 9′–10′ axes of the anthrone subunits than in the **B** form.

IX. THE PHOTOCHEMICAL INERTNESS OF THE TRIPLET MANIFOLD PHOTOINTERMEDIATES *D*, *B*, *E* AND *F*

The triplet manifold photointermediates of the bianthrylidene series (**D**, **B**, **E** and **F**) enjoy the unique distinction of absolute photochemical inertness towards the reverse photochemical process ($\mathbf{D}, \mathbf{B}, \mathbf{E}, \mathbf{F} \overset{h\nu}{\rightarrow} \mathbf{A}$). This photostability (which to the best of our knowledge has not been explicitly considered before) is in direct contrast with the high photochemical reactivity of the fundamental modifications **A**. Compared with other photochromic systems this stability is no less remarkable. Thus it sharply contrasts the ring-opening photoreactivity of the **C** photoisomers of bianthrylidene-type molecules and of the whole large group of the closely related 4a,4b-dihydrophenanthrenes. To understand this special situation we need to consider first the conformation of the core region in the four triplet products **D**, **B**, **E** and **F**. This core region (consisting of the 9,9′ double bond and of the four adjoining single bonds) is very strongly deformed, having been subjected to strong torsion about the 9,9′ bond in **D**, **B** and **F** and to significant folding along the 9,9′ axis in **E** and in **F** as well. All the torsional deformations and most of the folding deformations are absent in the corresponding **A** forms. In the absence of 1 and 1′ substituents the core region in the **A** forms is planar, while in the 1,1′-substituted molecules it is folded to some extent about the 9,9′ axis, though less than in the photoisomers **D**, **B**, **E** and **F**. In **D**, **B**, **E** and **F**, upon excitation, the four essential single bonds contract while the central 9,9′ double bond expands. Large changes in geometry occur going from ground to excited state (or falling back) as in these molecules changes in bond length, torsional angles and out of plane deformations are very strongly coupled to strong non-bonded repulsions on one hand and to electronic density changes on the other. As a result of the large geometry changes accompanying the excitation (or de-excitation) a large number of low frequency totally symmetric normal modes acquire large Franck–Condon overlap factors (cf. Ref. 77). This phenomenon was previously treated in the related case of sterically hindered stilbenes[77]. As a result, the **B**, **D**, **E** and **F** forms as other sterically hindered non-planar aromatics undergo fast and efficient radiationless transitions from their excited states to their ground states. To recapitulate, we consider radiationless transitions (this description applies certainly to aromatics and to polyenes) as taking place by crossing from the upper electronic state (relaxed at low viscosities, constrained at very high viscosities) to a virtual isoenergetic highly excited vibrational substate of the lower electronic state. The rate

constant (k) of a radiationless transition (in a common formulation of the theory) is given by the product of the density of states (ρ), the square of the electronic coupling factor (J) between the two states, and the total mean Franck–Condon factor $\bar{F}$ for an energy gap E[77].

$$k = (2\pi/h)\, J^2 \cdot \rho \cdot \bar{F}(E)$$

Thus, unlike the situation in planar molecules, severely deformed non-planar systems such as **D**, **B**, **E** and **F** command a considerable number of large (one mode) Franck–Condon factors for the excited singlet or triplet to ground state gap[77]. In addition, the density of vibronic states in the lower electronic state (isoenergetic with lowest vibrational level of upper state) is also increased by the presence of low frequency out of plane deformations. All these factors combine to increase strongly the rates of radiationless internal conversion processes, deactivating efficiently the excited singlet and triplet states of **D**, **B**, **E** and **F**.

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CHAPTER 7

Chemiluminescence of quinonoid compounds

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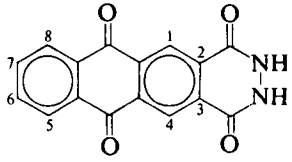
I. INTRODUCTION

Chemiluminescence is the emission of light from electronically excited molecules whose excitation is produced from chemical reactions by direct energy transformation, and not, or nearly exclusively not, from heat. The most general mechanistic theory of the formation of such excited states is that of appropriate electron transfers[1-3]: a reaction product is formed in a way that at least part of the electrons are transferred to the lowest unoccupied molecular orbital (LUMO). It depends on the energetics of the chemical reactions involved, whether a first excited singlet state (leading to fluorescence emission) or a first excited triplet state (yielding phosphorescence) is formed as the primary excited species. This primary excited species can be the light emitter only when it luminesces in the visible

range of the spectrum ('direct chemiluminescence')—otherwise a fluorescer must be present to which the excitation energy can be transferred ('indirect chemiluminescence'). For further details see Ref. 4. This chapter is restricted to chemiluminescence in the visible range of the spectrum and does not deal with IR or UV chemiluminescence.

Quinone/hydroquinone systems are characterized by electron transfer processes, since they are redox systems. One should therefore expect in these systems chemiluminescence reactions, and they have actually been observed although some of them exhibit very low chemiluminescence quantum yields. Moreover, if oxygen is present in such chemiluminescent reactions of quinone/hydroquinone systems there appears to be the possibility of formation of excited singlet oxygen species.

Some quinone derivatives such as the anthraquinone dicarboxylic acid hydrazide (**1**)[25, 26] are chemiluminescent on oxidation—evidently not as quinones but as hydrazides of the well-known luminol type.

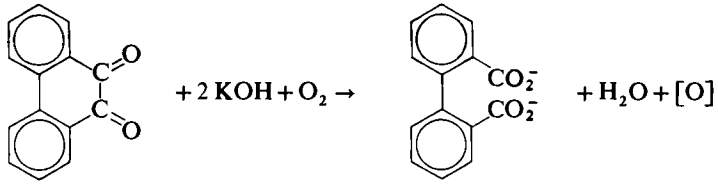


(**1**)

The oxidative elimination of the hydrazide nitrogen in **1** follows a reaction path involving a quinodimethane peroxide (see Section VI). This chapter will discuss the chemiluminescence of the following types of compounds: quinones; semiquinones and hydroquinones; quinone derivatives with cyclic hydrazide groups of the luminol type; diazaquinones; quinone imines and related compounds, e.g. flavins; and quinodimethanes.

II. QUINONES, SEMIQUINONES AND HYDROQUINONES

The earliest observations of the chemiluminescence of a quinone was reported in 1883[5], when it was observed that a colourless light emission occurs when ethanolic potassium hydroxide solutions of phenanthrene quinone (**2**) are shaken with air. It was proposed that **2** is transformed to diphenic acid:

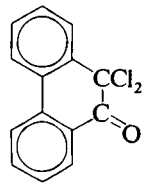


(**2**)

The dichloro derivative (**3**) also yielded light emission under the same reaction conditions, probably via **2** formed by hydrolysis in the alkaline medium. The quantum yield as well as the excitation mechanism have been unknown.

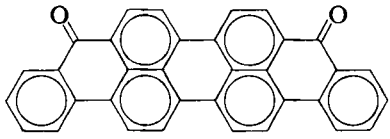
A. Violanthrone

Reacting violanthrone (**4**) with dibenzal diperoxide (**5**) in paraffin oil at 250°C produces a light-red chemiluminescence[6]. A brilliant red chemiluminescence is also given by **4** on

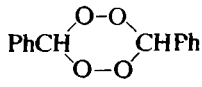


(3)

treatment of its chloroform solution with aqueous alkaline hydrogen peroxide and gaseous chlorine, i.e. on oxidation with singlet oxygen[7a]. This rather complicated example



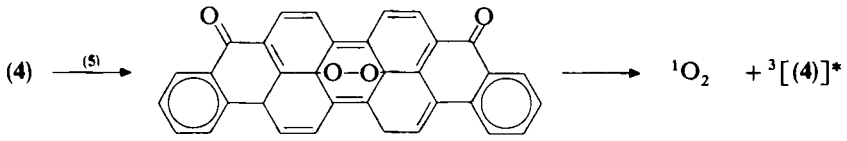
(4)



(5)

of a quinone chemiluminescence is reported before the discussion of simpler quinones because it has been investigated especially thoroughly using modern methods and mechanistic concepts, and also taking into account the role of excited singlet oxygen in the chemiluminescence.

The first investigator of the chemiluminescence of **4** suggested the following mechanism[6]:



(6)

Oxidation of **4** leads to the formation of the endoperoxide **6** which decomposes to give singlet oxygen and **4** in its excited triplet state, and the latter was claimed to be the emitter. Such chemiluminescent decomposition of endoperoxides of fluorescent aromatic hydrocarbons has been known since 1937[7a,b,8].

The solvent chloroform in the original biphasic system[6] can be replaced by pyridine which simultaneously serves as base so that the chemiluminescence of **4** can be performed in a homogeneous phase.

In subsequent investigations[9,10] the role of singlet oxygen was firmly established in the violanthrone chemiluminescence. It was stated that the same red emission can be obtained by treatment of **4** in dibutylphthalate solution with singlet oxygen produced by microwave discharge, and that the emitting species is not an excited triplet but the first excited singlet state of **4**. This species is also the emitter in the above-mentioned chemiluminescent reaction of **4** with dibenzal diperoxide (**5**)[11]. The excitation of **4** occurs by energy transfer on a transient excited triplet state of **4** by triplet benzaldehyde and/or singlet oxygen monomers and collisional pairs.

B. Other Quinones, Hydroquinones and Semiquinones

A large number of simple quinones and hydroquinones have been described to yield chemiluminescence on oxidation or reduction. The quantum yields were always low or very low ('ultraweak' chemiluminescence, i.e. chemiluminescence with quantum yields of 10^{-8} or less).

In most of these cases the formation of singlet oxygen and the chemiluminescence emission of the latter appears to be the decisive mechanistic pathway. It appears reasonable to think that intermediate reduction products of quinones such as semiquinones or even hydroquinones are the electron donors. Stauff and coworkers[12] and other authors[13] previously proposed the following electron transfer steps:

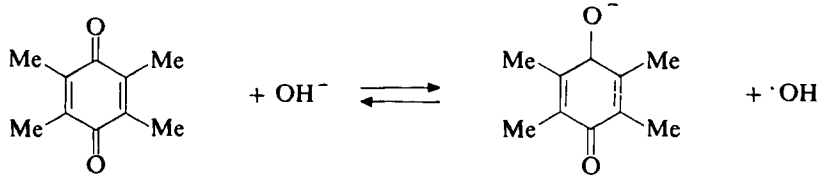
$$O_2 + D \rightarrow O_2^- + D^+ \qquad (D = \text{electron donor})$$

$$O_2^- + O_2 \rightarrow (O_4)^-$$

$$(O_4)^- + O_2^- \rightarrow (O_2O_2)^* + O_2^{2-}$$

The following quinones exhibited chemiluminescence on treatment of their aqueous alkaline solutions with oxygen or by electrochemical reduction: duroquinone[12], benzoquinone[14], methylbenzoquinone[14], 1,4-naphthoquinone[14], 9,10-anthraquinone[14], 9,10-anthraquinone-2-sulfonate[15].

Whereas in most cases of reduction of quinones the above-mentioned mechanism of the formation of singlet oxygen appears rather clear since the quinones are transformed first into the corresponding semiquinones or hydroquinones which in turn could act as electron donors, the situation is more difficult in the case of duroquinone where it was postulated[12]

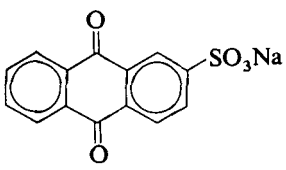


(7)

that a redox reaction should occur between 7 and hydroxyl ion to give the semiquinone and hydroxyl radicals. However, since the reaction takes place in an alcoholic medium, the actual mechanism may involve ^-OR ions as the electron donors*. Comparing the redox potentials of the systems duroquinone/durosemiquinone and $HO^-/\cdot OH$ the equilibrium should be by far on the left side. That, nevertheless, semiquinones are involved in this type of chemiluminescence could be proved by the fact that ESR spectra demonstrate the presence of durosemiquinone anions in alkaline solutions of duroquinone[15]. Moreover in all cases investigated so far the respective semiquinones always produced higher light yields than the parent quinones.

However, there are examples where chemiluminescence of quinones does not require oxygen at all, or where at least the light emission is caused both by excited singlet oxygen and by other compounds formed in certain oxidation reactions. Thus, the semiquinone of 9,10-anthraquinone-2-sulfonate (**9**) produced by reduction of 9,10-anthraquinone-2-sulfonate (**8**) at pH 12.5 using a platinum cathode yields chemiluminescence not only by its reaction with oxygen but also with ferricyanide[16]. When the hydroquinone (**10**) is oxidized by ferricyanide the light yield is twice that of the corresponding reaction of the semiquinone (**9**). It was suggested that excited forms of the quinone (**8**) and of the

* We are indebted to Prof. Joachim STAUFF for this remark.



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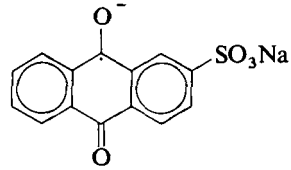

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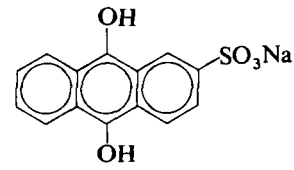
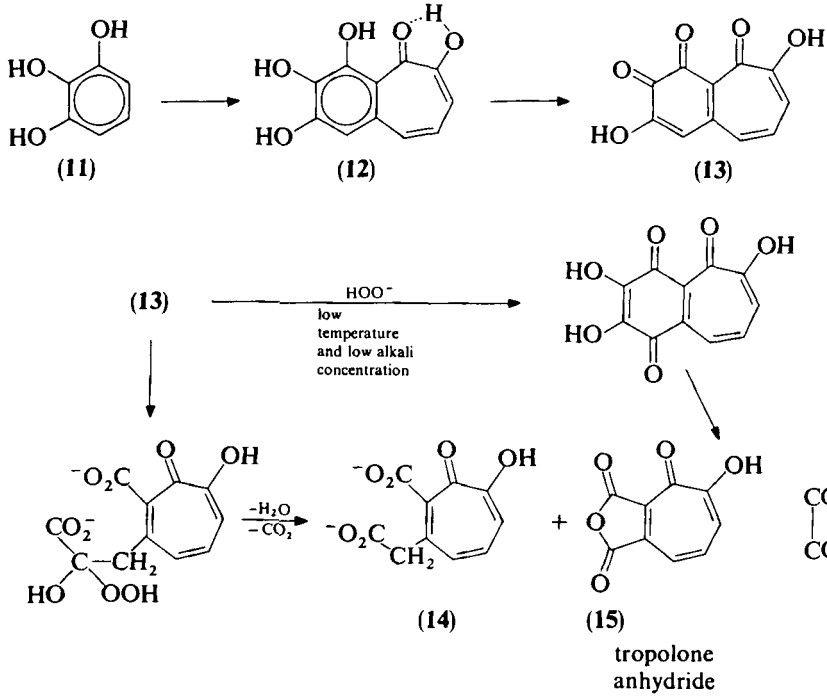


(10)

semiquinone (9) are the emitters in their triplet state, since the wavelengths of the emissions were higher than those of the corresponding singlet states[16]. Perhaps, although evidence is still lacking, the chemiluminescence in quinone/semiquinone/hydroquinone systems is a special case of CIEEL (chemically initiated electron exchange luminescence; for a general treatment of this general concept of chemiluminescence see Ref. 1).

Another case is the well-known Trautz-Schorigin reaction[17], i.e. the oxidation of pyrogallol with hydrogen peroxide and formaldehyde in aqueous alkaline solution is chemiluminescing with a red emission mainly caused by singlet oxygen[18,19]. However, more detailed investigations demonstrated that an additional emission is observed in the range of 400–600 nm. This has been ascribed to oxidation products of pyrogallol (**11**) which are formed via purpurogalline (**12**) as the first intermediate[18], since purpurogalline itself, on oxidation with different oxidants such as O_2, ozone, hypochlorite, permanganate or electrolytic oxidation in aqueous alkaline solution (pH 9–11) was found to yield chemiluminescence at 400–600 nm with quantum yields of 10^{-7}–10^{-6} Einsteins mol^{-1}. No chemiluminescence occurred in acidic media (pH 3.5–7) with different oxidants, e.g. Fe^{3+}, $Fe(CN)_6^{3-}$, H_2O_2/peroxidase, or by heating. The rate-controlling step is suggested to be the nucleophilic attack of HOO^- ions on purpurogalloquinone (**13**):



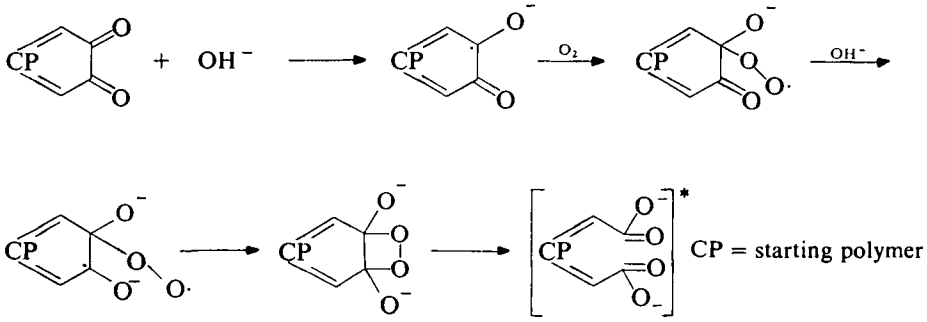
Light emission is produced by the oxidative degradation of the quinone **13** by which excited tropolone derivatives are formed. These compounds, **14**, **15** and perhaps similar tropolone derivatives fluoresce in the range of the spectrum of the purpurogalline chemiluminescence.

Formation of purpurogalloquinone has been established to be the key intermediate in pyrogallol oxidation[18,20,21]. This reaction has been studied as a model for the generally very weak chemiluminescence of polyhydroxyphenols regarded as models for humic acids.

C. Humic Acids, Melanins and other Quinone Polymers

Autoxidative polymerization of hydroquinone, purpurogalline or adrenochrome yields products which on photolysis yield weak chemiluminescence[22]: the irradiation is suggested to initiate electron transfer reactions which in the presence of oxygen produce excited molecular singlet oxygen (cf. Section II.B), whereas in the absence of oxygen some excited quinone is formed as emitting species.

Adrenochrome polymers[23] chemiluminesce after photo-oxidation in alkaline media with quantum yields of 10–510 photons per second, the maxima of this emission are observed at 480–500, 570 and 615–650 nm. Radical scavengers reduce the quantum yield by 20–97 %. The mechanism is suggested to be an oxidative ring-opening of *ortho*-semiquinone structures analogous to that of purpurogalline, a dioxetane being the key intermediate:



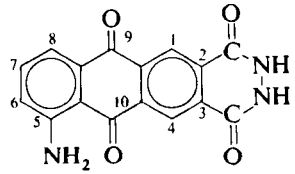
The excited products formed in this way are postulated to be the emitters of the light in the spectral range lower than 600 nm whereas the longer wavelength emission (at 615–650 nm) stems from excited singlet oxygen.

Although quinone structures are very probably involved in this type of chemiluminescence, one has to be aware of the fact that a definite determination of the mechanism of these complex reactions will be extremely difficult since only a very small part of the molecules involved lead to electronically excited products. Above all, the exact structure of humic acids is only very approximately known at present.

III. ANTHRAQUINONE HYDRAZIDES

9,10-Anthraquinone-2,3-dicarboxylic acid hydrazide (**1**) chemiluminesces weakly on oxidation with O_2 in DMSO solution and potassium *t*-butylate as base[24,25] but practically not in aqueous alkaline hydroperoxide[26]. The emission maximum of **1** in the aprotic system is at 580 nm, the quantum yield is ca. 4 % of that of a luminol standard[25].

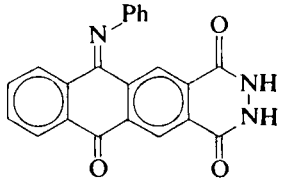
The 1-, 5- and 6-amino derivatives of **1** exhibited an interesting behavior of the normally chemiluminescence-enhancing effect of the electron-donating amino group. It was found



(16)

that only the 5-amino compound (**16**) was strongly chemiluminescent in the aqueous system (93% light yield of luminol) as well as in the aprotic one (273% that of luminol!), whereas the 1-isomer had only 0.37% of the luminol light yield in the aprotic system and gave no light at all in the aqueous one.

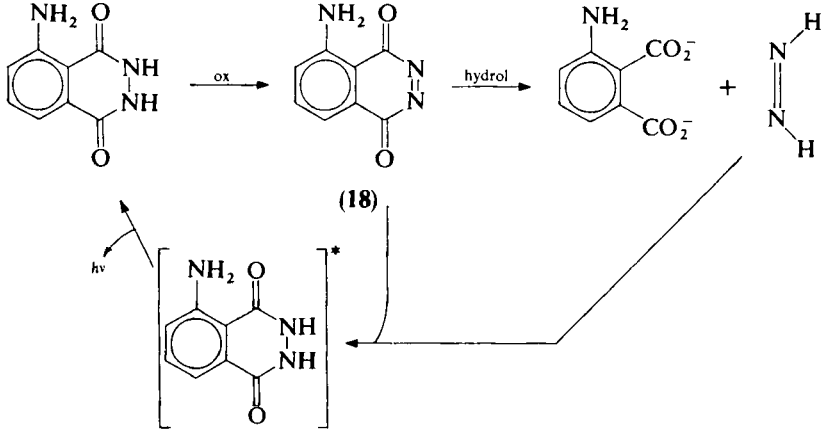
The phenylimine derivative (**17**) gave less than 10% of the quantum yield of its parent compound (**1**).



(17)

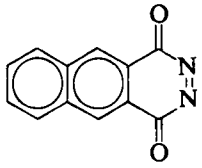
IV. DIAZAQUINONES

In the first paper on luminol chemiluminescence, Albrecht[27] had already suggested a diazaquinone (5-aminophthalazine-1,4-dione) (**18**) as an intermediate in the reaction mechanism, although such compounds were unknown at that time, and the role of the diazaquinone had been interpreted incorrectly, as shown later by further experimental evidence. The first diazaquinones were prepared by Clement[28] and by Kealy[29] but none of them was chemiluminescent, due to the fact that their oxidative hydrolysis produced non-fluorescent dicarboxylates.



(18)

The diazaquinones **19** and **20** were synthesized by dehydrogenation of the corresponding hydrazides at temperatures of ca. $-50°C$[30, 31]. **19** and **20** are deeply violet-colored crystalline substances which undergo nitrogen elimination at 0°C. They are very prone to nucleophilic attack at their carbonyl groups. Oxidation by alkaline hydrogen peroxide results in chemiluminescence whose emission spectrum matches that of the corresponding hydrazide and the fluorescence spectrum of the dicarboxylates **21** and **22**, respectively.



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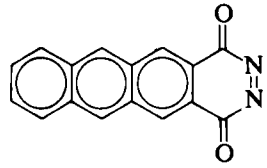

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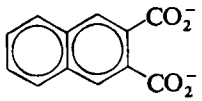

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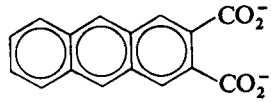
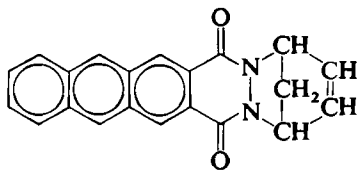


(22)

Whereas the chemiluminescence of benzophthalazine-1,4-dione (**19**) was investigated in an inhomogeneous aqueous system (where the diazaquinone is practically insoluble)[48] a very thorough investigation of the naphthophthalazine-1,4-dione (**20**) was performed in homogeneous dimethyl phthalate solution using anhydrous hydrogen peroxide and diethylamine as base[30]. Trapping the diazaquinone by cyclopentadiene with which a Diels–Alder adduct (**23**) is very rapidly formed it could be made probable that a diazaquinone is also formed as intermediate in the hydrazide chemiluminescence reaction[30].



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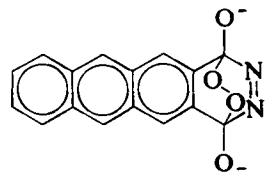

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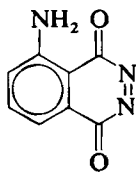

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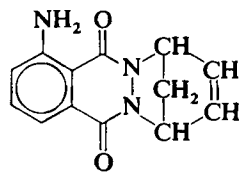

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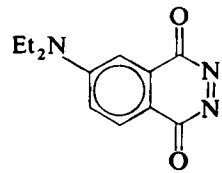


(27)

The requirement of an additional oxidant demonstrates that it is not the diazaquinone itself which on mere hydrolysis yields the chemiluminescence but an oxidation product of the diazaquinone, which is very probably the endoperoxide (**24**). The theories concerning its chemiluminescent decomposition are described in Section VI.

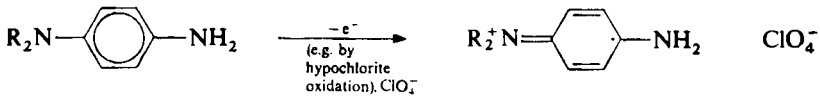
'Luminol diazaquinone' (5-aminophthalazine-1,4-dione, **18**) has not yet been obtained in analytically pure form probably due to the easy formation of by-products during the dehydrogenation of the hydrazide by oxidative degradation of the primary amino group. However, the corresponding Diels–Alder adduct (**26**) was isolated from luminol solutions undergoing ferricyanide oxidation in the presence of cyclopentadiene[31].

Recently the diazaquinone **27**, obtained by dehydrogenation of 7-diethylaminophthalic acid hydrazide, has been described[32].

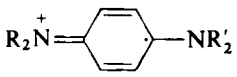
V. QUINONE IMINES AND RELATED COMPOUNDS

A. Wurster's Red and Wurster's Blue

Compounds of the Wurster's Red (**28**) and Wurster's Blue type (**29**) are semiquinone analogs which chemiluminesce in reactions with aromatic or heterocyclic radical anions



R = Me **(28)**



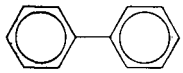
(**29**, R = R′ = Me)

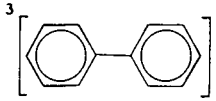
acting as electron donors[33–36]. This reaction has been investigated very thoroughly: quantitative relations were established between the reduction potential of the respective electron donor molecules and the nature of the excited state formed from the electron donor. Irrespective of whether the latter was directly formed in its first excited (so-called 'energy-sufficient') singlet state, or via first excited triplet states which, e.g. by triplet–triplet annihilation reaction give rise to the first excited singlet state, the latter is in all cases studied the emitting species.

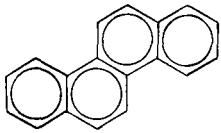
Some chemiluminescent systems of aromatic hydrocarbon radical anions[37] are shown below:

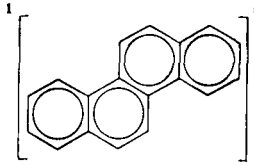
with Wurster's Red perchlorate:

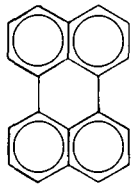
Excited species.

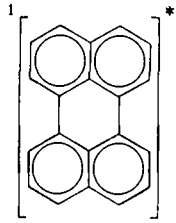




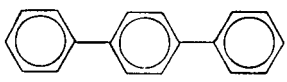


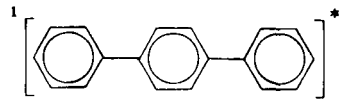


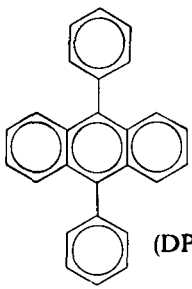




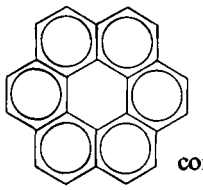
with Wurster's Blue perchlorate:





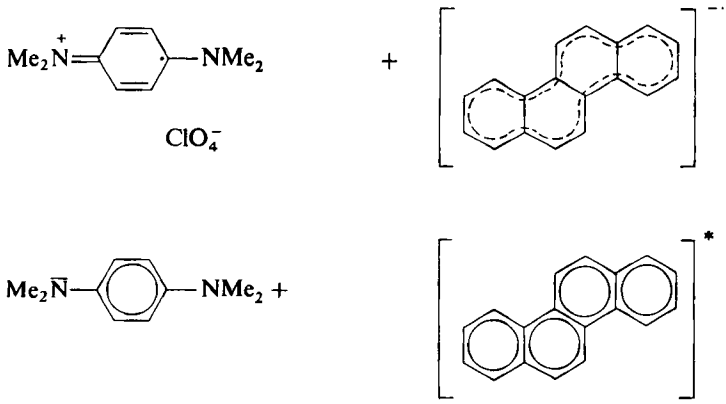


(DPA) ^{1}DPA*



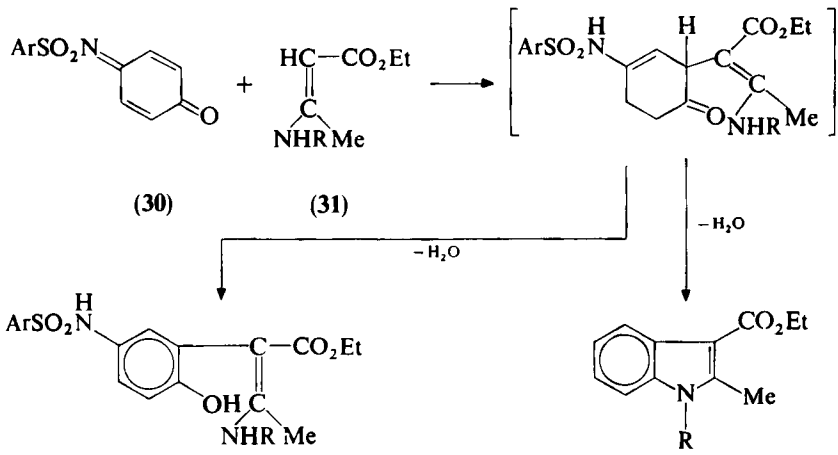
coronene ^{1}coronene*

The reaction between Wurster's Blue and chrysene radical anion may be quoted as an explicit example:



B. *N*-Arylsulfonyl benzoquinone Imines

Condensation of *N*-arylsulfonyl benzoquinone imines of the type **30** with *N*-arylamino crotonates (**31**) yields chemiluminescence provided the crotonate is substituted with phenyl groups (R = Ph) whereas R = alkyl or cycloalkyl leads to non-chemiluminescent reactions[38]. This reaction leading to substituted indoles appears to



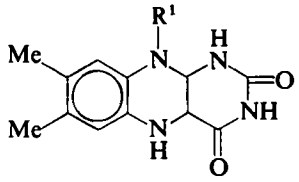
involve no radical intermediates—at least none detectable by ESR. The excitation mechanism is not yet clear. Interestingly the quinone imines (**30**) produce chemiluminescence also on reaction with aliphatic amines such as butyl amine, benzyl amine and diethyl amine[39]. This evidently demonstrates that the excitation mechanism is different from that of the indole formation for which as mentioned above phenyl groups must be present on the amino crotonate nitrogen atom. Moreover, in the chemiluminescent reaction of **30** with simple amines free radicals with rather high lifetimes were detected.

C. Flavins

The bioluminescence of bacteria involves the reaction

Dihydroflavin mononucleotide ($FMNH_2$ = **32**) + O_2 + RCHO $\xrightarrow{\text{enzyme}}$ FMN (**33**) + RCOOH + $h\nu$

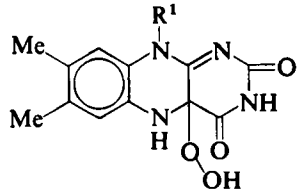
(RCHO = long-chain aliphatic aldehyde)



$FMNH_2$ (**32**) + enzyme (E) $\rightleftharpoons$ $FMNH_2 \cdot E$

Intermediate I

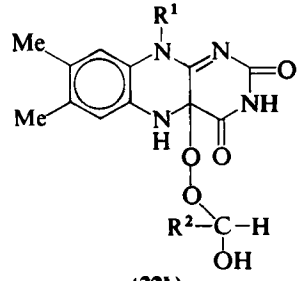
$FMNH_2 \cdot E + O_2$ ⟶



· E

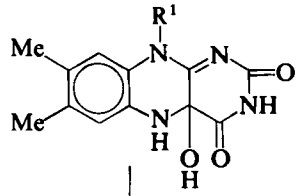
Intermediate II
(**32a**)

II + R^2CHO ⟶

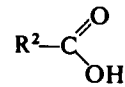


(**32b**)

(**32b**) ⟶

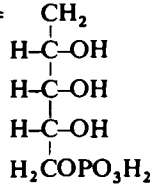


+

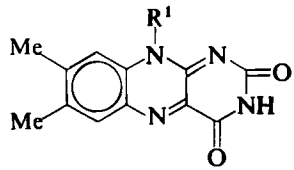


(**32c**)

R^1 =



R^2 = *n*-alkyl



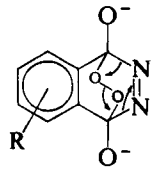
+ H_2O

FMN (**33**)

The emitting species (maximum of the blue–green emission ca. 510 nm) is the 4a-hydroxyflavin intermediate **32c**[40]. Aside from all important biochemical and other implications concerning the mechanism of this reaction (for reviews see Refs 41, 42) the flavin system and its dihydro derivative as iso-alloxazine systems may be classified as 'extended quinone' imine derivatives. The first step in the oxidation of $FMNH_2$ involves the addition of molecular oxygen to the 4a position of the flavin ring[40], a peroxide (**32a**) being formed. The end products—in the luminescent reaction—are formed via a peroxy-semiacetal (**32b**) which results from the reaction of the peroxide with the long-chain aldehyde.

VI. QUINODIMETHANE DERIVATIVES

It appears to be solidly established that the oxidation of diazaquinones, under appropriate conditions, yields a chemiluminescence very similar to or even identical with that of the corresponding hydrazides showing among other features the same maximum of the emission spectrum and the same end product. However it is still uncertain whether the generally assumed peroxide (**34**) actually is the key intermediate whose decomposition into

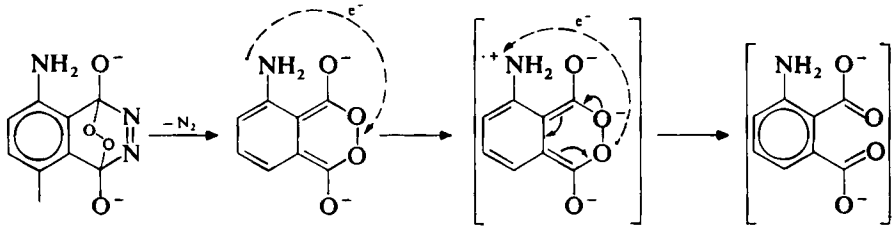


(**34**)

molecular nitrogen and *o*-dicarboxylate is the light-producing step. Since a synchronous electrocyclic decomposition of **34** (following the inserted arrows) is a thermally allowed process according to the Woodward–Hoffmann rules[43,44], it has been proposed by Michl[45] and by Schuster[2] that the decomposition of the peroxide **34a** (i.e., **34**, with R = 5-amino) proceeds in two steps:

(1) elimination of N_2 with formation of the quinodimethane compound (**35**);

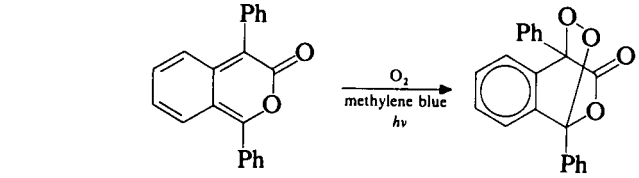
(2) intramolecular electron transfer from the amino group of luminol (and from higher condensed aromatic systems such as anthracene) to the peroxide group, followed by cleavage of the latter and re-aromatization involving the return of the transferred electron to the amino group:



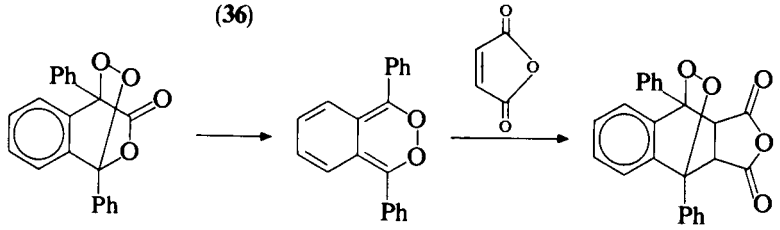
(**34a**) (**35**)

For the time being the existence of both postulated compounds **34a** and **35** is still hypothetical.

However, an example has been provided for an *o*-quinodimethane chemiluminescence[46,47]. The very unstable quinodimethane peroxide (**37**) could be trapped as its

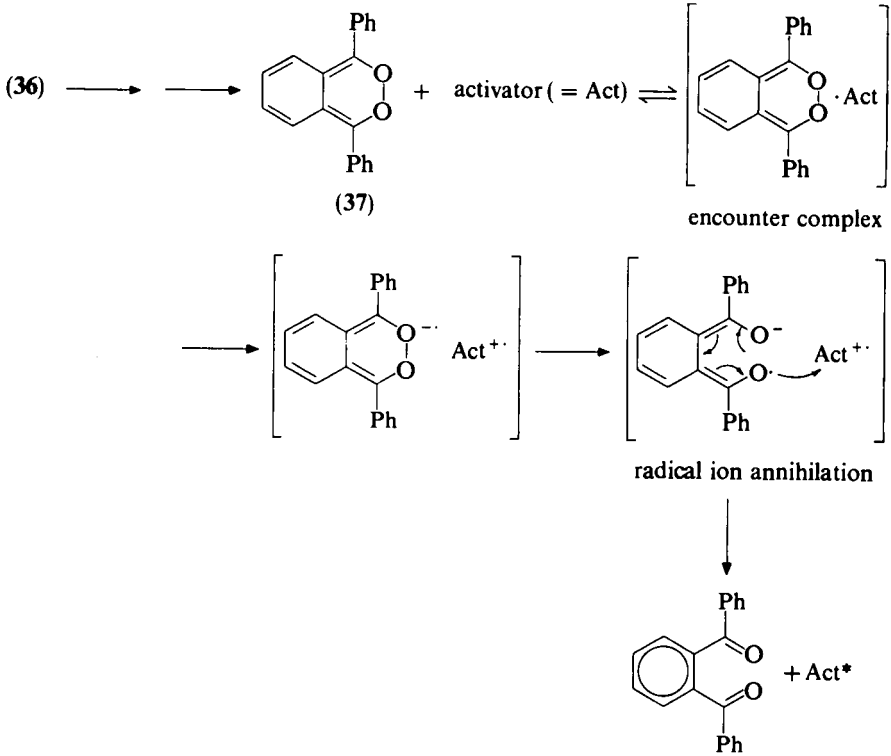


(36)



(37) (38)

Diels–Alder adduct with maleic anhydride (**38**). In the presence of 'activators' such as perylene, acridine orange or 9,10-diphenylanthracene, the photo-oxidation of the isocoumarine derivative (**36**) yields indirect chemiluminescence whose emission matches that of the fluorescence of the activator. An intramolecular electron transfer mechanism has been proposed as the cause of this chemiluminescence:



The electron transfer steps take place in a solvent cage (symbolised by the brackets in the scheme above).

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The Chemistry of Quinonoid Compounds, Vol. II
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CHAPTER 8

Recent advances in the synthesis of quinonoid compounds

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I. INTRODUCTION

After the publication of the early volumes on the quinonoid compounds in this series in 1974[1], several reviews and books treated this field[2-7]. Especially, references 5 and 6 comprehensively cover the literature published until the early 1970s. In the following decade, great progress took place in synthetic organic chemistry, and many sophisticated methodologies and new reagents have been developed and utilized for the synthesis of quinonoid compounds with complex structures. Particularly, the advances in organometallic chemistry extensively contributed to this field. Synthetic methods with high regio- and stereoselectivity have great importance in modern organic synthesis. Some of them have been applied to the synthesis of naturally occurring quinones, most of which possess versatile interesting physiological and biological activities. In Section VII, we discuss total and fragment synthesis of selected natural quinonoid products, as a good demonstration for these reactions in quinone synthesis.

II. OXIDATION METHODS

Quinones have an higher oxidation state than the corresponding synthetic precursors, i.e. the aromatic hydrocarbons, phenols, hydroquinones and catechols. Consequently, the oxidation method consists of one of the major routes to quinones which does not require a change in the carbon framework. The oxidation method offers the best procedure, especially for preparation of quinones with rather simple structure. In this section, we discuss the recent progress, which includes the finding of several new oxidation reagents and mainly the improvement and modification of reactivity and selectivity of well known methods. In order to obtain quinones in high efficiency from commercially available compounds, it is recommended to start with phenols as precursors rather than with hydrocarbons, due to the ease and high product selectivity of their oxidation. Several methods are compared with each other in order to enable the reader to choose an appropriate oxidation method.

In the synthesis of naturally occurring quinones, one can find many successful examples of oxidative quinone formation starting from substrates with rather complex functionality and compare the applicability of the various oxidation methods.

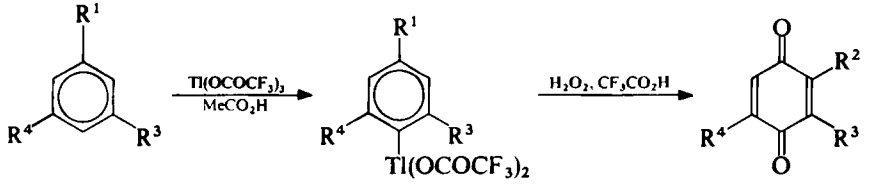
A. Aromatic Hydrocarbons

Only condensed polycyclic aromatic hydrocarbons have been reported to be successfully oxidized to the corresponding quinones. Because of severe oxidation conditions and the powerful reagents required in this conversion, most other functional groups as well as the

produced quinones themselves frequently suffer further oxidation. However, for a large scale production, this route is attractive, because of the inexpensive supply of raw materials. On the other hand, under laboratory conditions other oxygenated precursors, such as phenols or aromatic ethers, have great advantage as starting materials due to their higher susceptibility toward oxidation, and they can be selectively converted to the corresponding quinones under mild conditions. Typical examples of reported procedures are listed in Table 1.

Among the many metallic oxidants, the high valent cerium, Ce(IV), gives satisfactory results, regardless of stoichiometric or catalytic conditions[8,9]. Ammonium cerium(IV) sulfate (CAS)[10] prepared from cerium sulfate and ammonium sulfate in diluted acid gives quinones in better yields than ammonium cerium(IV) nitrate (CAN)[11]. The major problem encountered in these types of oxidation is the low product selectivity. For example, 2-alkylnaphthalenes and phenanthrene give the corresponding two isomeric quinones, respectively, in comparable yields. A similar selectivity is also observed in oxidation with $Mn_2(SO_4)_3$, which usually gives better yield than CAN[12]. Anodic oxidation with cerium sulfate or CAN as a mediator is reported to give improved yields than those obtained under stoichiometric conditions[13]. A two-phase oxidation by ammonium persulfate in the presence of catalytic amounts of CAS, $AgNO_3$, and a surfactant also gives results similar to those mentioned above[14]. Chromic acid is a classically well known oxidant, but it requires large amounts of an acidic solution and prolonged reaction time. This defect is due to the low solubility of chromic acid in most organic solvents whereas the aromatic hydrocarbons are soluble in the reaction media. Both phase transfer method in the presence of a quaternary ammonium salt[15] and oxidation in organic solvent with pyridinium fluorochromate (Py-HF-CrO_3)[16] give much improved results, and oxidation of 2-methylnaphthalene and phenanthrene affords selectively 2-methylnaphthoquinone and 9,10-phenanthrenequinone, respectively. The latter oxidant, prepared from anhydrous chromic acid and hydrofluoric acid in pyridine, oxidizes these hydrocarbons in acetic acid media within a few hours. Oxidation of anthracene is one of the easiest examples and all of the aforementioned oxidants give excellent yields.

Electrophilic substitution by thallium trifluoroacetate (TTFA) occurs at a *para* position of a substituted benzene (**1**) and gives the arylthallium(III) derivative (**2**)[18–20], which can be reoxidized to the *p*-quinone (**3**) with pertrifluoroacetic acid in yields ranging from fair to good (equation 1 and Table 2)[21]. A 1,2-migration of the alkyl group from a phenolic *para*

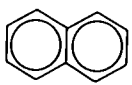
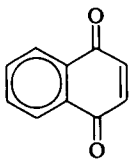
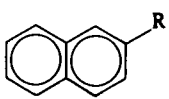
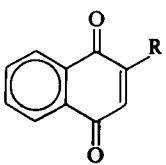
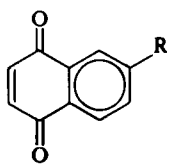


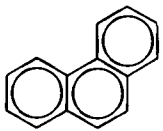
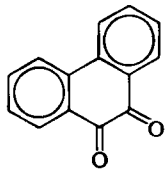
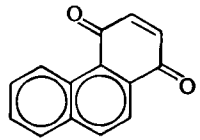
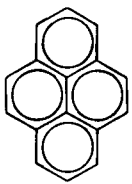
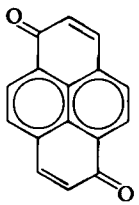
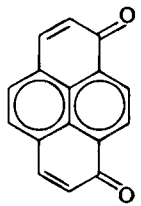
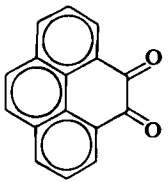
(1) (2) (3)

(1)

position to the *meta* one is observed in this reaction. From the mechanistic standpoint, intermediary formation of **5** and then the phenol derivative (**6**) is proposed, and the latter would be reoxidized by regenerated TTFA to the corresponding quinol (**7**), which will afford the quinone (**8**) with or without migration of the alkyl group (Scheme 1). Scheme 2 is an example of a variant of the TTFA oxidation. The aromatic substitution of **9** by Tl(III) gives **10** which gives an intramolecular lactonization to **11**. Alchoholysis gives the phenol

TABLE 1. Oxidation of aromatic hydrocarbons

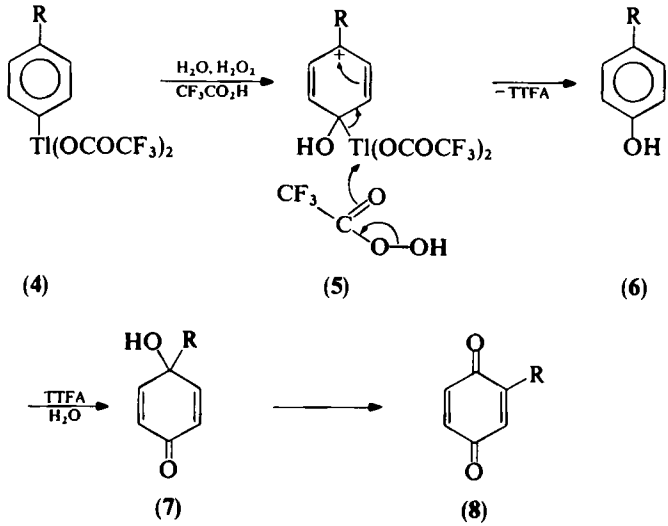
Aromatic hydrocarbon	Oxidant	Quinone (% yield)			Reference
	$Ce(SO_4)_2$, $2(NH_4)_2SO_4$ dil. H_2SO_4		(90–95)		10
	CAN[a]		(20)		11
	$Mn_2(SO_4)_3$		(75)		12
	H_2CrO_4, n-$Bu_4N^+HSO_4^-$ two-phase reaction		(39)		15
	e^-, $Ce(SO_4)_2$, HNO_3		(81)		13
					
R = t-Bu	$Ce(SO_4)_2$, $2(NH_4)_2SO_4$ dil. H_2SO_4	R = t-Bu	(45)	(26)	10
R = Me	$Mn_2(SO_4)_3$	R = Me	(55)	(10)	12

R = Me	H_2CrO_4, n-$Bu_4N^+HSO_4^-$ two-phase reaction	R = Me	(56)	—	15
					10
	$Ce(SO_4)_2$, $2(NH_4)_2SO_4$ dil. H_2SO_4		(60)	(15)	
	CAN[a]		(27.4)	(11.5)	11
	$Mn_2(SO_4)_3$		(32)	(19)	12
	pyridine·HF·CrO_3		(72)		16
	$PhIO_2$		(46)		17
				 	
	e^-, CAN[a]		(65)		13
	$PhIO_2$		(12)	(15) (14)	17

[a] CAN = ceric ammonium nitrate.

TABLE 2. Oxidation of aromatic hydrocarbons by TTFA[21]

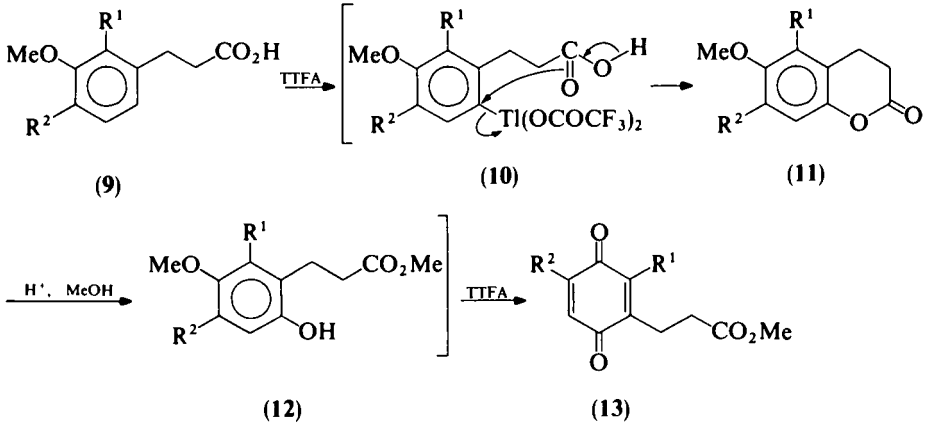
Aromatic hydrocarbon (1)			Quinone (3)			
R^1	R^3	R^4	R^2	R^3	R^4	% yield
H	H	H	H	H	H	65
Me	H	H	Me	H	H	68
Et	H	H	Et	H	H	70
Me	Me	H	Me	Me	H	55
Me	Me	Me	H	Me	Me	50
t-Bu	H	H	H	H	H	50
			t-Bu	H	H	20
Cl	H	H	H	H	H	42
MeO	H	H	H	H	H	61
naphthalene			1,4-naphthoquinone			60



SCHEME 1

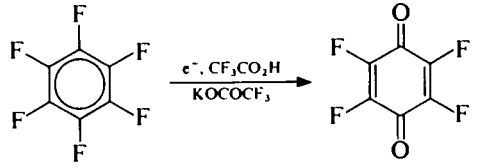
derivative (**12**), which is further oxidized to **13**[22]. Aerobic oxidation of aromatic hydrocarbons is another attractive method relevant to industrial processes. Oxidation of anthracene with air by $RuCl(PPh_3)_3$ as a catalyst gives 9,10-anthraquinone in 55% yield[23]. In this process, the use of hydrogen peroxide, which is assumed to be generated *in situ* in the oxidation with air, instead of molecular oxygen as an oxidant gives the quinone in almost quantitative yield[23,24].

Although anodic oxidation is expected to have great advantage for the preparation of large quantities of quinones, it has not been established as a reliable methodology yet. In most cases, overoxidation and/or oxidative decomposition is the obstacle to the general application of this method. Special cases are perfluorinated aromatic hydrocarbons. For example, hexafluorobenzene (**14**) is converted to the corresponding *p*-quinone (**15**) in 75% yield and octafluoronaphthalene gives the quinone in 60% yield[25] (equation 2).



R^1 and/or R^2 = MeO

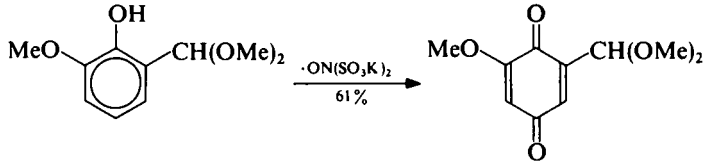
SCHEME 2



(2)

B. Monohydric Phenols

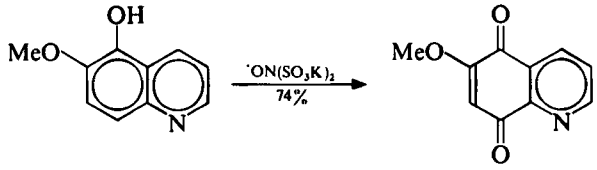
In the course of organic syntheses, it is frequently necessary to convert phenols to quinones. Fremy's salt ($\cdot ON(SO_3K)_2$) (**16**) is still used as a reliable reagent in this conversion[26]. It is suitable mainly for small scale experiments, since the preparation of Fremy's salt is rather tedious and it is difficult to prepare it in quantity due to its instability. Despite these defects, it is frequently a good choice from many other oxidants, because of its excellent *p*-quinone selectivity, wide applicability and the good yields obtained. It is worthwhile to mention the recent comparison of the oxidation by this reagent with other oxidation methods. Vaniline (**17**) cannot be oxidized by Fremy's salt, while the corresponding dimethyl acetal (**18**) affords a *p*-quinone (**19**) under the same conditions



(3)

Ref. 28

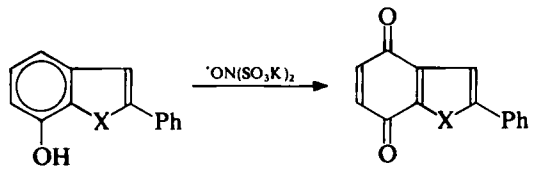
(equation 3)[28]. This oxidation is much more efficiently performed by the O_2–salcomine system, while 5-hydroxy-6-methoxyquinoline (**20**) can be oxidized to the corresponding quinolinoquinone (**21**) by Fremy's salt in better yield than with O_2–salcomine (equation 4)[28]. Although Fremy's salt is known to be a specific oxidant to afford *p*-quinones (equation 5)[27], phenols **24**[28], **27**[29] and **30**[29] give the mixture of the corresponding *o*- and *p*-quinones in the oxidation with Fremy's salt, even when their *p*-position is unsubstituted (equations 6–8)[29]. This *o*-quinone selectivity can be elucidated either by change of the electron density of intermediary phenoxy radicals or by changing the steric environment around the *para* positions.



(4)

Ref. 28

(20) **(21)**

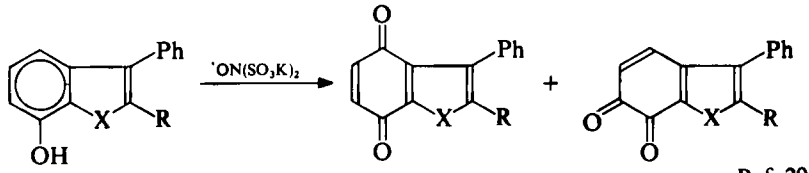


(5)

Ref. 29

(22) **(23)**

X = O, S

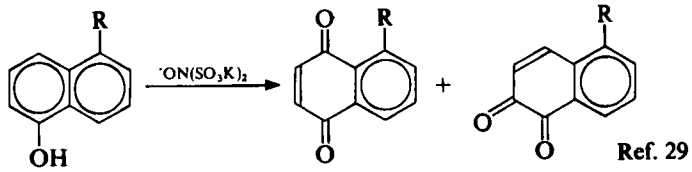


(6)

Ref. 29

(24) **(25)** **(26)**

X = O, S, NH, NMe; R = H, Me

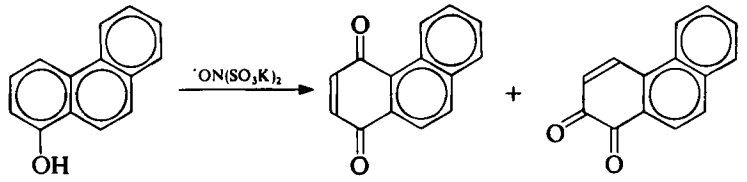


(7)

Ref. 29

(27) **(28)** **(29)**

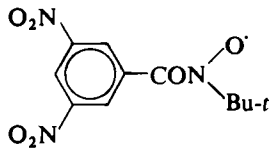
R = alkyl, halogen, NO_2, NHAc



(8)

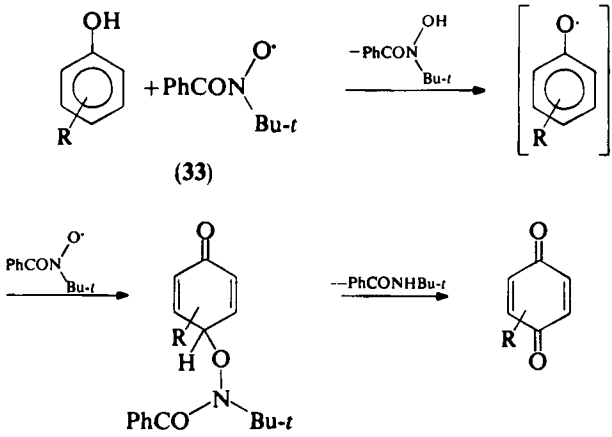
(30) (31) 46.6% (32) 42.4% Ref. 29

Another defect encountered in the oxidation with Fremy's salt is its insolubility in organic solvents and since it requires an aqueous alcoholic medium, it cannot be applied to highly lipophylic substrates. In order to improve the solubility problem two modifications are reported. First, in the analogy to the reaction of Fremy's salt, organic nitroxides are used for the oxidation of phenols. *N*-Benzoyl- (**33**)[30] and *N*-(3,5-dinitrobenzoyl)-*t*-butylnitroxyls (**34**)[30, 31] are prepared and oxidation of phenols is effected in an organic



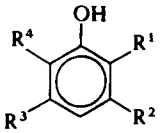
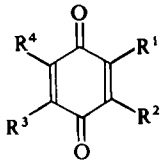
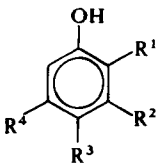
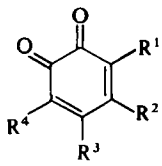
(34)

solvent. Simple phenols are oxidized in almost comparable yields to those obtained with Fremy's salt except in a few cases. As a typical exception, 1,4-benzoquinone itself cannot be obtained by the treatment of phenol with **33**. Comparison of the two oxidizing agents in phenol oxidation is shown in Table 3. **34** is considered as a more powerful oxidant than **33**,



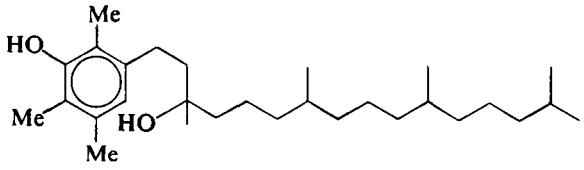
SCHEME 3

TABLE 3. Comparison of the oxidation of phenols to the corresponding quinones by nitroxides[30]

Phenol				Quinone (% yield) with (Fremy's salt)	with (PhCON(Bu-*t*)O·)
					
H	H	H	H	81	0
Me	H	H	Me	75	86
H	Me	Me	H	99	0
Me	H	Me	H	87	42
H	*t*-Bu	H	H		60
MeO	H	H	MeO		60
H	MeO	MeO	H	76	60
Cl	H	H	Cl		46
Me	Me	Me	Me	87	67
					
H	*t*-Bu	H	H		70
H	H	*t*-Bu	H	80	51
t-Bu	H	*t*-Bu	H		87
1-Naphthol		1,4-Naphthoquinone		81	72
2-Naphthol		1,2-Naphthoquinone		91	84

and is capable of oxidizing even allylic or benzylic alcohols to the corresponding carbonyl compound. In the second modification of the oxidation by Fremy's salt, two equivalents of a phase-transfer quaternary ammonium salt catalyst are used to convert Fremy's salt to the lipophylic ammonium nitrosodisulfonate. Tricaproylmethylammonium chloride (**35**) gives **36** (equation 9), which is soluble in most organic solvents and **36** can oxidize the extremely lipophylic phenol **37** to **38** in a quantitative yield (equation 10), while Fremy's salt is completely ineffective on reaction with **37**[32]. This modification is potentially applicable to a wide range of hydrophobic phenols.

$$\underset{\textbf{(16)}}{\cdot ON(SO_3K)_2} + 2\underset{\textbf{(35)}}{(n\text{-}C_8H_{17})_3N^+Me\ Cl^-} \longrightarrow \underset{\textbf{(36)}}{\cdot ON[SO_3^-N^+Me(C_8H_{17}\text{-}n)_3]_2} \qquad (9)$$

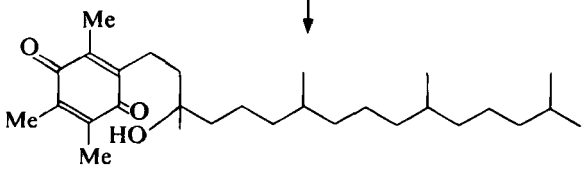


(37)

(10)

$+ \cdot ON[SO_3^- N^+ Me(C_8H_{17}\text{-}n)_3]_2$

(36)



(38)

Benzeneselenic anhydride, $(PhSeO)_2O$ (**39**), oxidizes phenols to the corresponding *o*-quinones in good yields and high product selectivities, even when the *para* position is unsubstituted[33–36]. This method is especially useful for oxidation of hydroxypolycyclic aromatics (Table 4). In some cases, the *p*-quinone is obtained as in the oxidation of **40** to **41**. The *ortho* selectivity is ascribed to a rapid [2, 3] sigmatropic rearrangement of an intermediarily produced phenyl selenyl ether (**42**) and a successive loss of benzeneselenol (PhSeOH) (Scheme 4).

TABLE 4. Oxidation of phenols to *o*-quinones by phenylselenic anhydride

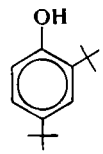
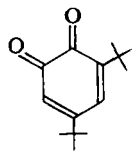
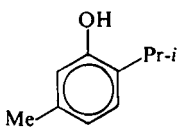
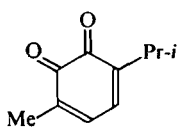
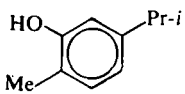
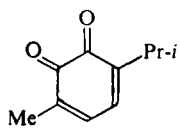
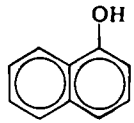
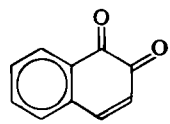
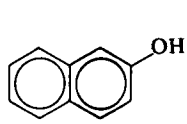
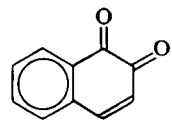
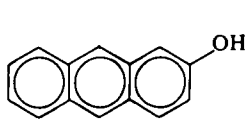
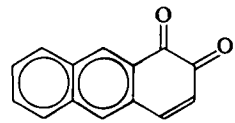
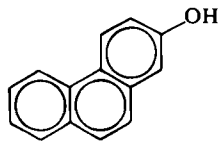
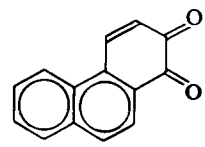
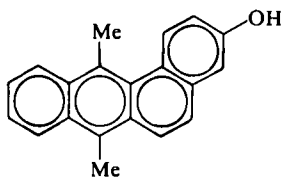
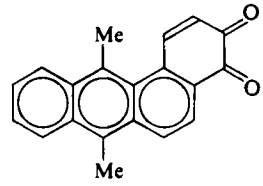
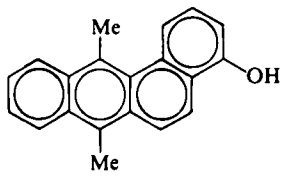
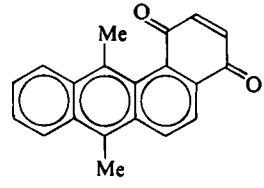
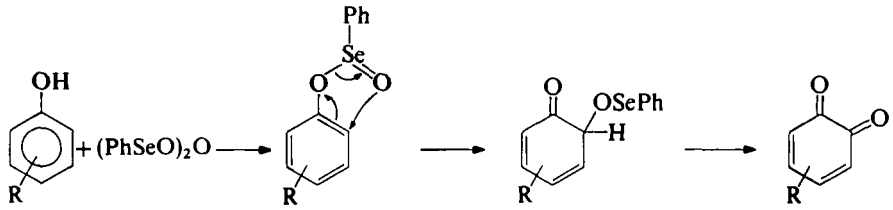
Phenol	*o*-Quinone	(% Yield)	Reference
		(68)	34
		(59)[a]	34
		(60)	34

TABLE 4 (continued)

Phenol	*o*-Quinone	(% Yield)	Reference
		(62–65)[b]	34, 36
		(73)	34, 35
		(54)	35
		(56)	35
		(80)	35
		(60)	35
(40)	(41)		

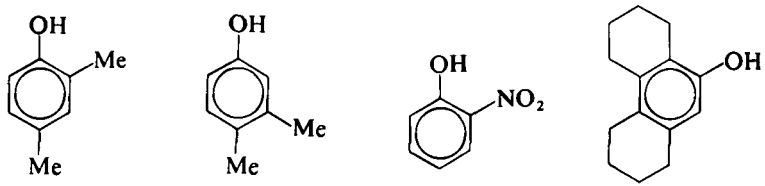
[a] The corresponding *p*-quinone is formed in 15% yield.
[b] 1,4-Naphthoquinone is formed in 5–10% yield.

Phenols **43–45** give complex reaction mixtures and phenol **46**, in which the *para* position is blocked, gives the corresponding *o*-quinone as a minor product accompanied by several side products. In the oxidation of paracyclophanes (**47**) the *o*-quinone **48** is sometimes accompanied by the corresponding *p*-quinones (**49**) (equation 11). Consequently, the

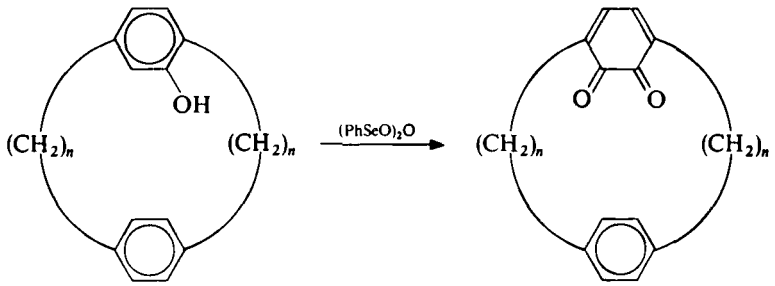


(39) (42)

SCHEME 4



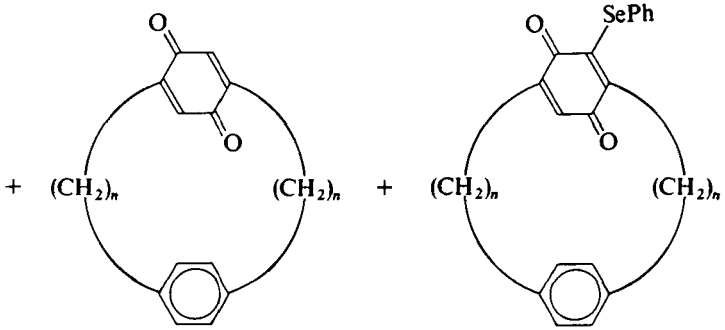
(43) (44) (45) (46)



(47) (48) (11)

$n = 2$ 37.3%

$n = 3$ 40.3%

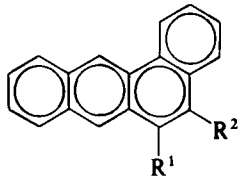


(49) (50)

$n = 2$ 39.4%

$n = 3$ 13.3%

selectivity of this reagent is sensitive to the structure of substrate and its substituent(s)[38]. A similar *ortho* selective oxidation of the polycyclic aromatic phenols (**51**) in good yield is attained by using molecular oxygen[37]. Iodosobenzene (PhIO) and iodoxybenzene ($PhIO_2$)

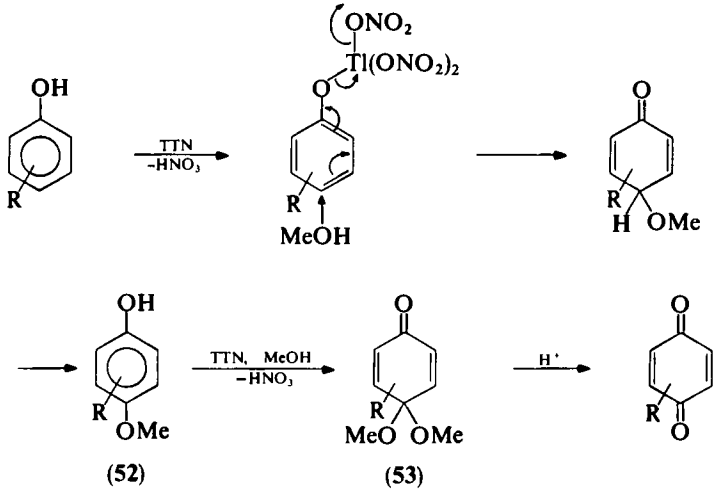


(**51**)

$R^1 = H, R^2 = OH$

$R^1 = OH, R^2 = H$

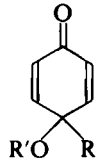
also exhibit selective *o*-quinone formation in good yield in the presence of a protic acid or a Lewis acid catalyst[39]. In contrast, thallium(III) derivatives, especially TTFA, exhibit specific *para* oxidation of phenols[40–42]. Thallium trinitrate (TTN)[43] in methanol oxidizes 2,6-disubstituted phenols to the corresponding *p*-quinones in good yields (70–85%). The mechanism is similar to that supposed for TTFA oxidation of phenols, and involves the successive formation of quinol monomethyl ether (**52**) and the quinone monoacetal (**53**) (Scheme 5). When the *para* position of the phenol (**6**) is substituted by an alkyl group R,



(**52**) (**53**)

SCHEME 5

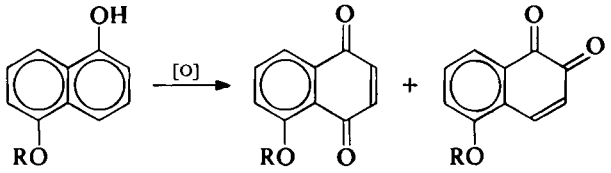
TTN oxidation in MeOH gives the corresponding quinol (**54**) (R = alkyl, R′ = H)[43]. However, thallium triperchlorate, $Tl(ClO_4)_3$, gives 2-alkyl-1,4-benzoquinones (**8**) from the corresponding 4-alkylphenols (**6**) (R = Me, $(CH_2)_2OAc$, $(CH_2)_2OCOCH_2Cl$) in 60%



(54)

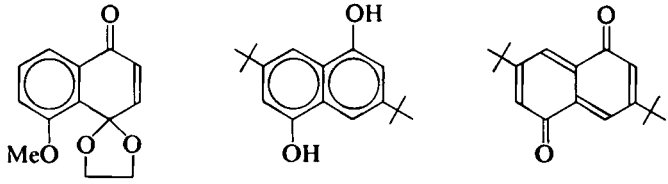
perchloric acid, a medium which accelerates the dienone–phenol rearrangement of the intermediary quinol **54** (R′ = H)[44].

One interesting problem is the selective oxidation of 1,5-dihydroxynaphthalene (**55**, R = H) or its monomethyl ether (**55**, R = Me), which affords juglone (**56**, R = H) or its methyl ether (**56**, R = Me) together with their *ortho* analogs (**57**) (equation 12). These



(55) (56) (57) (12)

compounds are important precursors of many naturally occurring quinones, i.e. anthracyclinones and pyranonaphthoquinones (Section VII). For this reason, various reagents are examined in order to realize higher *para* selectivity. The comparison of oxidizing reagent and reaction conditions (Table 5) is useful for the choice of the appropriate oxidation reagent and conditions of related phenols. Interestingly, singlet oxygen[45] and TTN[48] specifically give the *p*-quinone (**56**) regardless of R group. When **55** (R = Me) is treated with TTN, ethylene glycol and methyl orthoformate, the corresponding quinone monoketal (**58**) becomes the major product. 2,3-Dichloro-5,6-dicyanobenzoquinone



(58) (59) (60)

(DDQ) shows marked contrast to the other oxidants discussed above and affords **60** from **59** in quantitative yield[49].

Oxidation of phenols with molecular oxygen in the presence of *N,N′*-bis (salicylidene)ethylenediiminocobalt(II) (salcomine) (**61**, $n = 2$) gives juglone in good yield in spite of concomitant formation of the corresponding *o*-quinones (**57**)[50,52].

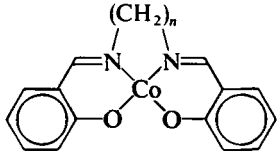
Transition metal catalyzed oxidation with molecular oxygen is extensively developed due to the simplicity of its manipulation and use of the following metal catalysts was

TABLE 5. Comparison of oxidation methods of 1,5-dihydroxynaphthalene and its derivatives

R in **55**	Oxidation method	% yield **56**	% yield **57**	Reference
H	CeO_2, H_2O_2	18		51
H	O_2-CuCl	80		61
H	$MeCO_3H$–$MeCO_2H$	45–55	28	46
H	Ⓟ-$C_6H_4SeO_2H$[a]	70		47
	t-BuOOH			
H	$Tl(NO_3)_3$	64	26	48
Me	$Tl(NO_3)_3$-celite	72		48
H	O_2-salcomine	71	14	50, 52
Me	Fremy's salt	trace	91.6	29
H	$^1O_2$	70		45
Me	$^1O_2$	43		45
Me	$^1O_2$	68.8	17.2	50
Ac	$^1O_2$	30	35	50

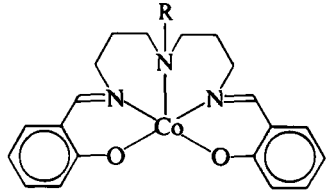
[a] Polymer bound-phenylselenic acid.

reported: **61** (n = 2)[28,45,53–59], **61** (n = 3)[55], **62** (R = Me)[55], **62** (R = polystyrene)[55], **63**[55], **64a**[55], **64b**[55] and **64c**[54,60]. By using these metal catalysts, only 2,6-disubstituted phenols



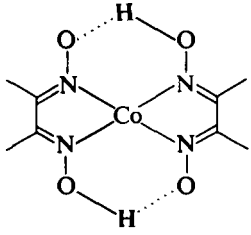
(**61**)

n = 2 (Co(salen))
n = 3 (Co(salpn))



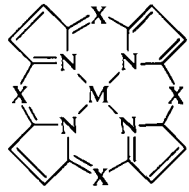
(**62**)

R = Me (Co(salen-Mdept))
R = polystyrene (Co-polysaldpt)



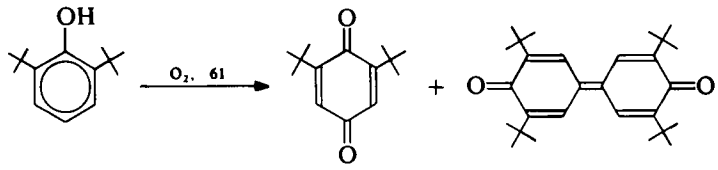
(**63**)

$Co(dmgH)_2$



(**64**)

a, X = CPh, M = Co (CoTPP)
b, X = CPh, M = MnCl (MnTPPCl)
c, X = N, M = Co (CoPc)

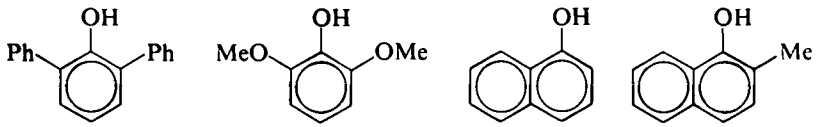


(13)

(65) (66) (67)

MeOH–H_2O[56]	44%	56%
DMF[53]	83%	0%

such as **65** give *p*-quinones in good to excellent yields (equation 13). A definite solvent effect is recognized on the product selectivity between diphenoquinone (**67**) and *p*-quinone, which can be exclusively obtained in DMF, whereas both compounds are formed in aqueous methanol. Similar results are obtained in the preparation of quinones in the oxidation of the phenols and naphthols **68–71**.



(68) (69) (70) (71)

A μ-oxo cupric complex, $Cu_4Cl_4O_2$(MeCN), which is prepared *in situ* from CuCl in acetonitrile, as well as the cobalt complexes shown above afford similar results[61].

The classical chromic acid oxidation of phenols, which is used under a modification of two-phase Jones oxidation conditions[62], gives *p*-quinones in reasonable yields. It becomes an alternative and practical method for Fremy's salt, TTN, or TTFA oxidation to obtain simple *p*-quinones in quantity.

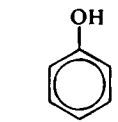
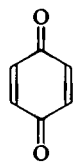
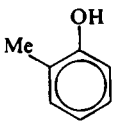
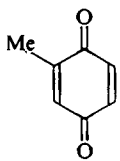
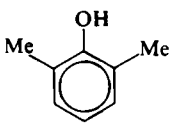
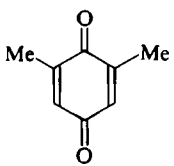
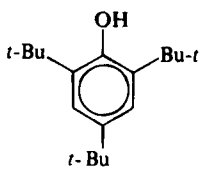
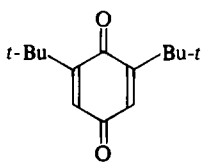
p-Halogenated phenols are susceptible to oxidation to *p*-quinones by CAN[63,64] and H_5IO_6[65]. However, the latter reagent frequently affords the *o*-quinone instead of the *para* derivative.

Under electrolytic conditions, phenols substituted with electron donating group(s) at *o*- or *p*-positions generally give several products with a distribution which depends on the electrolytic conditions[67]. Electrolysis in aqueous acidic media is the favored method to avoid undesirable side reactions, such as phenol coupling and semiquinone formation, and to maximize the efficiency of direct quinone formation. The quinone formation is also very sensitive to the reaction conditions, involving the solvent, the supporting electrode, the anodic material, the applied potential, etc. For a large scale synthesis, this method is advantageous over Fremy's salt oxidation. Selected results are listed in Table 6.

The less common oxidation with lead tetraacetate (LTA) was applied to the preparation of the naphthazarin derivative (**75**) which is relevant to anthracycline synthesis from **72** (equation 14)[66]. The reaction is very sensitive to the purity of the reagent and there remain problems in reproducibility and applicability to other phenols. The mechanism may involve the intermediacy of either **73** or **74**.

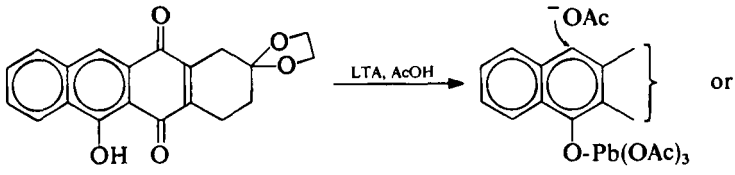
Generally, the Fe^{3+} catalyzed H_2O_2 oxidation, i.e. by Fenton's reagent, is too drastic for oxidation of arenes and possesses little synthetic utility. However, the polymethoxybenzenes, **76** and **79**, are easily oxidized to afford the corresponding methoxy-*p*-quinones

TABLE 6. Anodic oxidation of phenols to the corresponding quinones

Phenol	Electrolytic conditions[a]	Product (% yield)		Reference
	1 M H_2SO_4/Pb		(68)	68
	1 M H_2SO_4/Pb		(62)	68
	1 M H_2SO_4/PbO_2		(100)	69
	MeOH/$LiClO_4$/C		(50)	74
	aq. MeCN/$NaClO_4$/Pt		(85)	70

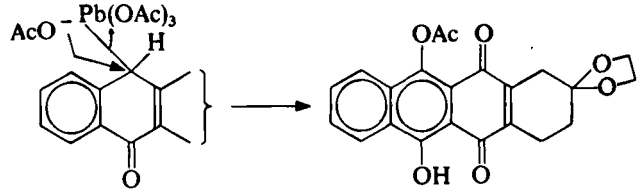
aq. MeOH/Na_2SO_4/Pt	(total 51)	71
aq. MeCN/Et_4NClO_4/Pt	(48)	72
aq. citric acid/$NaHPO_4$/C	(33)	73

[a] Solvent/(supporting electrolyte)/anode.



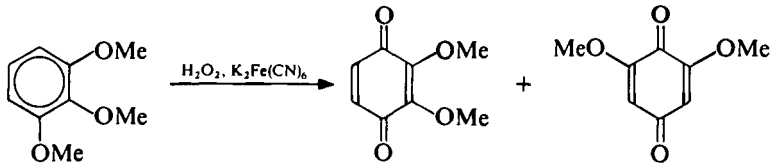
(72) (73)

(14)



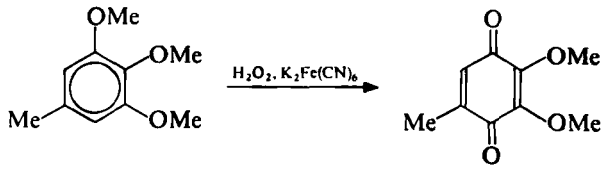
(74) (75)

77, **78** and **80**, respectively, in moderate to good yields (equations 15 and 16)[75]. The quinones obtained are important starting materials for the synthesis of ubiquinone and related compounds.



(15)

(76) (77) (78)



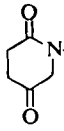
(16)

(79) (80)

C. Hydroquinones and Catechols

Interconversion of hydroquinones or catechols to quinones is known to be a famous redox reaction and the low oxidation/reduction potentials of these systems is utilized even in electron transport relay in biological systems. From the synthetic standpoint, the two components of the oxidation/reduction systems are considered to be equivalent regardless of their oxidation state. Classically well known and established oxidants, e.g. Ag_2O, Ag_2CO_3, $FeCl_3$, etc., still preserve their synthetic utility for these systems. In the last decade, many additional reagents have been examined and joined this group (Table 7). In this section, we discuss several oxidants, whose general applicability have been demonstrated. For other reagents listed in Table 7, further exploitation is necessary in order to establish their utility.

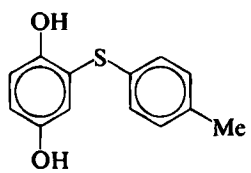
TABLE 7. Oxidizing agents applied for hydroquinones

Oxidizing agent	Reference	Oxidizing agent	Reference
KO_2, crown ether (two-phase system)	76	$BaMnO_4$	88
NaOCl, $R_4N^+X^-$ (two-phase system)	77	$[AgPy_2]MnO_4$	89
PhIO	78	$Fe_2(SO_4)_3$	90
$PhIO_2$	78	$Tl(NO_3)_3$	43
$Bu_4N^+IO_4^-$	78	$(p\text{-}MeOC_6H_4)_2TeO$	91, 92
$NaIO_4$; $NaIO_4$, $R_4N^+X^-$ (two-phase system)	78, 81	$(p\text{-}MeOC_6H_4)_2TeO_2$	93
$NaIO_4$ on silica gel	79	$HgBr_2$	94
Ⓟ-$C_6H_4CH_2N^+Me_3X^-$[a] $X^- = IO_3^-, IO_4^-$	80	$Ce(NH_4)_2(NO_3)_6$	95
$PhI(OAc)_2$	82	$Ce(OH)_3OOH$	96
$PhI(OCOCF_3)_2$	83	*o*-Chloranil	97, 98
Ph_2SeO	84	DDQ	99
$(PhSeO)_2O$	35, 36	*t*-BuN(COPh)O·	30
Ⓟ-$C_6H_4SeO_2H$[a], *t*-BuOOH	47		100
$KMnO_4$, crown ether	85	NCS-Et_3N	101
MnO_2	86, 87	$Ph_2S[OC(CF_3)_2Ph]_2$	102
MnO_2-HNO_3	87	O_2-CuCl	61

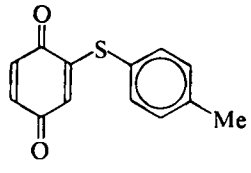
[a] Polystylene bounded reagent.

Sodium hypochlorite in the presence of phase transfer catalyst oxidizes hydroquinones to the corresponding quinones in yields ranging from moderate to good and it gives acceptable results especially for polyalkylated hydroquinones[77]. This method, however, could not be applied to other quinones with inherent instability under basic conditions, since at the rather high pH value (pH = 8–10) of the applied aqueous solution, decomposition of the quinones will take place.

Hypervalent iodine oxides are the reagents of choice due to their general applicability and higher product selectivity[78]. Among them, tetrabutylammonium periodate (Bu_4NIO_4) and sodium periodate in the presence of a phase transfer catalyst give excellent yields for a wide range of hydroquinones[78]. Relevant to the homogeneous system, silica gel[79] and polymer-supported modifications[80] are equally useful for this purpose. The former reagent[79] can quantitatively oxidize the hydroquinone **81** to the corresponding quinone **82** while preserving the sulfide group intact. Commercially available[86] or freshly

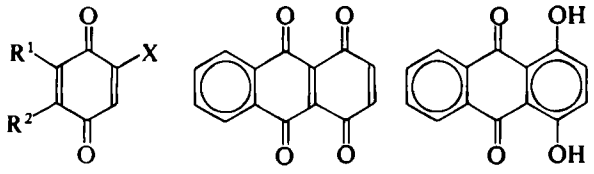


(81)



(82)

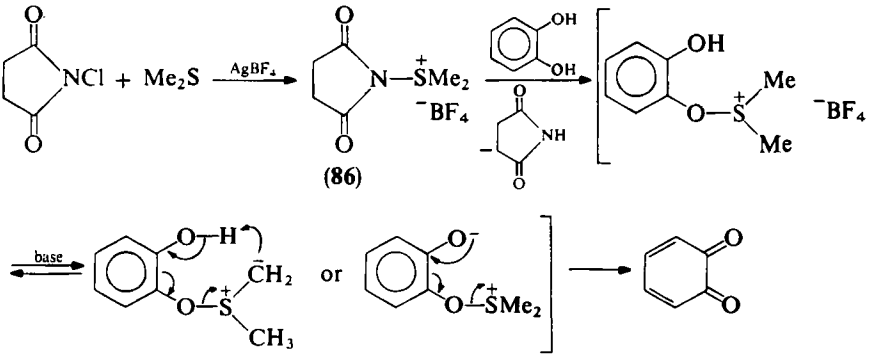
activated manganese dioxide[87], is an excellent and inexpensive reagent which is applicable for synthesis of wide range of quinones such as **8** (R = Me, CN, COMe, CO_2Me) and **83** (R^1, R^2 = H or Me; X = MeCO, PhCO, MeO_2C).



(83) **(84)** **(85)**

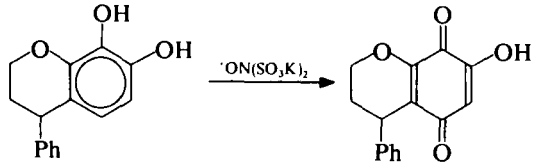
Nitric acid impregnated manganese dioxide, which is a more powerful oxidizing reagent than the forms mentioned above, is suitable for the preparation of highly reactive quinones, such as 1,2-benzoquinone and 9,10-anthraquinone from the corresponding hydroquinones, which can not be oxidized by activated MnO_2[87]. Quinone **84** is also obtained in 86% yield from **85**.

Ceric ammonium nitrate also possesses sufficient oxidizing ability toward hydroquinones and it demonstrated this conversion in high yields[95]. It is worth while to mention in this respect oxosulfonium cation (**86**)[103], known as Corey–Kim reagent, which can be prepared from *N*-chlorosuccinimide (NCS) and dimethyl sulfide in the presence of silver tetrafluoroborate. It can oxidize hydroquinones and catechols to the quinones in high yields at low temperature (−20 to −50 °C)[100]. An almost similar reaction with NCS and Et_3N can be achieved without significant loss of efficiency[101]. These reactions are thought to be an extension of the Swern oxidation[104] and in both cases a base, usually Et_3N, is essential for completion of the reaction. This is apparently connected with the formation of intermediate 1:1 complexes between the hydroquinone and the sulfonium cation which prevents both an overoxidation and a successive nucleophilic addition of the substrate to the quinone (Scheme 6). Some exceptional cases, which were reported in the oxidation of



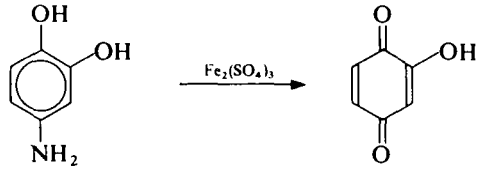
SCHEME 6

catechols, demonstrate the importance of the choice of the oxidant. When Fremy's salt[105] and Fe(III)[90] are applied to catechol derivatives, **87** and **89**, the corresponding *p*-quinones, **88** and **90**, respectively, are preferentially obtained, instead of the corresponding *o*-quinones (equations 17 and 18).



(17)

(87) (88)

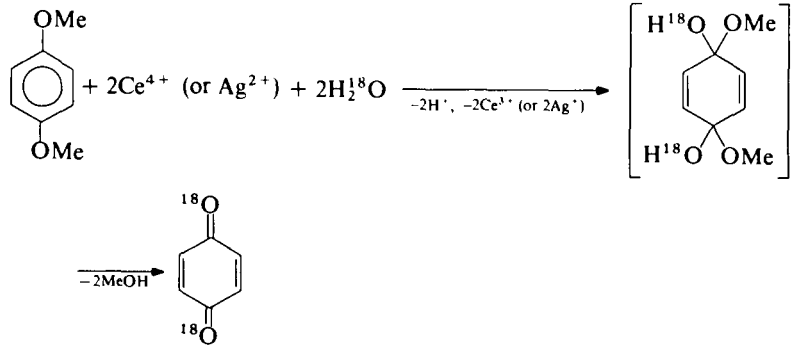


(18)

(89) (90)

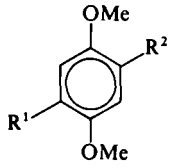
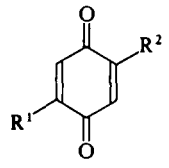
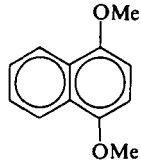
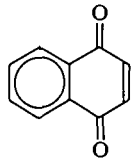
D. Aromatic Ethers and Hydroquinone Mono- and Diethers

For the synthesis of simple quinones, the title compounds are not the precursors of choice, since the corresponding phenols and hydroquinones are more easily oxidized under many established conditions. However, these materials are of great importance in quinonoid compound synthesis for the following reason. In the course of preparation of naturally occurring quinones, the reactive quinonoid moiety must frequently be protected against destruction under various reaction conditions. The hydroquinone dialkyl ether or quinone diacetal are very convenient and useful such synthons. Hydroquinone diether is oxidized to the corresponding quinone by silver (II) oxide (AgO)[106] or by cerium ammonium nitrate (CAN)[107] with high efficiency. These reagents are recognized now as the standard oxidizing reagents with general applicability, and they replace traditional oxidants such as nitric acid and chromic acid. The yields obtained in oxidations of various hydroquinone dimethyl ethers by CAN are given in Table 8. A similar mechanism is proposed for the oxidation by CAN or AgO. It involves two successive electron transfers and nucleophilic addition of water, as clarified by isotope labeling experiments with ^{18}O-enriched water (Scheme 7)[107]. There are two important differences in the oxidations by

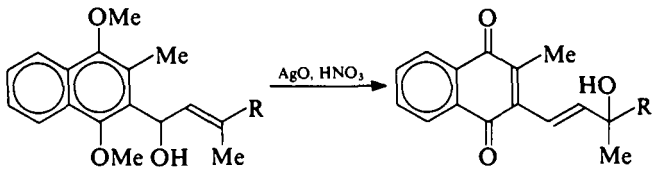


SCHEME 7

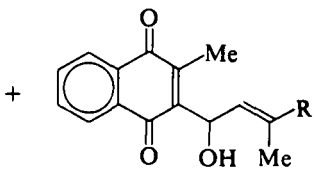
TABLE 8. Oxidation of hydroquinone dimethyl ethers in aqueous acetonitrile with CAN[107]

Hydroquinone dimethyl ether		Quinone, % yield
		
R^1	R^2	
H	H	57
Me	Me	95
Me	CH_2OH	73
Me	$CH=C(Me)NO_2$	65
Me	$CH_2CH(Me)NHCO_2Bu\text{-}t$	61
MeO	$CH_2CH(Me)NHCOPh$	35
		 94

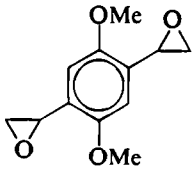
AgO and CAN: (1) CAN can be applied under mild conditions, while AgO requires strong acidic conditions; (2) AgO gives *o*-quinones in moderate yields from the corresponding catechol dimethyl ethers, while CAN usually affords a mixture of several oxidized products and is therefore less useful for oxidation of these substrates. For example, the acid-sensitive compound **91** affords inevitably an allylic rearranged quinone **92** accompanied by a normal oxidation product **93** when oxidized with AgO under acidic conditions (equation 19)[108]. Other acid sensitive groups such as epoxide can also not survive under acidic



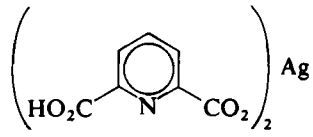
(91) (92)



(93) (19)

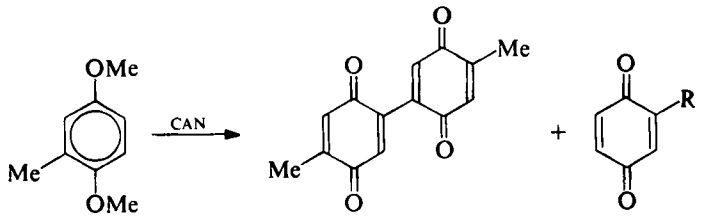


(94)

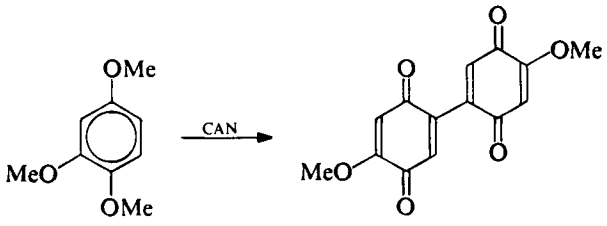


(95)

conditions. To overcome these problems, silver dipicolinate (**95**) was examined as a substitute to AgO, and it oxidized **94** to the corresponding quinone in a moderate yield[109]. When monoalkyl- or monoalkoxy-hydroquinone dimethyl ethers, e.g. **96** and **98**, are treated with CAN, the corresponding dimeric products, i.e. **97** and **99**, respectively, are obtained in preference to the 'expected normal quinones' (equations 20 and 21)[157].



(96) (97) (8, R = Me) (20)



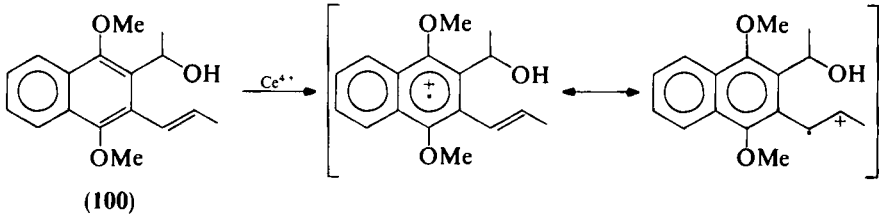
(98) (99) (21)

As a special example, vinylquinone **100** bearing a hydroxy group at the benzylic position gives the unusual cyclization product **101** instead of **102**[110]. This reaction would occur via cyclization to a pyran ring and concomitant hydroxylation of the generated benzylic cation, as shown in Scheme 8.

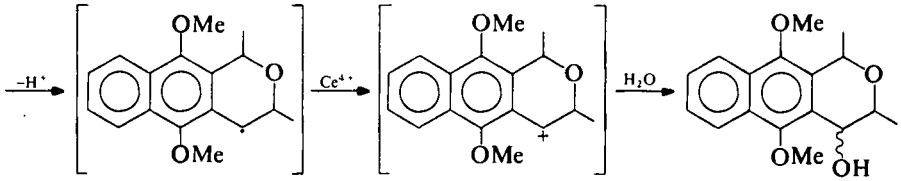
In the case of the quinoline or isoquinoline dimethyl ethers, e.g. **103** and **104**, when either R, R^1, or R^2 is an alkoxy group, the corresponding *o*-quinones are preferentially obtained with CAN[111]. Consequently, it is difficult to predict the product selectivity in the oxidation of polyalkoxybenzenes by CAN.

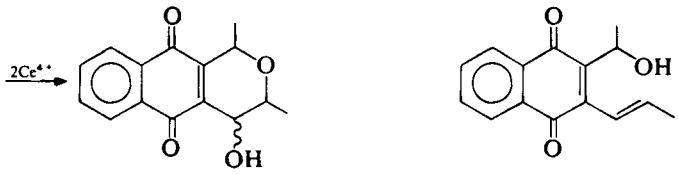
Nitric acid impregnated MnO_2 is also useful for the similar conversion and in many cases a good yield is achieved (equation 22)[112a]

Oxidation of 1,2,4-trimethoxybenzene derivatives usually gives a mixture of the corresponding *o*- and *p*-quinones. This problem is frequently encountered in the synthesis of naturally occurring quinones. For the selective *para* oxidation, nitric acid gives better results than other oxidation reagents[112b,c].



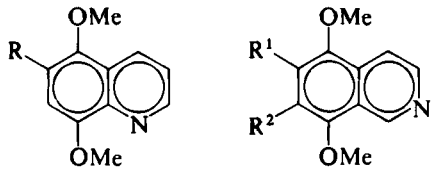
(100)



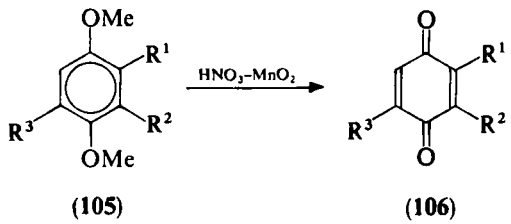


(101) (102)

SCHEME 8



(103) (104)

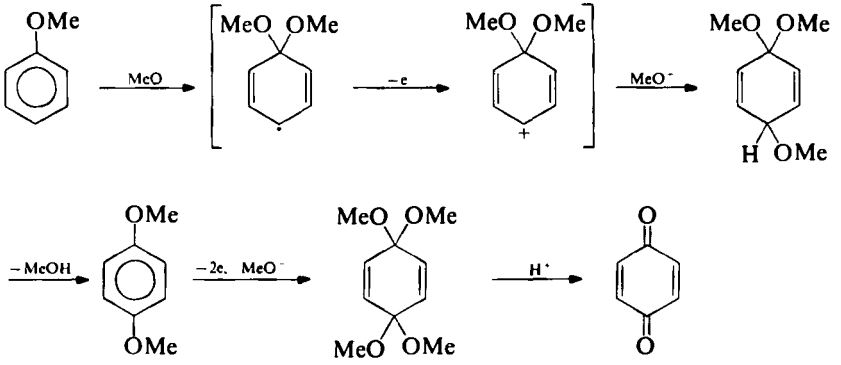


(105) (106)

(22)

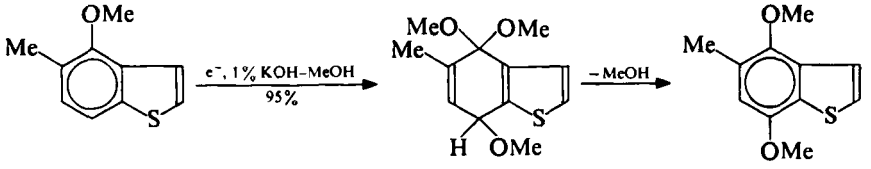
R^1, R^2, R^3 = H, Me, Et; R^1R^2 = $-CH=CHCH=CH-$

Indirect oxidation of phenol ethers and hydroquinone diethers via their quinone dialkyl acetals is realized by anodic oxidation in alkaline alcoholic media. Aromatic ethers and hydroquinone diethers are excellent precursors in anodic oxidation to quinone dialkyl acetals, which can be deprotected to the corresponding quinones in acidic media. Its applicability to a wide range of these precursors makes this method a standard one[113,114]. The following mechanistic pathway is established (Scheme 9). In basic alcoholic media,

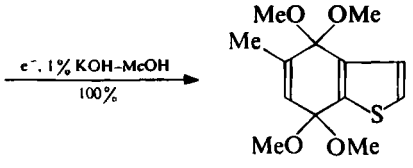


SCHEME 9

typically 1% KOH–MeOH, an alkoxy radical, which is produced from the alkoxy anion via single electron oxidation, will initially attack the *ipso* position to the alkoxy group of the aromatic ether. Successive oxidation and nucleophilic addition of alkoxide anion will afford the hydroquinone diether, which is ultimately oxidized to the corresponding quinone diacetal[115]. Consequently, both phenol ethers and hydroquinone diethers are considered to be equivalent to one another in this oxidation. Several relevant examples are shown in equations 23–25.

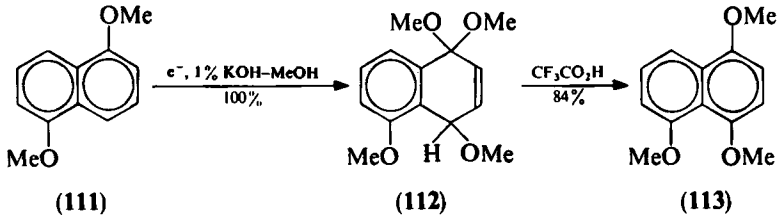


(107) (108) (109)

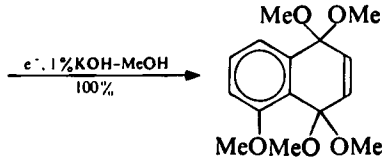


(110)

Ref. 116 (23)

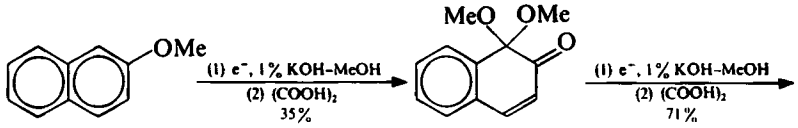


(111) (112) (113)

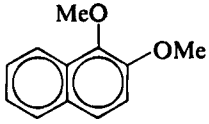


(114)

Ref. 117 (24)



(115) (116)



(117)

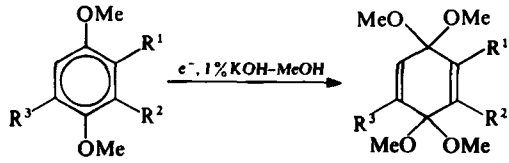
Ref. 118 (25)

4-Methoxy-5-methylbenzo[*b*]thiophene (107) undergoes a four-electron oxidation in one pot without isolation of intermediates **108** and **109**, to afford the corresponding dimethyl acetal (**110**), which is also obtained from the dimethyl ether (**109**) under the same conditions[116]. On the other hand, 1,5-dimethoxynaphthalene (**111**) under the same conditions gives the two-electron oxidized product **112**, which does not spontaneously aromatize to **113**[117]. In spite of these differences in the feasibility of aromatization of the initially oxidized product, phenol ethers and hydroquinone diethers are useful starting materials for this conversion. In most cases, both compounds afford the quinone dialkyl acetals in almost comparable yields. However, sometimes there is a considerable difference in the yields by two methods and the hydroquinone dialkyl ether shows a higher efficiency, as shown in the above example[118].

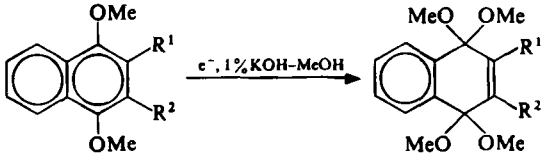
Dimethyl acetal formation from anodic oxidation of simple hydroquinone dialkyl ethers is summarized in Table 9[119]. This oxidation is also realized for hydroquinone dimethyl ethers with rather complex structures. Several examples of its application to the total synthesis of natural products are given in Section VII.

When a substrate carries an oxidizable functional group, e.g. OH, CHO, this group does not survive intact under the applied conditions of anodic oxidation as shown in equations 26–30. When a free hydroxy group is present at the proximal position, it will

TABLE 9. Anodic oxidation of hydroquinone dimethyl ethers[119]

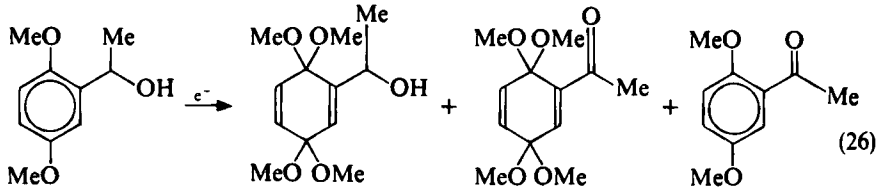


R^1	R^2	R^3	% Yield
Br	H	H	78[a]
Br	H	Br	58[a]
Me	H	H	80[a]
Me_3Si	H	H	93[a]
Me	Me	Me	63[a]
CH(OMe)Me	H	H	92[a]
	H	H	88[a]
$CH_2CH{=}CH_2$	H	H	81[a]
NHAc	H	H	17[b]
$(CH_2)_2CO_2Me$	H	H	61[b]
$(CH_2)_2CONHMe$	H	H	68[b]
$(CH_2)_2CONH_2$	H	H	50[b]
$CH{=}CHCO_2Me$	H	H	46[b]



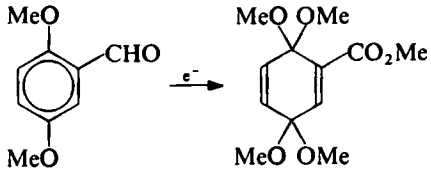
R^1	R^2	% Yield
H	H	74[a]
Me	H	75[a]
MeO	H	83[a]
Me	MeO	82[a]
Me	Me_3Si	80[a]
Br	H	84[b]
Br	Me	85[b]
Br	Br	50[b]
$-CH{=}CHCH{=}CH-$		32[a,c]

[a] Electrolysis in a single cell.
[b] Electrolysis in a divided cell.
[c] See Ref. 120.

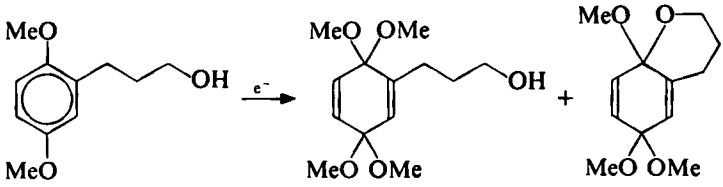


(118) (119) (120) (121) (26)

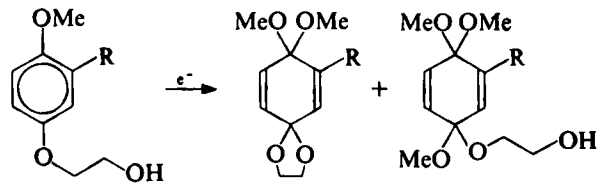
Ref. 121



(122) (123) Ref. 121 (27)

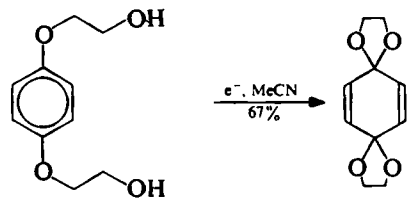


(124) (125) (126) Ref. 121 (28)



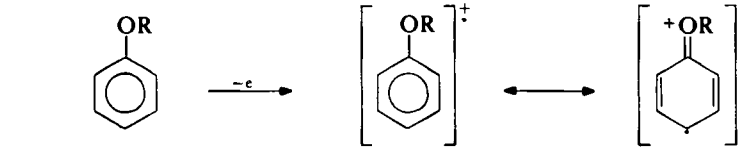
(127) (128) (129) Ref. 122 (29)

R = H, Me, Br, MeO major minor

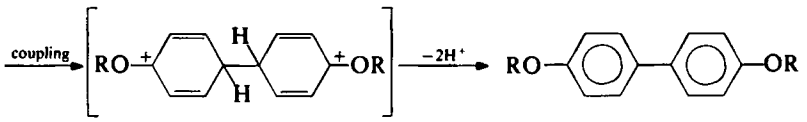


(130) (131) Ref. 123 (30)

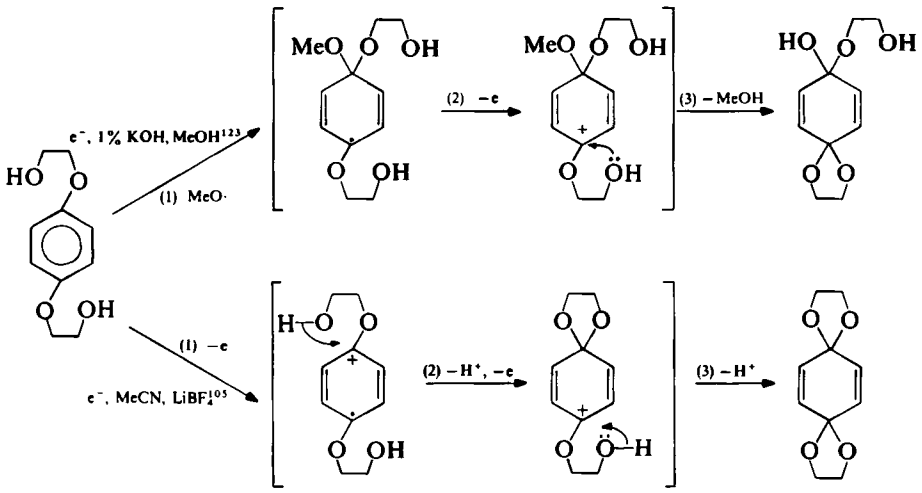
intramolecularly react to form a cyclic acetal[121, 122]. In neutral or aprotic media, anodic oxidation of phenol ethers requires a rather higher potential compared with the basic oxidation, and phenolic coupling to afford a biphenol derivative becomes a major pathway since a single-electron oxidation will preferentially occur at the aromatic ring to give the relatively stable cyclohexadienyl cation radical **132** (Scheme 10)[124]. This mechanistic difference between these two media is also reflected in the oxidized products shown in the example given in Scheme 11[115,123,125].



(132)

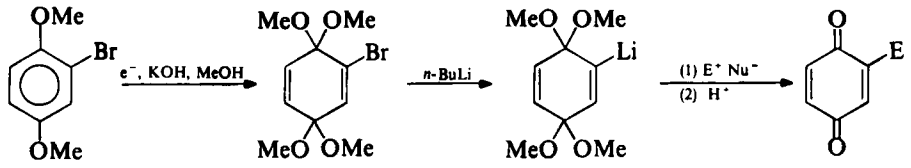


SCHEME 10



SCHEME 11

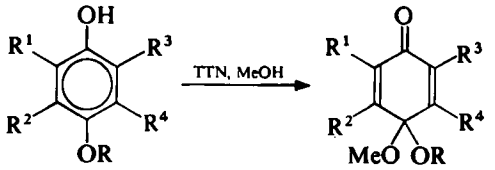
Another feature of the quinone bisacetals is their utility as synthetic equivalents of quinones with inverted charge affinity, i.e. 'umpolung'. The bisacetal of a haloquinone can be lithiated to the corresponding vinyl lithium derivative which reacts with electrophiles (Scheme 12)[126,127]. This conversion is capable of introducing various carbon functionalities into the quinone nucleus without oxidation after the nucleophilic reaction, and was applied to the synthesis of various naturally occurring quinones.



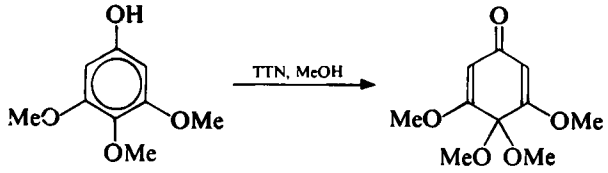
$E^+Nu^- = R^1R^2CO, RCO_2Me, RCOCl, RBr$

SCHEME 12

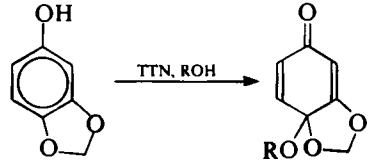
Similar oxidations of hydroquinone monoethers to quinone monoacetals can be achieved in an alcoholic solution by many other oxidants, such as CAN[128, 129], thallium trinitrate (TTN)[43, 48, 130], DDQ[131] and $HgO–I_2$[132] as shown by the following examples (equations 31–38).



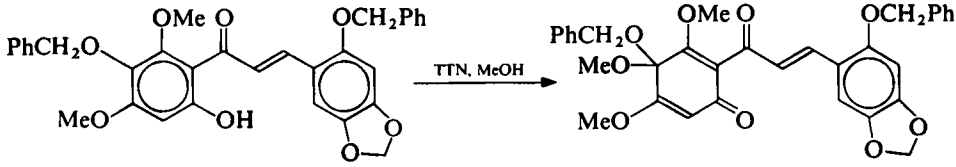
(133) (134) Ref. 43 (31)



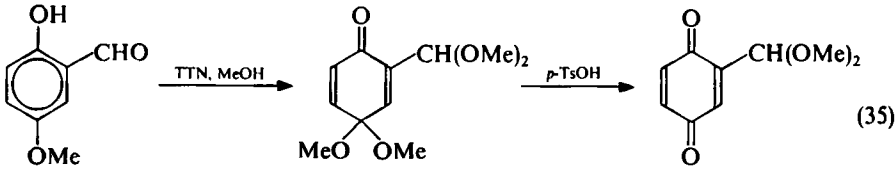
(135) (136) Ref. 43 (32)



(137) (138) Ref. 43 (33)

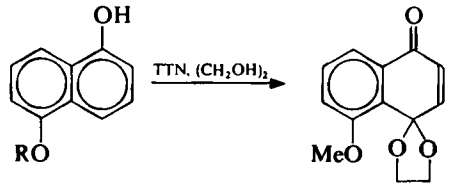


(139) (140) Ref. 43 (34)

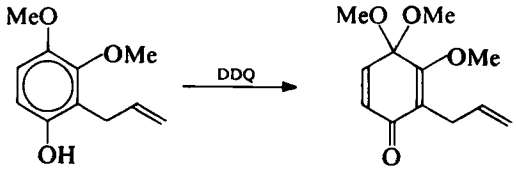


(141) (142) (143) (35)

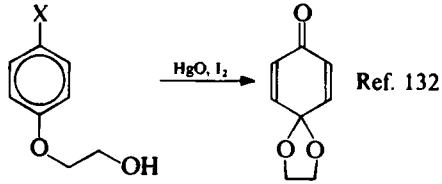
Ref. 130



(55) R = Me (58) Ref. 38 (36)

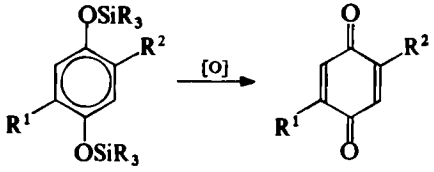


(144) (145) Ref. 131 (37)



(146) (147) Ref. 132 (38)

X = OR, halogen



(148) (149) (39)

Hydroquinone disilyl ethers (**148**), which are used as protected quinones less frequently than the dialkyl ethers, can be directly oxidized to the corresponding quinones by means of pyridinium chlorochromate (PCC) in dichloromethane[133], $FeCl_3$ on silica gel[134], or by anodic oxidation in methanol (equation 39)[135]. Comparison of these three methods shows that PCC is superior to the other reagents as judged by the yields given in Table 10. The other reagents applied to the oxidation of the corresponding dialkyl ethers are potentially applicable for oxidation of the disilyl ethers which are more reactive than the corresponding dimethyl ethers.

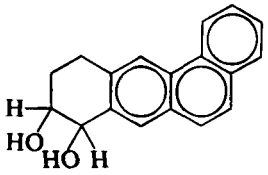
TABLE 10. Direct oxidation of hydroquinone di-(trialkyl)silyl ethers

(148)			% Yield of quinone (149)		
R_3Si[a]	R^1	R^2	PCC[c,133]	$FeCl_3/SiO_2$[134]	e[-d,135]
TMS	H	H	99	57	86
TBDMS	H	H	6	52	52
TMS	H	Me	62	76	
TBDMS	H	Me	90	59	
TMS	Me	Me	93	98	
TBDMS	Me	Me	80	99	
TMS	*t*-Bu	*t*-Bu	91		92
TBDMS	*t*-Bu	*t*-Bu	99	99	90
TMS	H	MeO	65		92
TBDMS	H	MeO	50		
TMS	H	Cl	[b]		92
TBDMS	H	Cl	[b]		

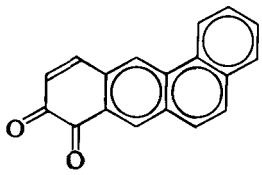
[a] TMS, trimethylsilyl; TBDMS, *t*-butyldimethylsilyl.
[b] No reaction.
[c] Pyridinium chlorochromate.
[d] Anodic oxidation.

E. Miscellaneous Reactions

o-Quinone (**151**) formation from the vicinal diol (**150**) without accompanying dehydration reaction can be accomplished by DDQ in refluxing dioxane[136]. More sensitive

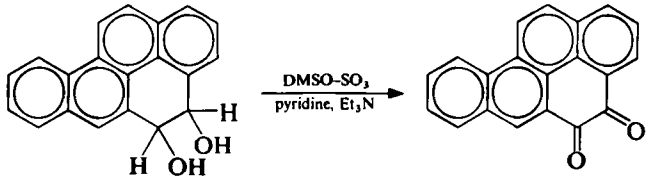


(**150**)



(**151**)

vicinal diols, such as **152** and **154**, which are prone to undergo both dehydration and oxidative cleavage, are successfully oxidized to the corresponding *o*-quinones, **153** and **155**, respectively, by means of Swern oxidation, i.e. with DMSO–SO_3 in pyridine–Et_3N[137] or with DMSO–Ac_2O[138] under carefully controlled conditions (equations 40 and 41). The former system gives an improved yield. In combination with the OsO_4 oxidation of a carbon–carbon double bond to a vicinal diol these methods allow the conversion of polycyclic aromatic hydrocarbons to the corresponding *o*-quinones.



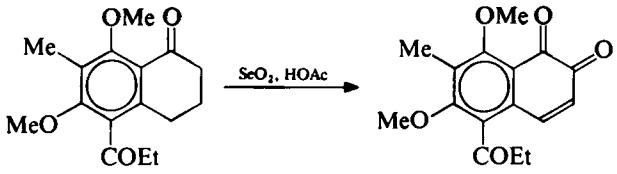
Ref. 137 (40)

(152) (153)

Ref. 138 (41)

(154) (155)

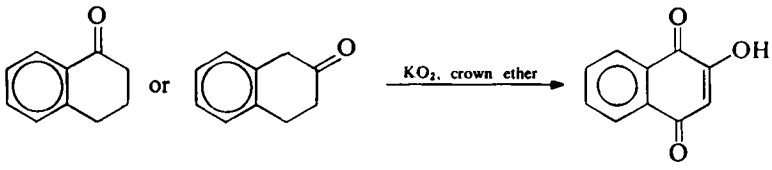
The tetralone derivative **156** is oxidized to the corresponding *o*-quinone (**157**) by selenium dioxide (equation 42)[139]. However, the superoxide formed from potassium



(42)

(156) (157)

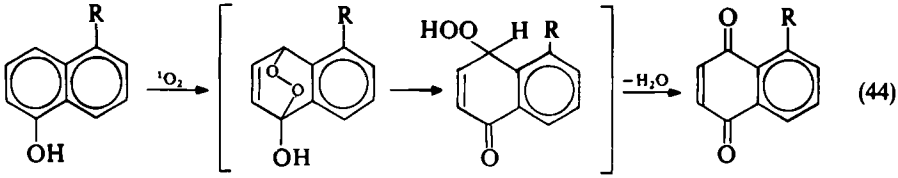
superoxide and a crown ether oxidizes both α- (**158**) or β-tetralone (**159**) to 2-hydroxy-1,4-naphthoquinone (**160**) (equation 43)[140]. The same product is also obtained from 1,2- or 1,3-dihydroxynaphthalenes[76].



(43)

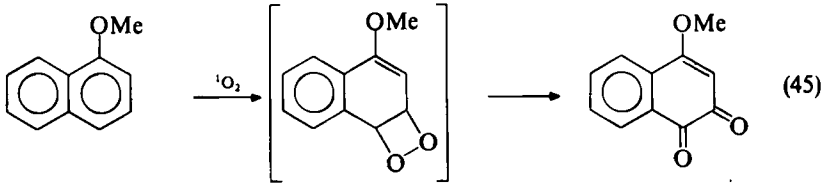
(158) (159) (160)

Singlet oxygen is a reactive and unstable intermediate, which oxidizes 1-hydroxy- (**27**) and 1-alkoxynaphthalenes (**163**) to the quinone (**28**, R = H) and **165**, respectively[45]. The peroxides **161**, **162** and **164** are assumed to be the intermediates in these reactions (equations 44 and 45). The difference of the $^1O_2$ addition modes is attributed to the different electron densities of these substrates.



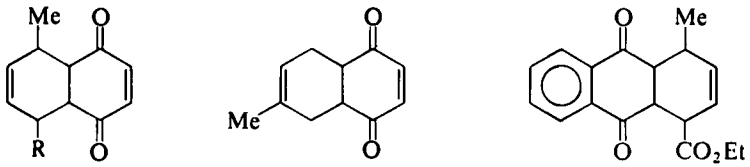
(27) (161) (162) (28) (44)

R = H



(163) (164) (165) (45)

Dehydration of the Diels–Alder adducts formed from conjugated dienes and quinones is one of the conventional and useful methods to prepare extended quinones with various functionalities. Activated manganese dioxide is found to affect the direct conversion of compounds **166–168** to the corresponding quinones with fully aromatized structures in moderate yields[141]. This reagent is claimed to be superior to other oxidants, such as



(166) (167) (168)

R = CO_2Et, CH_2OR

bromine, oxygen, DDQ, and chloranil, and is compatible with ether and carbonyl functionalities. In an alternative method for this transformation, it is also applicable for aromatization to the hydroquinone under basic conditions followed by a successive oxidation[142].

Although arylamines, as well as phenols, have been used as precursors to quinones, they are becoming less important, while satisfactory results are obtained by using traditional oxidizing agents (or methods) such as Fremy's salt[143], $H_2Cr_2O_7$[27,144,145], V_2O_5[145], $Fe_2(SO_4)_3$[90], $K_2Fe(CN)_6$[146], AgO[147], anodic oxidation[148] and photochemical oxidation[149].

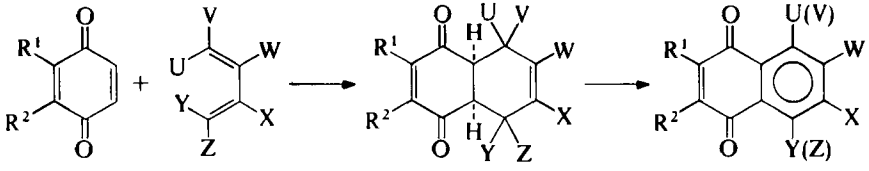
III. ANNULATION METHODS

Annulation reactions are frequently used both for the synthesis of quinone itself and for extension of an aromatic ring to a present quinonoid structure. Many examples are

available in the synthesis of naturally occurring quinones, especially anthracyclinones. Basic problems in annulation reactions are discussed in this section.

A. The Diels–Alder Reaction

A number of the combinations between quinones and conjugated dienes were reported for the extension of rings by means of the title reaction[150–152]. Recent progress is achieved in the use of heteroatom-substituted dienes and in the control of the regiochemistry between unsymmetrically substituted dienes and quinones, as shown in equation 46.



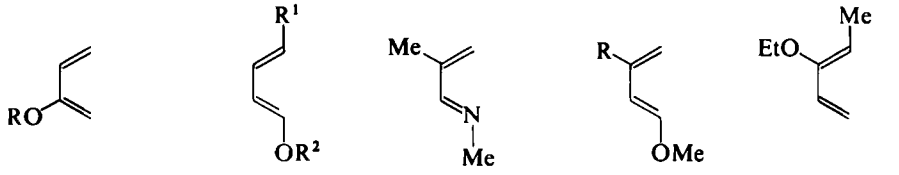
(169) (170) (171) (172)

U, V, W, X, Y, Z = H, alkyl, OR, OCOR, $OSiR_3$, SR, NR_2 (46)

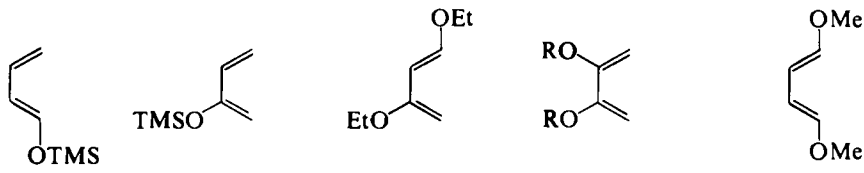
Asymmetric induction in the annulation of quinone by diene with an optically active auxiliary is discussed in Section III.A.4. These results extend the applicability of the title reaction for the synthesis of quinonoid compounds.

1. Heteroatom-substituted dienes

We first treat here the use of heteroatom-substituted dienes including silyl enol ethers, ketene acetals, conjugated enamines, etc. A large number of heteroatom-substituted dienes possessing electron-donating groups show excellent reactivity in these annulation reactions and selected examples of them are listed in Chart 1. Other related dienes used in the same reaction are given in a comprehensive compilation in Refs 150–152. When a Diels–Alder adduct to quinone carries an alkoxy group or acetoxy group at the allylic

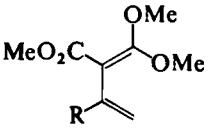


(173) (174)[153, 154] (175)[155] (176)[153, 156] (177)[157]

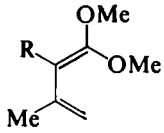


(178)[158] (179)[159] (180)[160] (181)[161] (182)[162]

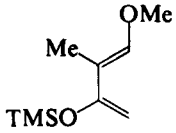
CHART 1 (continued)



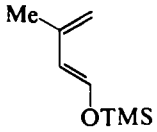
(183)[162-165]



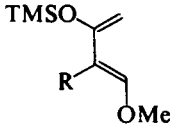
(184)[162-164]



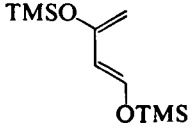
(185)[165]



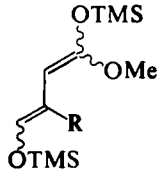
(186)[183]



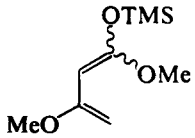
(187)



(188)[169]

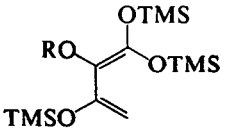


(189)[170]

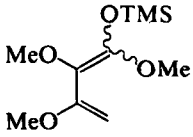


(190)[171, 172]

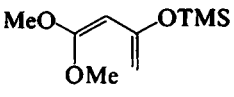
R = Me[160, 166, 167, 183]
R = Et[175]



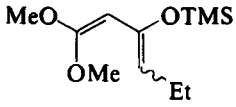
(191)[173a]



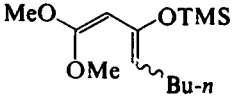
(192)[173b]



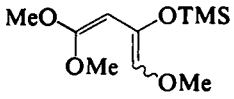
(193)[171, 174, 175]



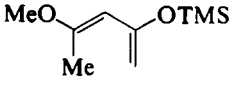
(194)[175]



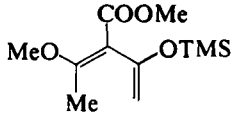
(195)[175]



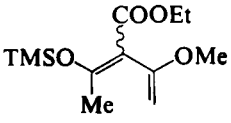
(196)[164]



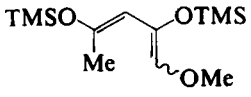
(197)[174, 176]



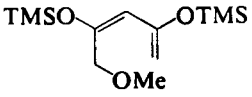
(198)[174, 176]



(199)[177, 178]

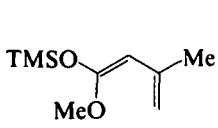


(200)[171]

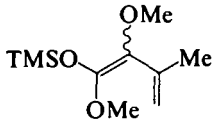


(201)[171]

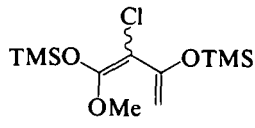
CHART 1 (continued)



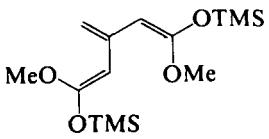
(202)[172]



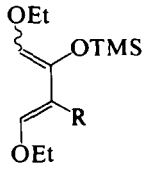
(203)[172]



(204)[172]



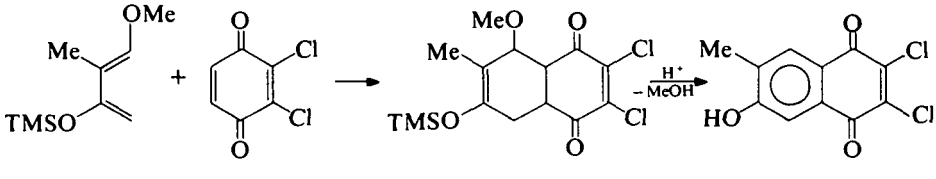
(205)[179]



(206)[168]

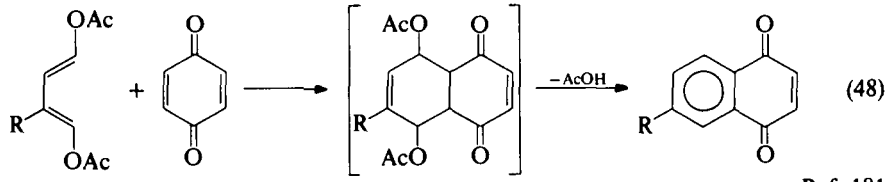
CHART 1

position, this group is easily eliminated during aromatization to the corresponding quinone under acidic conditions as shown in equations 47 and 48[180,181]. In some cases, this elimination spontaneously occurs during the Diels–Alder reaction. The ease of this



(185) (207) (208) (209)

Ref. 180 (47)



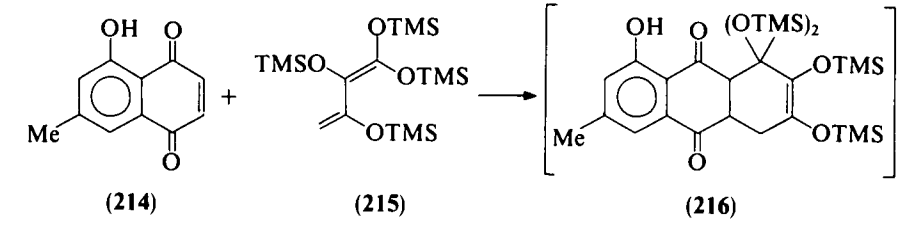
(210) (211) (212) (213)

R = Me R = Me R = Me

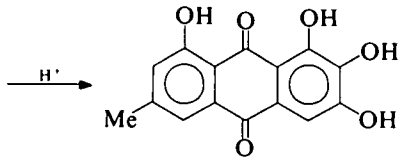
(48)

Ref. 181

elimination depends on the structure and the substitution pattern of the primary adduct. In the case of the ketene trimethylsilyl (TMS) acetal[182], **216** formed from **214** and **215** (equation 49) a hydroxyl group derived from acetal group remains in the product without elimination during the aromatization. However, after conducting the reaction of the 1-siloxydiene (**186**) under mild conditions, oxidation of the primary product with an appropriate oxidant, e.g. PCC, can preserve the oxygen functionality which originates

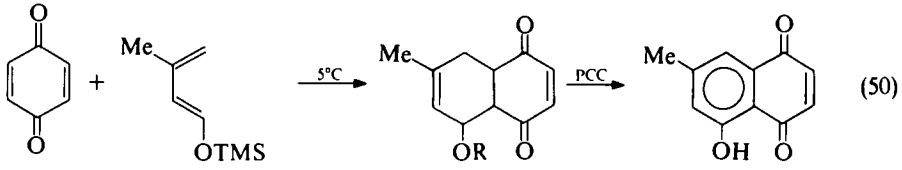


(214) (215) (216)



(217)

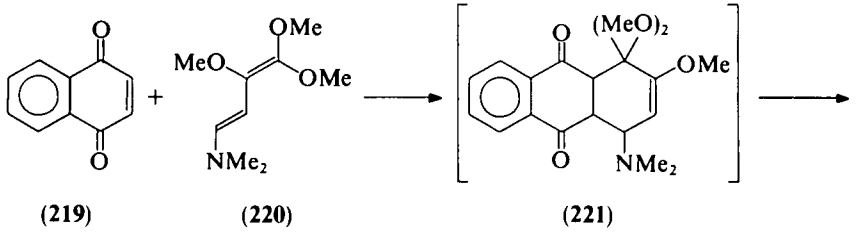
Ref. 182 (49)



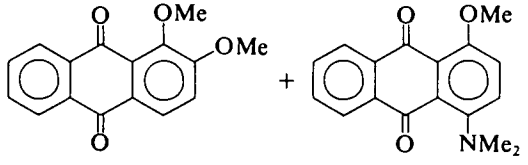
(211) (186) (218) (214) (50)

R = TMS, H Ref. 183

from the diene, without dehydrative aromatization (equation 50)[183]. When two groups which can be eliminated are present at both terminals of a conjugated diene, as in **220**[184], a competitive elimination is observed during aromatization. For example, the adduct **221** formed from **219** and **220** gives on aromatization both **222** and **223** and their ratio depends on the conditions of the work-up (equation 51). Under the mild conditions applied for the

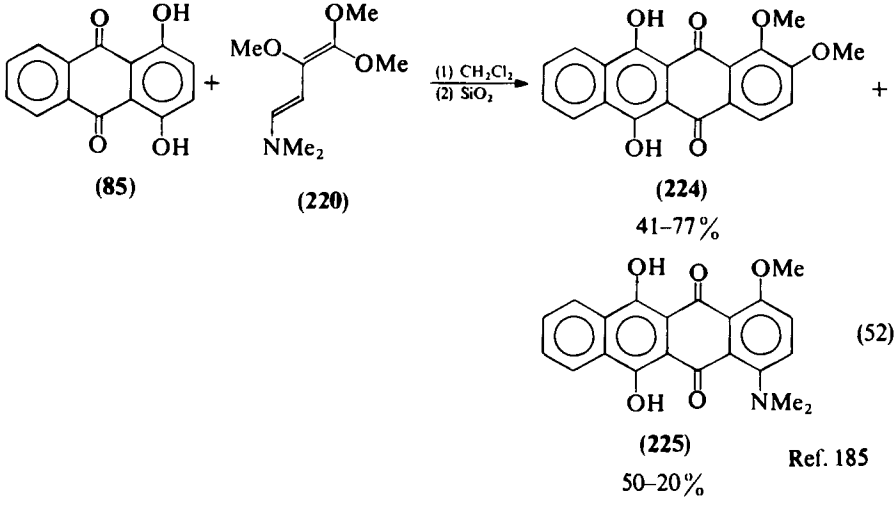


(219) (220) (221)



(222) (223) (51)

chromatographic separation, the two products **222** and **223** are obtained in almost equivalent yields, while under strongly acidic conditions the formation of **222** is preferred. Similarly, the reaction of **85** with **220** gives the two products **224** and **225** without any selectivity after chromatographic separation on silica gel[185] (equation 52). A few other examples of such an elimination from Diels–Alder adducts are given in equations 53, 54[164, 171].

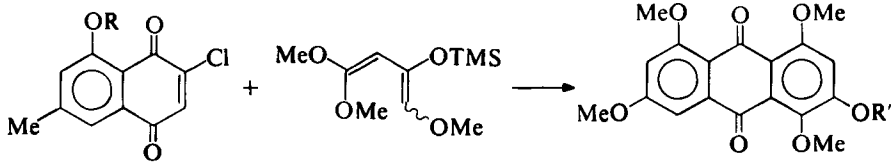


(85) (220) (224) 41–77%

(225) 50–20%

(52)

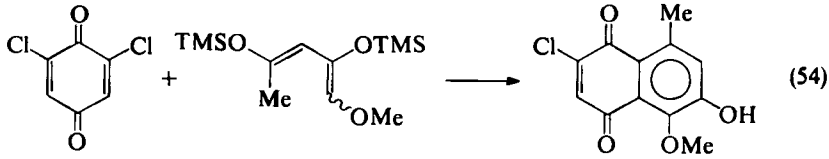
Ref. 185



(226) R = Me (196) (227)

Ref. 164

(53)

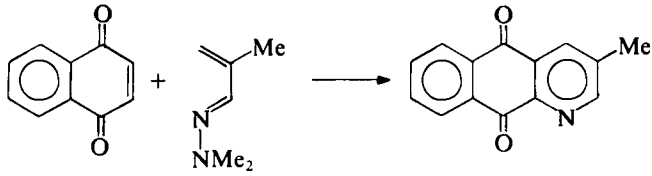


(228) (200) (229)

Ref. 171

(54)

In the case of the α,β-unsaturated *N,N*-dimethylhydrazone (**230**), which possesses a conjugated imine structure, the cycloaddition with the quinone **219** spontaneously gives the corresponding aromatized product **231** by elimination of dimethylamine (equation 55)[186]. These functionalized dienes are frequently used for the synthesis of naturally

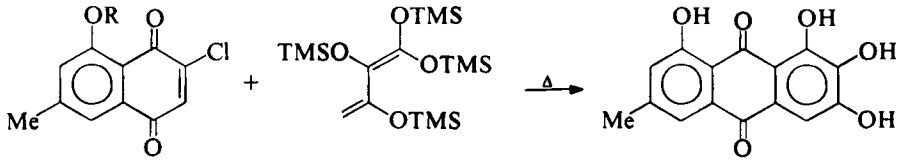


(55)

Ref. 186

(219) (230) (231)

occurring pigments with polyoxygenated anthraquinone structure as shown in equations 56 and 57.

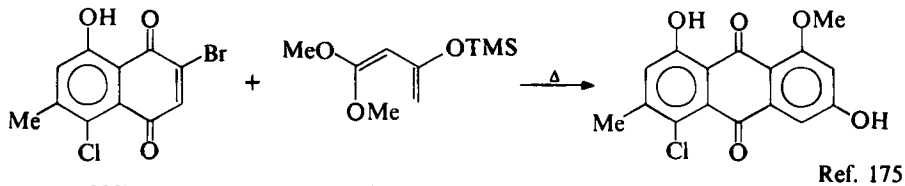


(226) (215) (217)

R = H

7-hydroxyemodine

Ref. 182 (56)

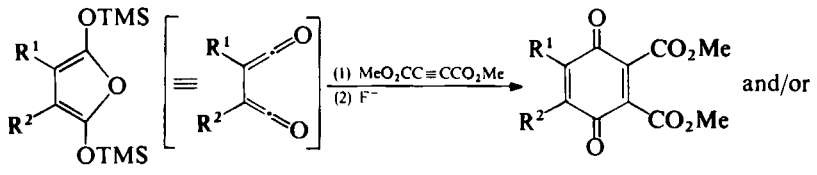


Ref. 175

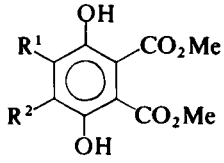
(232) (193) (233)

(57)

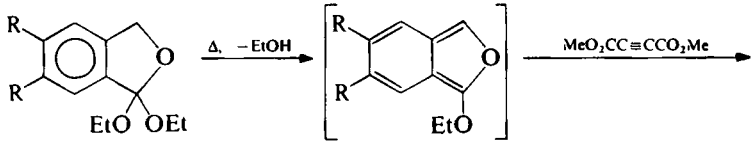
The quinone ring itself is prepared by annulation of functionalized dienes with an appropriate dienophile. 1,4-Disiloxyfurans (**234**), which are easily obtained by trimethylsilylation of the corresponding succinic anhydride derivatives, are considered to be the synthetic equivalent of the diketenes **235** and possess higher Diels–Alder reactivity than the corresponding furans. Diels–Alder reaction of **234** with dienophiles such as dimethyl acetylenedicarboxylate easily occurs to afford the corresponding quinone (**236**) and/or hydroquinone **237** (equation 58)[185–187]. The pyrolysis of the phthalide orthoesters (**238**) affords transiently isobenzofurans (**239**), which are trapped by dimethyl acetylenedicarboxylate to form **240** which spontaneously affords the corresponding hydroquinone monoether (**241**) (equation 59)[188]. Similarly, isobenzofuran (**244**) generated easily *in situ* from **242** via **243** cyclizes with a quinone to afford **245**. Acid treatment of **245** gives the extended quinone **246** after dehydration (equation 60)[189]. In an alternative synthesis involving 7-oxynorbornadiene intermediates such as **240**, *exo*-type tetraene (**248**), prepared in several steps from **247**[190], sequentially reacts with two moles of dienophiles (e.g. methyl vinyl ketone and benzyne (**250**)) to give first **249** and then **251**, which can be



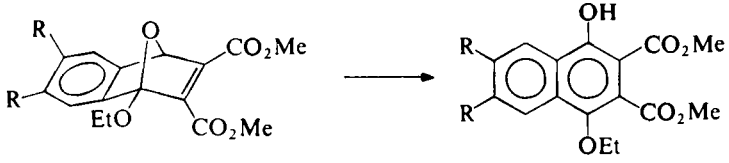
(234) (235) (236)



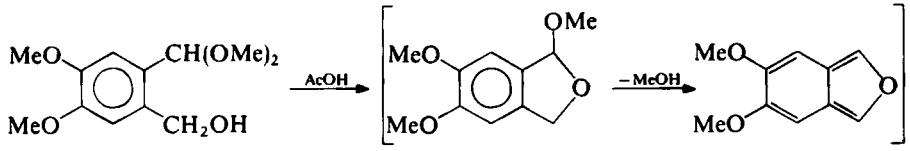
(237) (58)



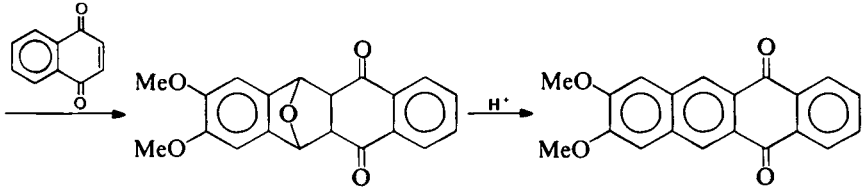
(238) (239)



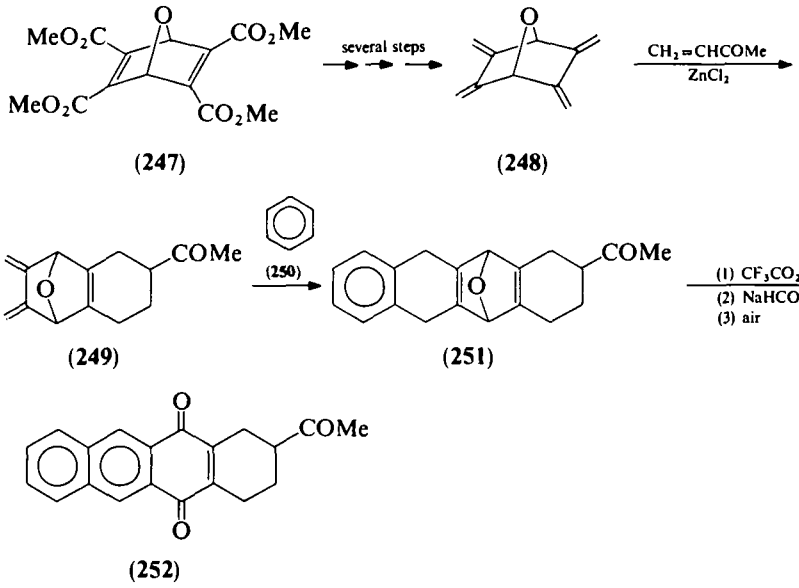
(240) (241) (59)
R = H, MeO



(242) (243) (244)

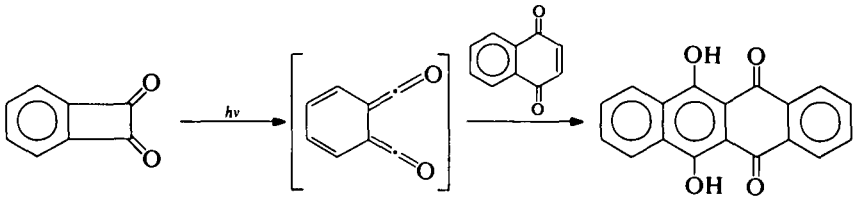


(245) (246) (60)



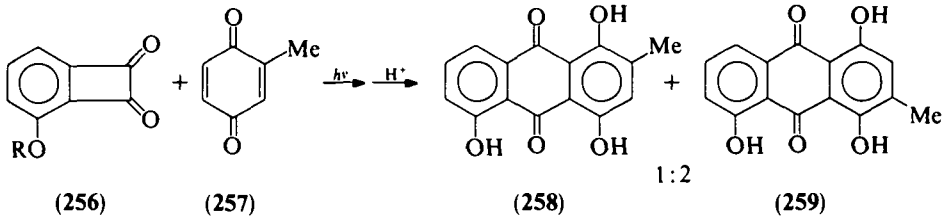
(61)

converted to anthraquinone (**252**) by treatment with acid (equation 61)[191]. Other unstable dienes, such as bisketene and *o*-quinodimethane, are also applied to the synthesis of quinones and for extension of the aromatic ring, respectively. Benzocyclobutene-1,2-dione (**253**) undergoes a Diels–Alder reaction with quinones or with electron-deficient olefins upon irradiation to afford Diels–Alder adducts such as **255**[192] but their yields are very low. This reaction is assumed to proceed via the intermediary formation of bisketene (**254**)



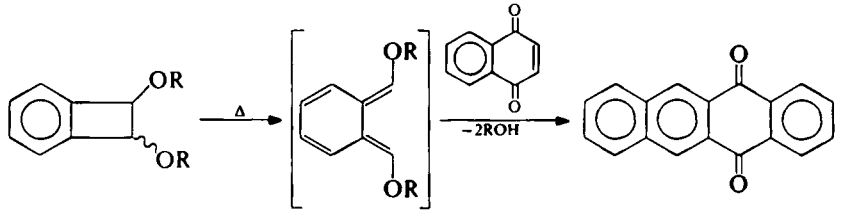
(62)

(equation 62). Extension of this reaction to the substituted benzocyclobutene-1,2-dione (**256**, R = Me) and quinones such as **257** gives mixture of the two possible regioisomers



(63)

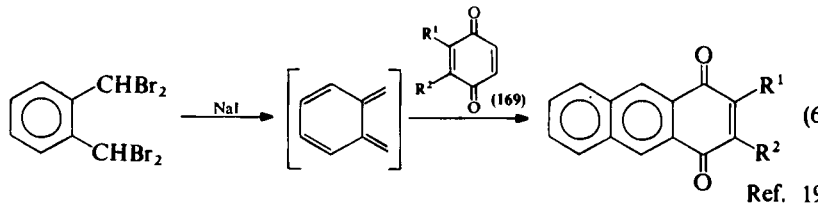
258 and **259** (equation 63)[192]. The annulation of unsymmetrically substituted benzocyclobutene-1,2-dione and a quinone under photochemical conditions does not show high regioselectivity[192]. Contrary to **256** the benzocyclobutene-1,2-diol derivative (**260**) under pyrolytic conditions generates a difunctionalized *o*-quinodimethane (**261**), which can be trapped by 1,4-naphthoquinone to afford naphthacenequinone (**262**) in good



(**260**) (**261**) (**262**) (64)

R = Me, Ac

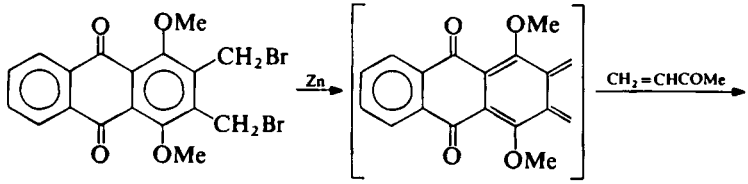
yield (equation 64)[193]. *o*-Quinodimethane (**264**) which is generated by a standard procedure of treatment of 1,2-bis(dibromomethyl)benzene with sodium iodide could be trapped by a quinone such as **169** or other dienophiles *in situ* to form extended quinones



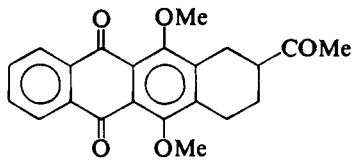
(**263**) (**264**) (**265**) (65)

Ref. 194

such as **265** (equation 65)[194, 195]. In a similar reaction, **267** which is generated from **266** is annulated with methyl vinyl ketone to **268** (equation 66). Under pyrolytic conditions, the



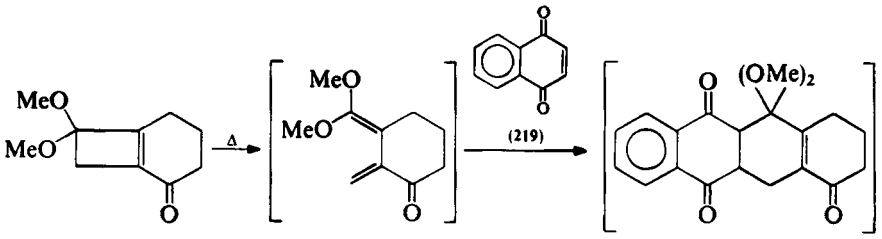
(**266**) (**267**)



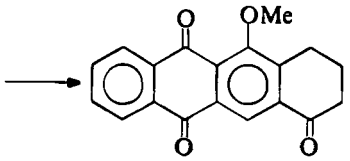
(**268**) (66)

Ref. 195

cyclobutanone dimethyl acetal (**269**) gives an intermediary vinyl ketene acetal (**270**), which is very unstable compared with the aforementioned vinyl ketene acetals, and is trapped by a quinone such as **219** to afford **271** which gives the naphthacenequinone **272** after

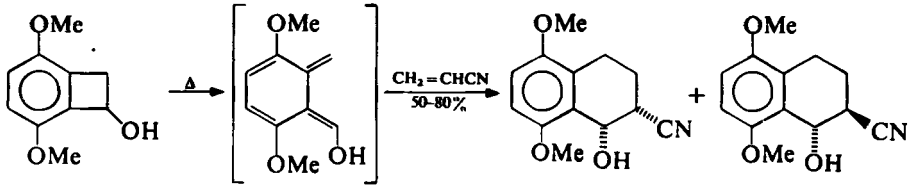


(269) (270) (271)



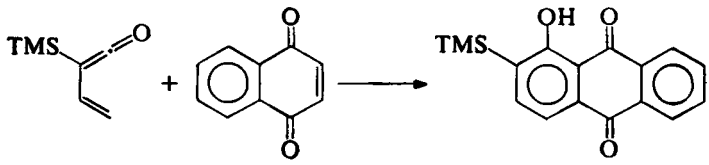
(272) (67)

oxidation (equation 67)[196a]. As a variant of the above examples, hydroxycyclobutene with a masked quinone (cf. **274**) cyclizes in a similar manner with acrylonitrile to afford exclusively an adduct (**275**) in a good yield (equation 68)[196b]. Other dienophiles, however,



(273) (274) (275) (276) (68)

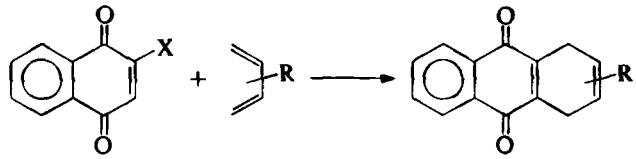
show low stereo- and product selectivity. In a relevant example, the (trimethylsilyl)vinylketene **277** which is synthesized from 1-(trimethylsily)propyne in two steps and is known to be a rather stable compound, also undergoes a Diels–Alder reaction with 1,4-naphthoquinone to form **278** (equation 69)[197].



(277) (219) (278) (69)

2. Halogen atom as a facile leaving group in control of regiochemistry

Aromatization of the Diels–Alder adduct of quinones unsubstituted at the 2 and 3 positions with dienes usually requires rather strong basic conditions necessary for enolization of carbonyl groups. When a quinone carries a good leaving group, which preferably has electron-withdrawing character for the sake of acceleration of the annulation, at the 2 or 3 position, the regeneration of the quinone structure will proceed rather easily. For this purpose, chloro-, bromo-, or sulfinylquinones[198] are frequently used to construct naphthoquinone or anthraquinones in good yield, as shown by the following



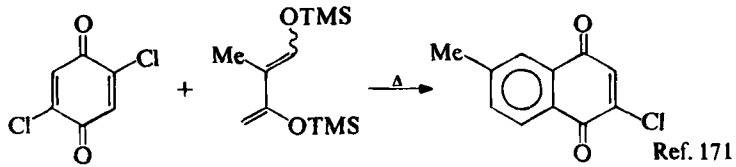
(70)

(279) (280) (281)

X = Cl, Br, SO_2R

example (equation 70). Haloquinones, especially, were extensively investigated and utilized in this respect as shown in the previous section (Section II.A.1, see also Refs 151 and 152).

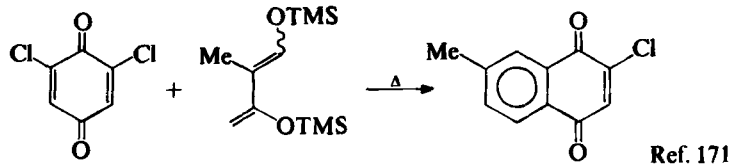
Another feature of the reaction of halogenated quinones in the Diels–Alder reaction is their influence on the regiochemical control of the addition by the electron-withdrawing character of the halogen atom. Typical examples are shown in equations 71–74. In every



(71)

Ref. 171

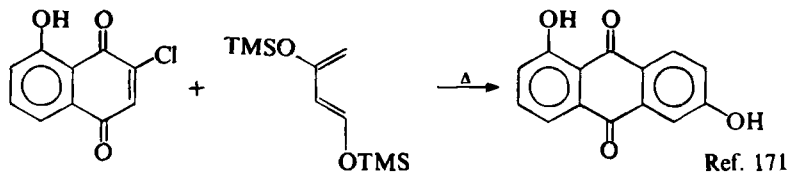
(282) (283) (284)



(72)

Ref. 171

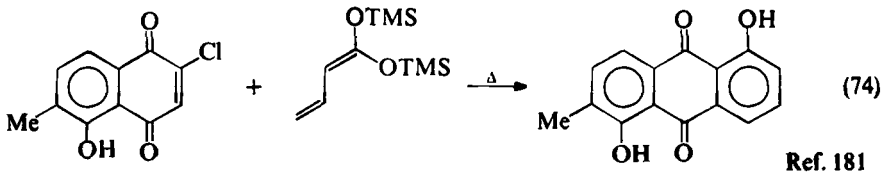
(228) (283) (285)



(73)

Ref. 171

(286) (188) (287)



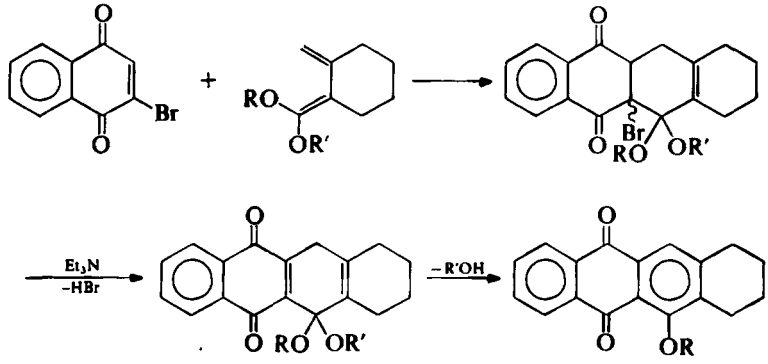
(74)

Ref. 181

(288) (289) (290)

case, the cyclization occurs in a very selective manner. This regiochemical outcome is well established in many examples and is rationalized by means of frontier molecular orbital theory[199].

During the course of the regeneration of the quinone structure, HX is eliminated from the primary Diels–Alder adduct, and in some cases it causes decomposition of other acid-sensitive groups in the molecule. For prevention of such an undesirable reaction, $SrCO_3$[179,200] or Et_3N[200] are used as acid scavengers. The latter base seems to be superior to the former[200] and aromatization would proceed by the route shown in Scheme 13.



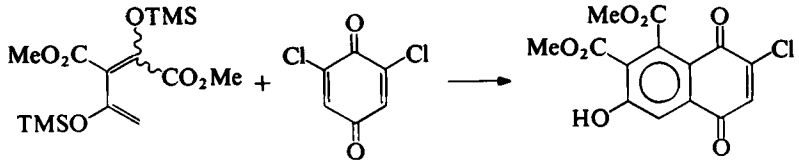
SCHEME 13

Sequential Diels–Alder reactions are developed in order to synthesize highly functionalized anthraquinones from dichlorobenzoquinones by taking advantage of the difference in reactivity between the starting quinone and the primary Diels–Alder adduct. For example, 2,6-dichlorobenzoquinone **228** reacts with diene **291** and the successive aromatization gives **292**. This is again treated with the second diene (**293**) to give tetramethylxanthocaccaic acid B (**294**) after aromatization (equation 75)[201]. Similarly, successive treatment of diene **191** with quinone **228**, then with diene **295** gives ceroalbolinic acid (**296**) after deprotection (equation 76)[178].

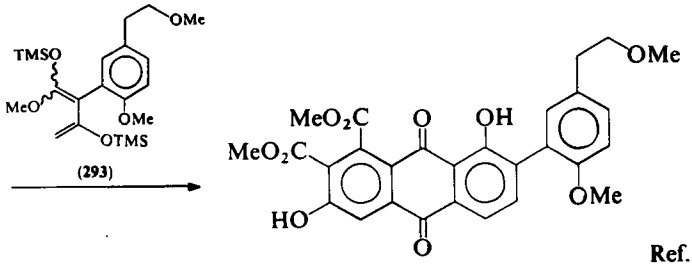
Two dienes, **297** and **299**, with very similar structures to one another are sequentially annulated with 2,5-dichlorobenzoquinone to afford the precursor for vineomycinone B_2 (**302**) (equation 77)[202].

3. Other dienes

Elimination of small molecules, such as CO_2 or $CH_2{=}CH_2$, from Diels–Alder adducts is a useful variation of the annulation as well as the dehydrohalogenative aromatization processes shown in the previous section.



(291) (228) (292)

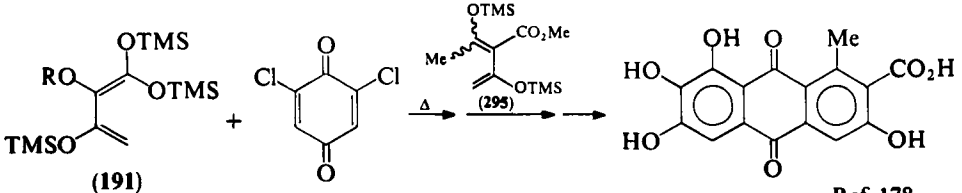


(293)

(294)

Ref. 201

(75)



(191)

R = Me

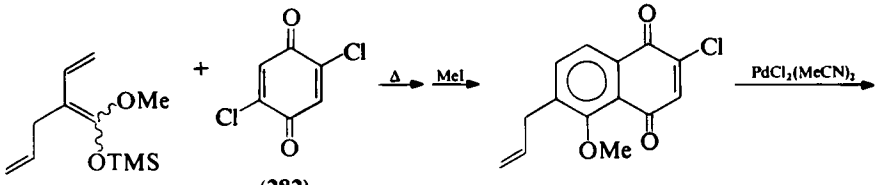
(228)

(295)

(296)

Ref. 178

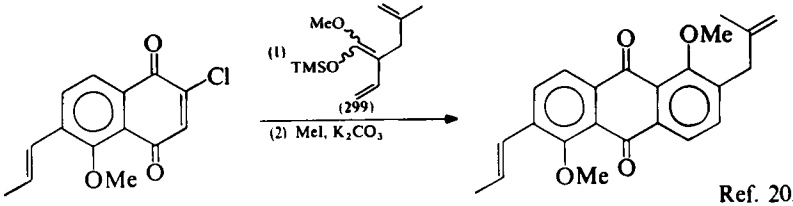
(76)



(297)

(282)

(298)



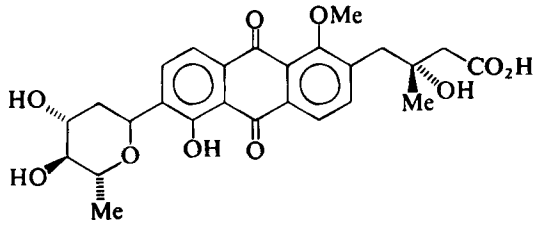
(300)

(299)

(301)

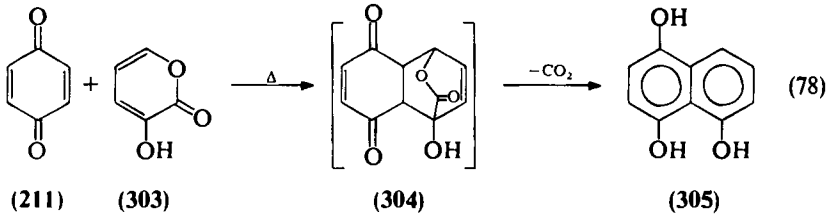
Ref. 202

(77)



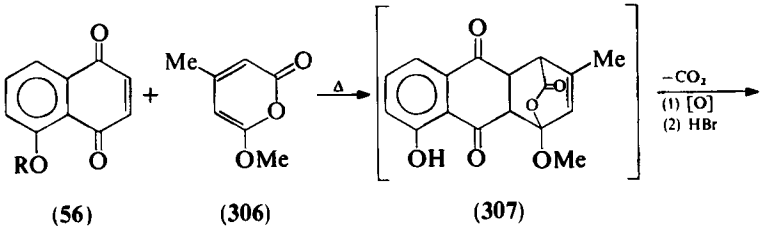
(302)

3-Hydroxy-2-pyrone (**303**) reacts with a 1,4-quinone (**211**) to afford a reduced form of juglone (**305**) probably via decarboxylation of the adduct (**304**) (equation 78)[203]. A similar result is obtained in the reaction of 6-methoxy-4-methyl-2-pyrone (**306**)[204] and extremely high regioselectivity is observed in the case of juglone (**56**, R = H) as a dienophile (equation 79)[205]. When juglone acetate instead of juglone is applied, no regioselectivity is observed in



(78)

(211) (303) (304) (305)



(79)

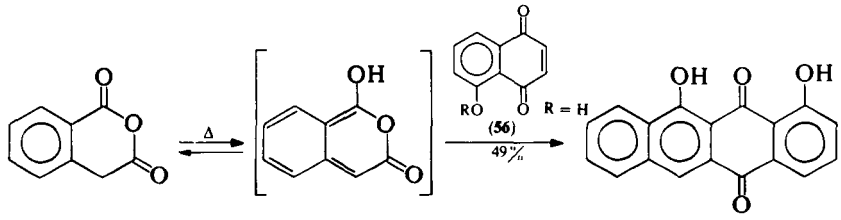
(56) (306) (307)

R = H

(308)

the analogous reaction. Relevant to pyrone derivatives, homophthalic anhydride (**309**) is considered as an equivalent synthone of the corresponding pyrone (**310**). At room temperature, the equilibrium between **309** and **310** favors the left side, while at elevated temperature **310** is trapped with juglone (**56**, R = H) to afford a quinone (**311**) in excellent regioselectivity (equation 80)[205].

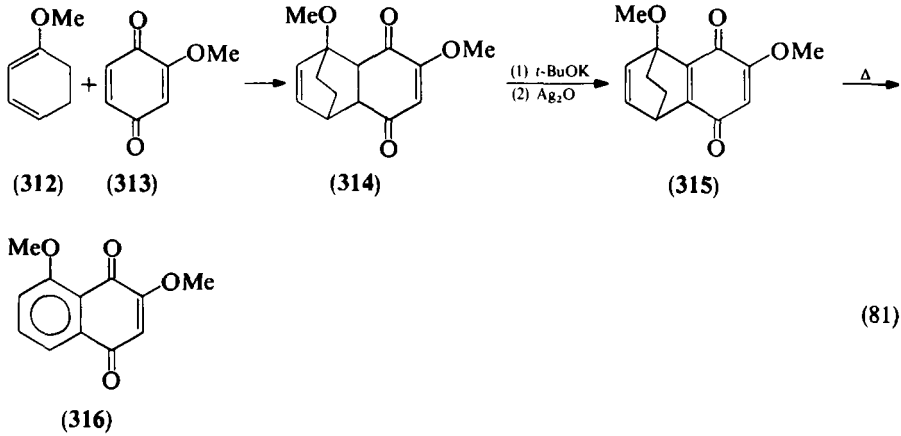
1-Methoxycyclohexadiene (**312**) reacts readily with quinones (e.g. **313**) to afford Diels–Alder adducts, which are converted to the corresponding quinones in two steps, i.e.



(309) (310) (311)

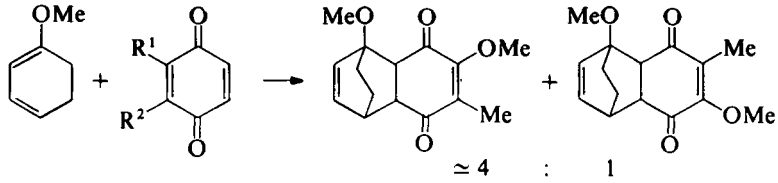
(80)

by enolization to the corresponding hydroquinone and then oxidation to the quinone. The successive pyrolysis gives 3-methyoxyjuglone methyl ether (**316**) (equation 81)[206,207]. When 2-methoxy-1,4-benzoquinone (**313**) is used as a dienophile, **316** is obtained stereoselectively, while 2-methoxy-3-methyl-1,4-benzoquinone (**169**, $R^1 = Me$, $R^2 = MeO$) gives two isomeric adducts (**317** and **318**) in $\simeq 4:1$ ratio (equation 82)[206].



(312) (313) (314) (315) (316)

(81)

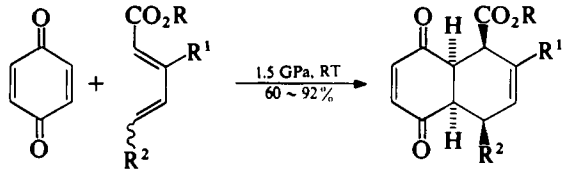


(312) (169) (317) (318)

$R^1 = Me, R^2 = MeO$

(82)

Electron-deficient dienes are considered to have insufficient reactivity toward 'usual' dienophiles, which favor electron rich dienes. Diels–Alder reactions of such dienes (**319**) with *p*-benzoquinone (**211**) at high pressure give the adducts **320** in good yields (equation 83)[208]. This cycloaddition does not proceed at atmospheric pressure even at elevated temperatures.



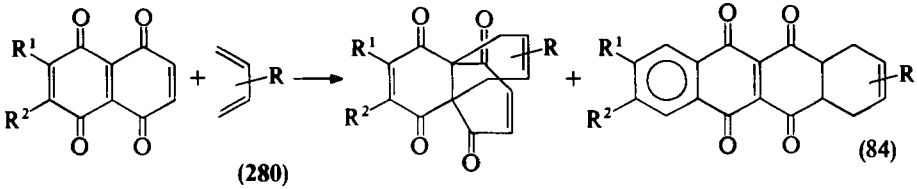
(83)

(211) (319) (320)

R = Me, Et, R^1 = H, Et
R^2 = H, Me, CH_2OSiMe_2Bu-*t*

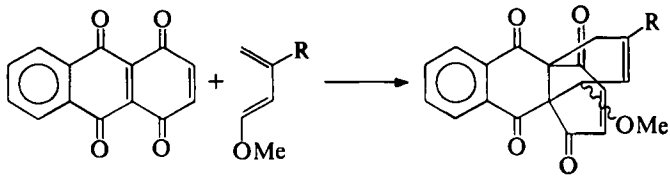
4. Regioselectivity and site-selectivity

When a diquinone, which possesses two reaction sites, undergoes a Diels–Alder reaction, the cyclization can occur at both sites as demonstrated by the formation of both **322** and **323** from **321** and **280** (equation 84). The site-selectivity is apparently dependent on the electronic nature of the applied diene. This problem is encountered at the Diels–Alder approach in anthracyclinone synthesis[5,209-215]. An electron-rich diene, such as isoprene, 1-alkoxy-1,3-butadiene (**174**), 2,3-dimethyl-1,3-butadiene, etc., attacks preferentially an internal double bond, while a less electron-rich diene, e.g. 1,3-butadiene, 1-acetoxy-1,3-butadiene (**174**, R^1 = H, R^2 = Ac) and 2,4-hexadiene, etc., cyclizes at the external double bond (equations 85 and 86). These phenomena are well explained by means of frontier



(84)

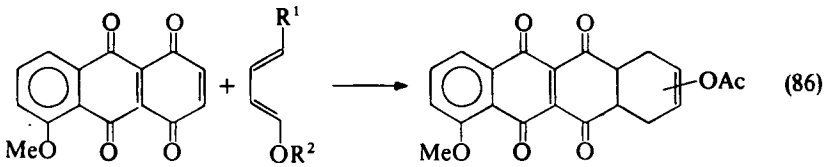
(321) (280) R = Me (322) (323) Ref. 209



(85)

Ref. 210

(84) (324) (325)



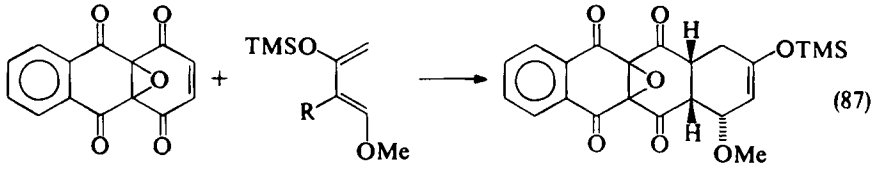
(86)

(326) (174) (327) Ref. 211

R^1 = H, R^2 = Ac

molecular orbital (FMO) theory which considers the interactions between the lowest unoccupied molecular orbitals (LUMOs) of quinone and the highest occupied molecular orbital (HOMO) of diene[216]. The LUMO and the secondary LUMO (SLUMO) of the diquinone concentrate on the internal and external double bonds, respectively. The magnitude of LUMO–HOMO interaction between two reactants is proportional to $(IP^{diene} - EA^{quinone})^{-1}$ when IP and EA are the ionization potential and the electron affinity, respectively. Consequently, the electron-rich diene would preferentially interact with the LUMO of the quinone. There will not be an appreciable difference in the (IP – EA) value of a less electron-rich diene toward the LUMO and the SLUMO of a diquinone, and hence it should not contribute at all to the selectivity. The site-selectivity of the less electron-rich dienes will therefore be determined by the steric factor, since steric hindrance at the internal double bond of the diquinone is larger than at the external double bond.

To avoid the undesirable internal attack by an electron-rich diene, protection of an internal double bond by an oxirane ring, which can easily regenerate the aromatic skeleton, was developed as demonstrated in equation 87[212].



(87)

(328) (187) (329)

R = H

A substituent on a quinone has a strong directing effect on the Diels–Alder reaction. A large number of examples were reported and the results concerning the preferred site of attack are summarized in Chart 2[199, 217]. A large difference in the regioselectivity of the

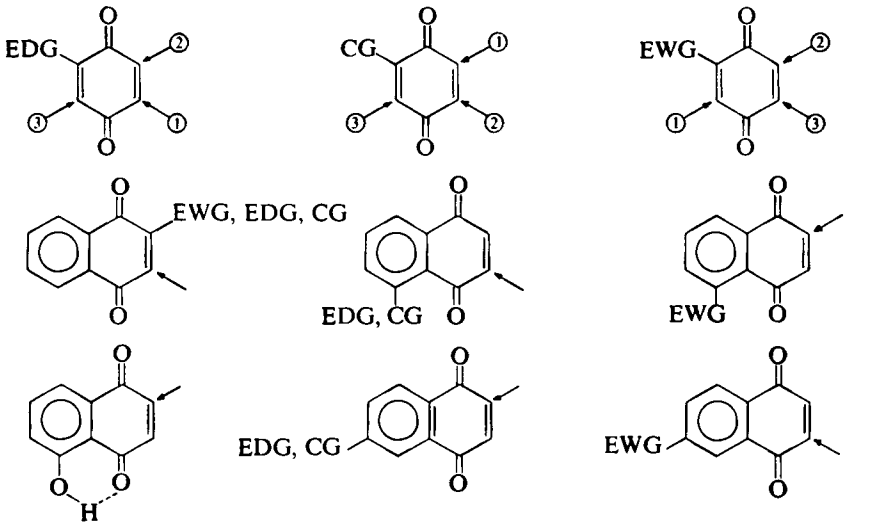
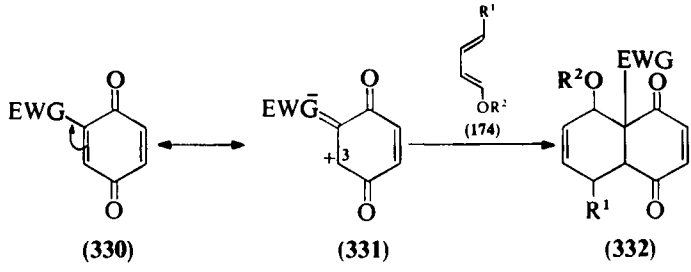
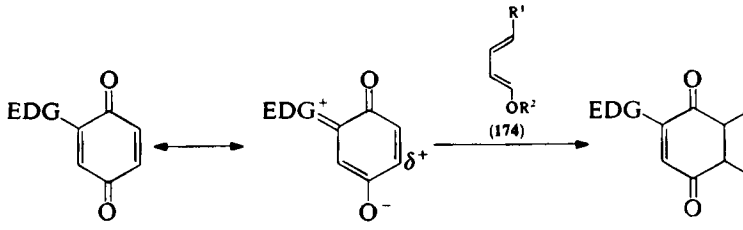


CHART 2. Site of attack of the nucleophilic terminus of a diene on substituted benzoquinones and naphthoquinones: EDG, electron donating group; EWG, electron-withdrawing group; CG, conjugating group. The numbers show the relative order of reactivity

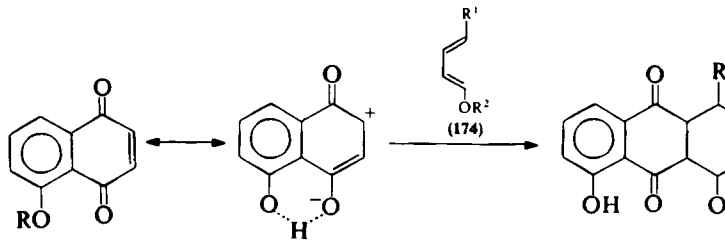
cyclization is observed between an electron-donating and an electron-withdrawing substituent. For example, the presence of an electron-withdrawing group on the benzoquinone generates a partial positive charge at the 3 position and an unsymmetrically substituted diene will cyclize with the quinone in such a way that its nucleophilic site will attack the positively charged center. Several examples are shown in equations 88–90. Other



(330) (331) (332) (88)



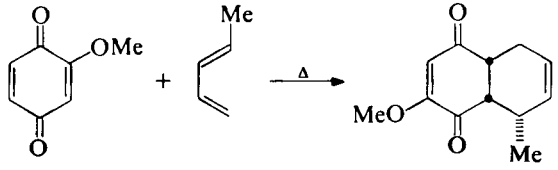
(333) (334) (335) (89)



(56) (336) (337) (90)

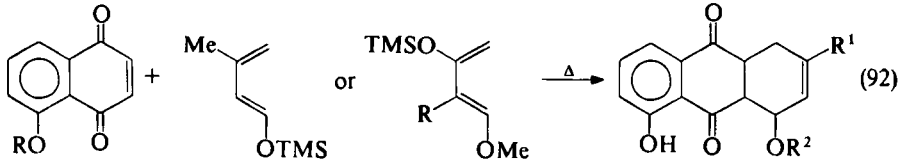
R = H

selected examples, which are rationalized by the charge distribution argument are given in equations 91–97. The remote control of regioselectivity in the reaction of **344** is attributed to a weaker hydrogen bonding to the carbonyl group at the 4 position rather than to that at the 1 position. Since the acetylamino group has a weakly electron-donating character, quinone **355** shows a very high regioselectivity to afford adduct **356** as the exclusive product. Further examples related to this regioselectivity are reported in the literature[225,226]. All these effects are also elucidated by means of the FMO theory[199,216,217].



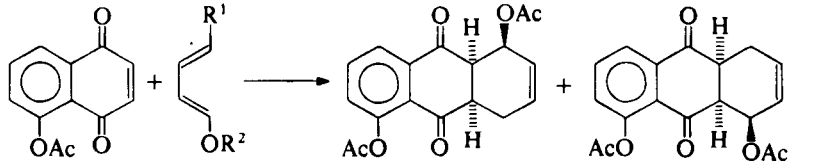
(313) (338) (339)

Refs 218, 219 (91)



(56) R = H (186) (187) R = H (340) R^1 = Me, R^2 = OTMS[183] R^1 = OTMS, R^2 = Me[220]

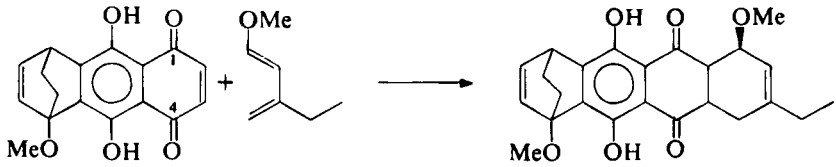
(92)



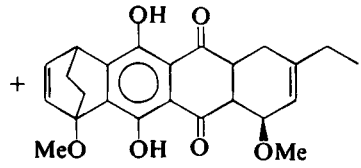
(341) (174) (342) (343) 3:1

R^1 = H, R^2 = Ac

Ref. 221 (93)

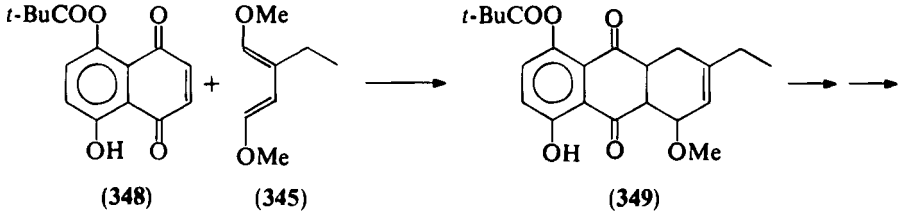


(344) (345) (346) > 80%

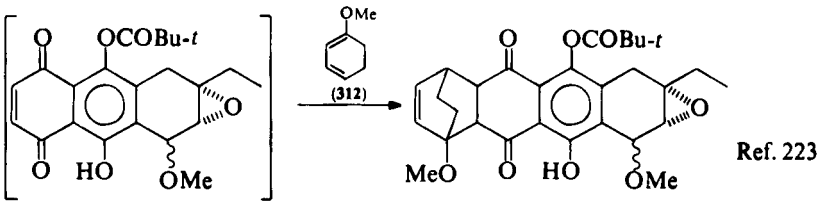


(347) < 20%

Ref. 222 (94)

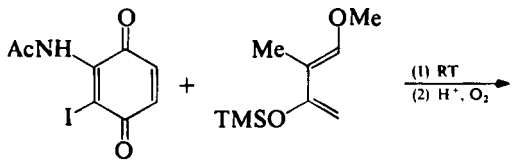


(348) (345) (349)

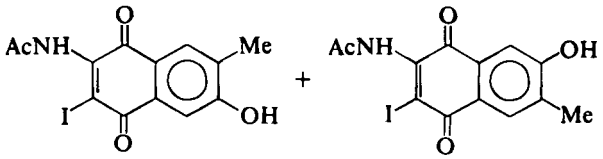


(350) (351)

Ref. 223 (95)



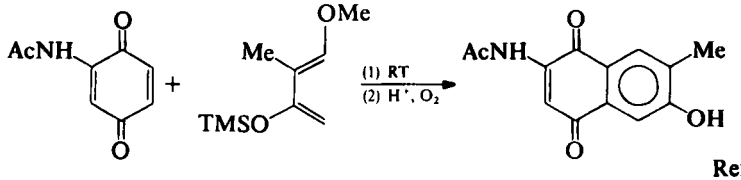
(352) (185)



12:1

(353) (354)

Ref. 224 (96)



(355) (185) (356)

Ref. 224 (97)

Since its earlier days, addition of a Lewis acid to the Diels–Alder reaction mixture is known to be able to control regioselectivity[227] and in some cases it resulted in a reversed selectivity. Several remarkable effects of Lewis acid are especially observed in the annulation of juglone derivatives. The reported results in these syntheses are summarized in Table 11. The role of the Lewis acid which enhances or reverses the regioselectivity is

TABLE 11. Lewis acid mediated Diels–Alder annulation

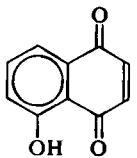
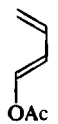
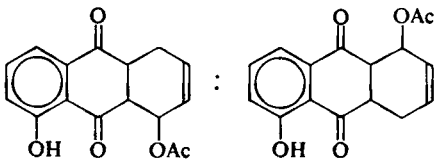
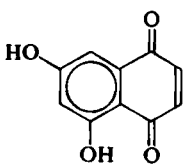
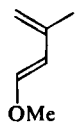
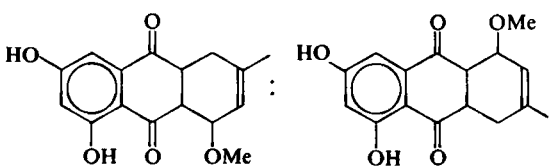
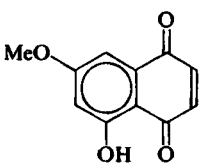
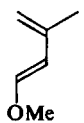
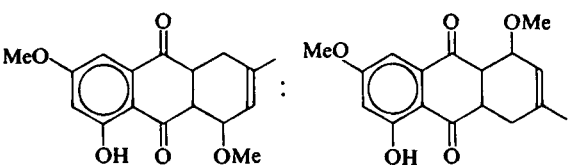
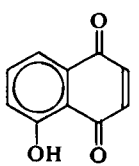
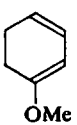
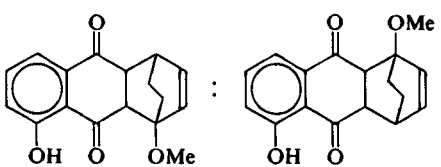
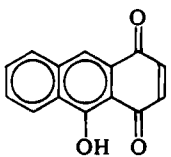
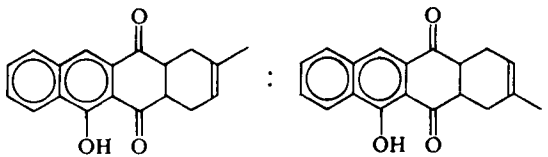
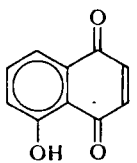
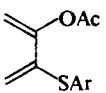
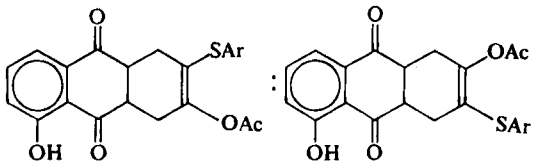
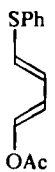
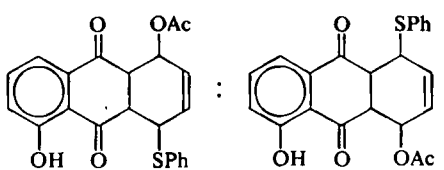
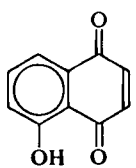
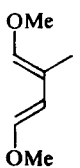
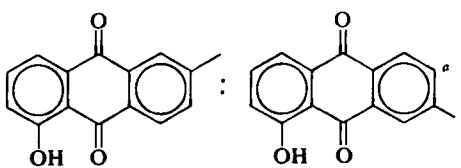
Quinone	Diene	Product	Product ratio without Lewis acid	Product ratio with Lewis acid (equiv.)	Reference
			3:1	$BF_3 \cdot OEt_2$(0.04) $\geqslant 99.5 : \leqslant 0.5$ 100:0	228, 229 230 231, 232
			45:55	$BF_3 \cdot OEt_2$ (0.05) 55:45 $BF_3 \cdot OEt_2$(0.4) $\geqslant 95 : \leqslant 5$ $B(OAc)_3$ (2) $\geqslant 95 : \leqslant 5$	229 229 229
			40:60	MgI_2(0.05) 35:65 MgI_2(0.5) $\leqslant 5 : \geqslant 95$	229 229
			95:5	MgI_2(0.4) 15:85	229

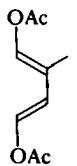
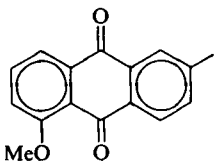
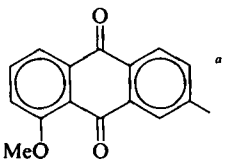
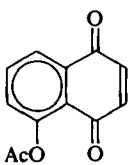
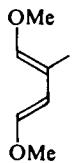
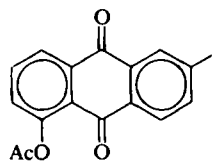
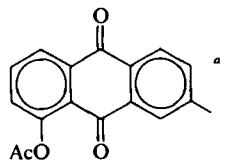
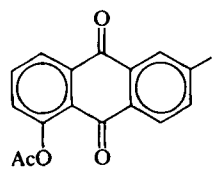
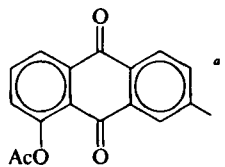
TABLE 11 (continued)

Quinone	Diene	Product	Product ratio without Lewis acid	Product ratio with Lewis acid (equiv.)	Reference
			11:10	$B(OAc)_3$ (excess) 100:0	230
			2:1	$BF_3 \cdot OEt_2$ (0.1–1.0) 0:100	231, 232
			2.3:1	$BF_3 \cdot OEt_2$ (0.1–1.0) 0:100	231, 232
			1:1.8	$BF_3 \cdot OEt_2$(0.5) 1:4.5 $AlCl_3$(0.5) 4.7:1	160 160

[a]

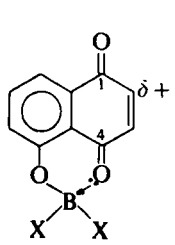
160
BF3·OEt2(0.5)
1:7.3
AlCl3(0.5)
1:4.5
1.2:1
160
AlCl3(0.5)
1:2:1
1:1
160
BF3·OEt2(0.5)
1:2.4
1:1.9
160
AlCl3(0.5)
1.3:1
160
1:1.1
OH
OAc
OMe
MeO

TABLE 11 (continued)

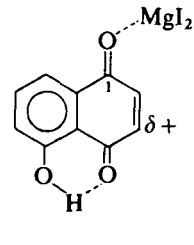
Quinone	Diene	Product	Product ratio without Lewis acid	Product ratio with Lewis acid (equiv.)	Reference
		 :  [a]	1:1.1	$AlCl_3$(0.5) 1:1.1	160
		 :  [a]	2:1	$BF_3 \cdot OEt_2$ (0.5) 4.7:1 $AlCl_3$(0.5) 2.75:1	160 160
		 :  [a]	2.6:1	$BF_3 \cdot OEt_2$(0.5) 2.0:1 $AlCl_3$(0.5) 1.4:1	160 160

[a] Products after aromatization

summarized as follows. (1) BF_3 and $B(OAc)_3$ easily afford complexes with juglone such as **357**, in which enhanced regioselectivity is observed due to the induced positive charge at the C(2). (2) In the case of MgI_2, a reversed regioselectivity is observed. It seems that

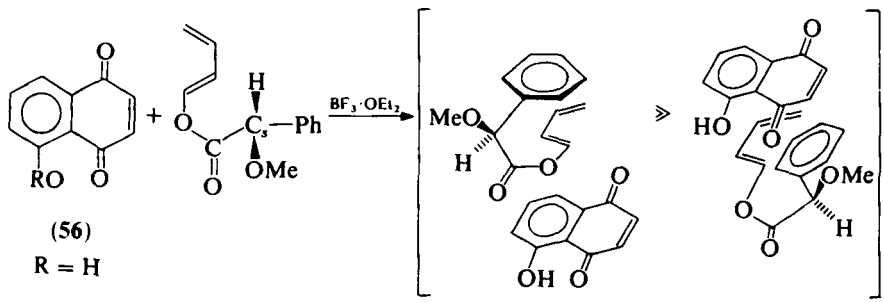


(357)



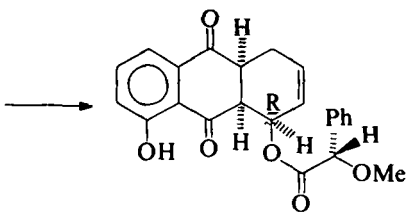
(358)

complexation at the C(1) carbonyl group (cf. **358**) dominates the selectivity rather than a bidentative complexation at the C(4) (cf. in **357**). This is apparently due to a higher steric hindrance and weaker acidity of MgI_2 than that of BX_3. (3) In the case of dienes substituted with sulfur and oxygen atom, the non-catalyzed reaction will be dominated by a sulfur substituent, while the Lewis acid catalyzed one will be controlled by the oxygen functionality, since the preferential complexation of Lewis acid to SR causes the decrease of electron-donating ability of the sulfide group. In some other examples, which show only a small change in the regioselectivity by the addition of Lewis acid, a systematic rationalization of the results is difficult, due to the presence of many competitive coordination sites for the Lewis acid among both the functionalized diene and the dienophile.



(56)
R = H

(359) (360) (361)

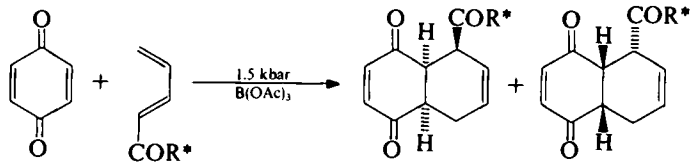


(98)

> 95% ee

(362)

The high regiochemical control in the Diels–Alder reaction was extended to asymmetric induction and an almost complete transfer of chirality was observed by use of (*S*)-*o*-methylmalonyl derivative (**359**)[233]. The reaction of **56** (R = H) with **359** gives **362** with higher than 95% enantiomer excess (equation 98). This efficient asymmetric induction is interpreted in terms of π-stacking interactions, shown in **360** and **361**, which increase the charge transfer interaction between the diene and the dienophile. 2,4-Pentadienoates (**363**) with various chiral alcoholic functionalities were examined in order to evaluate the asymmetric induction in the Diels–Alder reaction with *p*-benzoquinone (**211**)[234]. The reaction (equation 99) affords adducts in a high yield, while the asymmetric induction gives a moderate enantiomer excess.

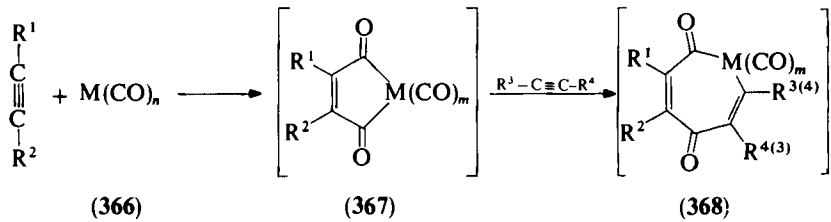


(99)

(211) (363) (364) (365)

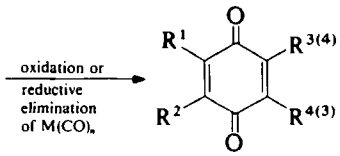
B. Metallacycles

Quinones or hydroquinones could be prepared from alkynes and metal carbonyls via metallacycles as shown in Scheme 14.



(366) (367) (368)

M = Mn, Fe, Co, Ni, Mo, Rh, Pt



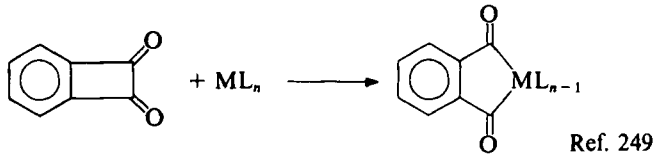
(369)

SCHEME 14

Numerous reports concerning this conversion have appeared since the 1940s, and the rather lower yields, the lack of general applicability, and the poor site-selectivity regardless of stoichiometric or catalytic use of metal carbonyls (**366**) did not draw much attention to the reaction, in spite of its potential for a facile construction of the quinone ring. The earlier

reports in this field have appeared in Refs 235 and 236, and the successive reports are given in Refs 237–244.

Since the assumption of Maitlis and coworkers[245] that malonyl (or phthaloyl) metal complex (**367**) is formed as an intermediate, many attempts has been made to prepare them in pure form[246,247] because the establishment of a general synthetic route to these metallacycles will open a convenient route to highly substituted and functionalized 1,4-quinones (**369**). Most of the reported methods, however, lack synthetic efficiency. Recently, the reaction between benzocyclobutenedione and low valent metal complex gave the desired phthaloylmetal complex in excellent yield[248–250]. The relative stability of these complexes toward air and moisture makes the preparation of them easy (equations 100–102).

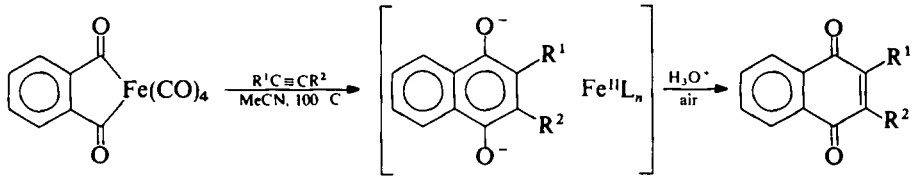


(100)

Ref. 249

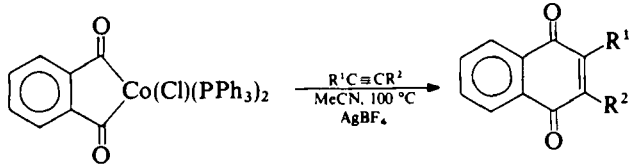
(**253**) (**370**)

ML_n = $Fe(CO)_5$, $ClCo(PPh_3)_3$, $CpCo(CO)_2$, $ClRh(PPh_3)_3$
ML_{n-1} = $Fe(CO)_4$, $ClCo(PPh_3)_2$, $CpCo(CO)$, $ClRh(PPh_3)_2$



(**371**) (**372**) (**373**)

(101)



(102)

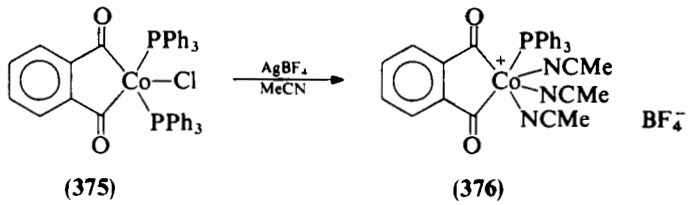
(**374**) (**373**)

Among the complexes, the iron and cobalt precursors are inexpensive sources of phthaloylmetal complexes, e.g. **371** and **374**, which afford, in turn, the corresponding naphthoquinones, e.g. **373**, in good to excellent yields on reaction with various kinds of alkynes at elevated temperature (Table 12)[249,250]. A complementarity in this annulation is observed between the iron and the cobalt complexes; for alkynes with electron donating groups R^1 and R^2 the cobalt complex gives superior results than the iron complexes. The generation of a six coordinate cationic cobalt complex is essential for the completion of this annulation. Silver tetrafluoroborate in acetonitrile gives with this cobalt complex the

TABLE 12. Annulation of phthaloylmetal complexes 371 and 374 with alkynes[249, 250]

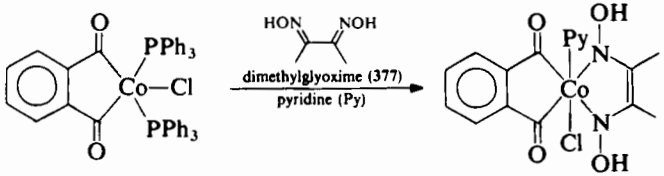
R^1	R^2	% Yield of 373 From the iron complex 371	From the cobalt complex 374
Me	Me	99	73
Et	Et	95	90
Ph	Ph	88	68
Ph	Me	100	78
n-Bu	H	95	65
Ph	H	94	57
t-Bu	Me	37	72
Et	$CH_2CH{=}CH_2$	75	80
EtO	Et	—	80
n-Bu	$SiMe_3$	22	68
Ph	$(CH_2)_2OH$	81	27
Me	CO_2Et	74	0
Et	COMe	68	0

tris(acetonitrilo)cobalt derivative (**376**). The dimethylglyoxime complex (**378**) is also obtained in pyridine in high yield (equations 103 and 104)[251] and gives an excellent



(103)

(375) (376)



(104)

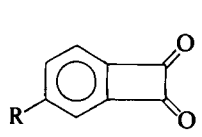
(375) (378)

TABLE 13. Annulation reaction with the phthaloylcobalt dimethylglyoxime complex (**378**)[251]

$R^1C{\equiv}CR^2$ R^1	R^2	Naphthoquinone (373) % Yield
EtO	Et	85
Et	Et	77
H	*n*-Bu	85
Me	CO_2Et	99
Me	$CH_2N(Ph)COMe$	70

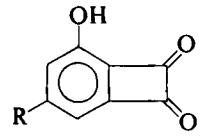
annulation reaction toward alkynes ranging from electron-rich to electron-deficient, and the problems mentioned above concerning this annulation are overcome by this method[251]. Several examples are shown in Table 13.

Since the substituted benzocyclobutenediones **379** or **380** have been synthesized[252], this method is applicable to a wide variety of naphthoquinones.



(379)

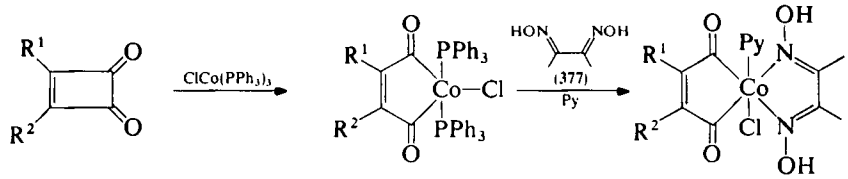
R = H, Me



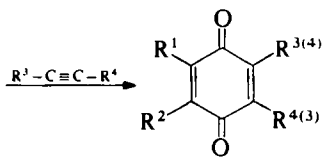
(380)

R = H, Me

Benzoquinones as well as naphthoquinone are prepared by an extension of this methodology, in which the maleoylcobalt dimethylglyoxime complex (**383**) prepared from **381** via **382** gives the corresponding benzoquinone(s) in good yield(s) (Scheme 15)[253]. This



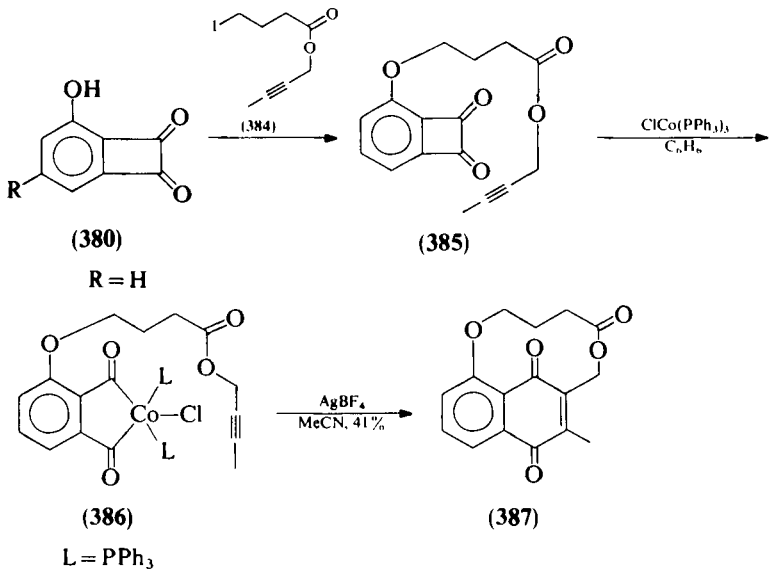
(381) **(382)** **(383)**



(369)

SCHEME 15

method is extremely useful for the preparation of tri- and tetrasubstituted benzoquinones as shown in Table 14. Two limitations, however, are observed in this reaction. First, only a limited number of alkyl- or alkoxy-substituted cyclobutenediones are available. Second, the combination of an unsymmetrical cyclobutenedione with unsymmetrical alkynes results in the formation of the possible two regioisomers, usually in appreciable percentages. In order to overcome these defects, an intramolecular cyclization is examined in the following synthesis of a juglone derivative (equation 105)[254]. In this example, a covalently bound benzocyclobutenedione (**385**) is converted to the corresponding cobalt complex (**386**). The length of binding side chain of the alkyne controls the regiochemical course and only one isomer is obtained.



(105)

TABLE 14. Preparation of substituted benzoquinones by the reaction of maleoylcobalt complexes (383) with alkynes[253]

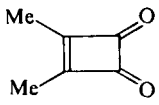
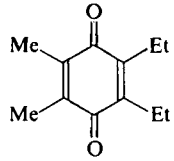
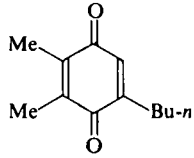
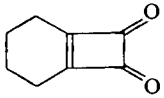
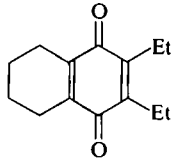
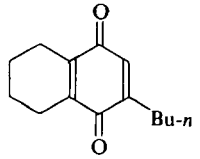
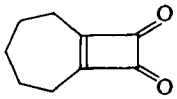
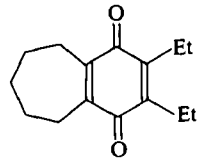
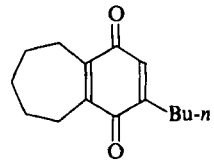
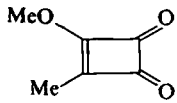
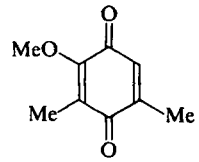
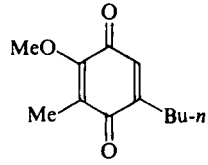
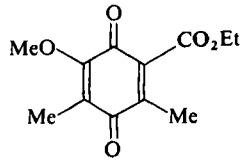
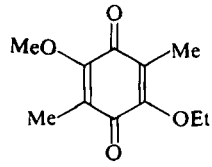
Cyclobutenedione (381)	Alkyne, $R^1C{\equiv}CR^2$ R^1	R^2	Benzoquinone	% Yield
	Et	Et		81
	H	*n*-Bu		85
	Et	Et		85
	H	*n*-Bu		79

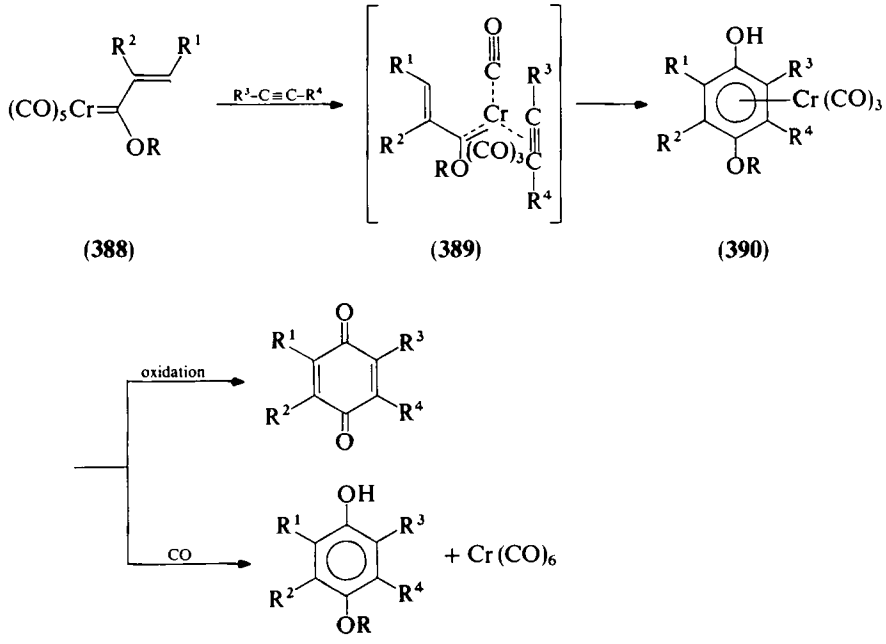
TABLE 14 (continued)

Cyclobutenedione (381)	Alkyne, $R^1C{\equiv}CR^2$ R^1	R^2	Benzoquinone	% Yield
	Et	Et		88
	H	*n*-Bu		84
	H	Me	 (5:1)[a]	81[b]
	H	*n*-Bu	 (3.7:1)[a]	89[b]
	Me	CO_2Et	 (3.7:1)[a]	64[b]
	Me	OEt	 (13.5:1)[a]	81[b]

[a] The major isomer is shown in this table. Isomeric ratio is shown in parentheses.
[b] Total yield of two regioisomers.

C. Metal Carbene Complexes

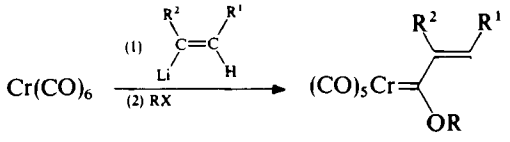
In the presence of an alkyne, a carbonyl chromium complex (**388**) with a saturated carbene ligand easily affords the corresponding alkyne–carbene–carbonyl complex, which undergoes a cycloaddition reaction to give a chromium complex of a quinone monoalkyl ether (**390**) (Scheme 16)[255-257]. This π-bonded chromium complex (**390**) is easily



(388) (389) (390)

SCHEME 16

demetallated either to a quinol monoether by treatment with CO or to the corresponding quinone by oxidative demetallation. The former method especially can regenerate the stable chromium hexacarbonyl which can be recycled in the preparation of the carbene complex as shown in equation 106. In this reaction, three components, i.e. α,β-unsaturated

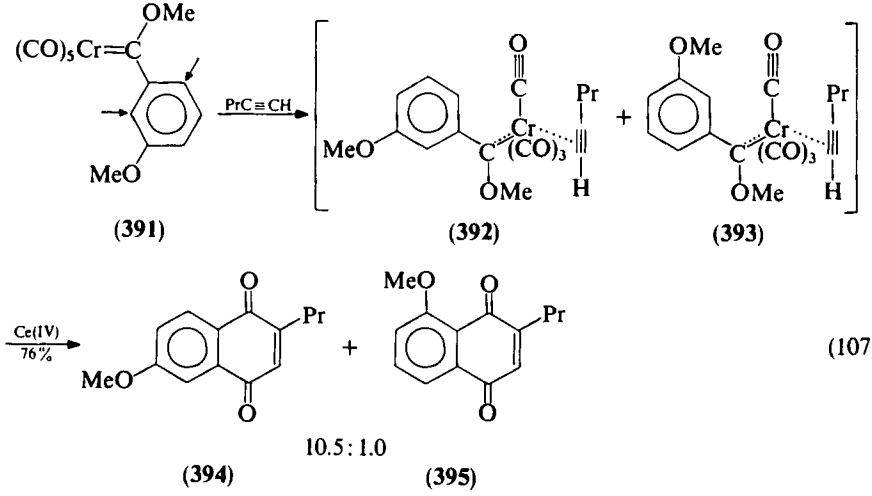


(388) (106)

alkoxycarbene, an alkyne and carbon monoxide, are cyclized together on the coordination sphere of chromium carbonyl to give **390**. This fundamental reaction has wide applicability for various alkynes and unsaturated metal carbene complexes, whose preparative method has already been established[258-262]. The yield is moderate to good and is affected by the

structure, reactivity and stability of the applied chromium carbene complex as well as of the alkyne (Table 15).

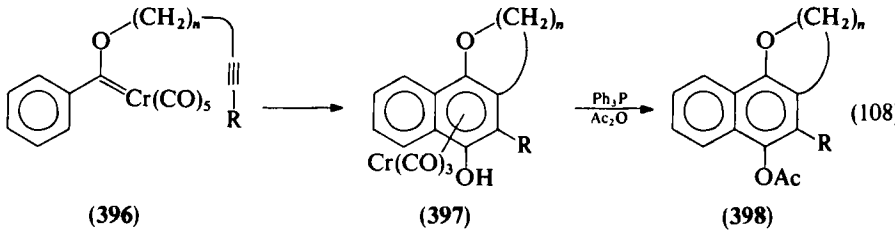
Whereas the reaction of symmetrically substituted carbene complexes ($R^1 = R^2$ in Table 15) raises no regiochemical problem in the quinone product, the combination of an unsymmetrically substituted alkyne and an aryl carbene complex as well as of metallacycles gives intrinsically two isomeric quinones and the more bulky group preferentially ends up nearest to the free OH group in the product. Several examples are also shown in Table 16. The electronic effects of the two substituents on the acetylene have less importance on the regioselectivity, but the yield is severely decreased by an electron-withdrawing group on the alkyne. In the reaction of several alkoxy-substituted aryl carbene complexes with alkynes, the regioselectivity increases with increasing the steric difference between the two substituents on the acetylene[266]. A terminal acetylene gives one isomer in high regioselectivity (equation 107). *Meta* substitution on the carbene complex shows the two



(107)

expected modes of cyclization at the sterically different *ortho* positions. From the regioselectivities observed in the cyclization of various systems with *meta* substituents of sterically and electronically different character (e.g. Me, F, CF_3), it can be concluded that both effects should be taken into account when explaining the product selectivity[266]. However, a systematic explanation has not yet been given.

In order to overcome these regiochemical problems in cyclization, an intramolecular reaction is designed (equation 108)[267, 268]. In **396**, the alkyne is covalently bound to the



(108)

R = H, $n = 2-4$, 16–38%
R = Me, $n = 2-4$, 62–81%

TABLE 15. Coupling of unsaturated chromium carbene complexes with alkynes

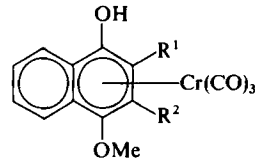
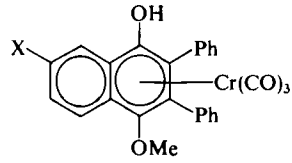
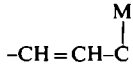
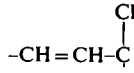
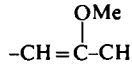
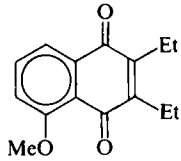
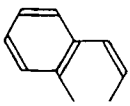
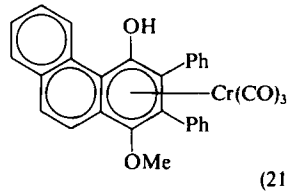
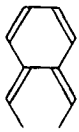
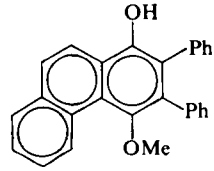
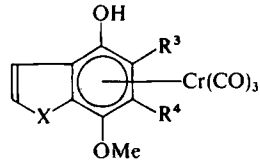
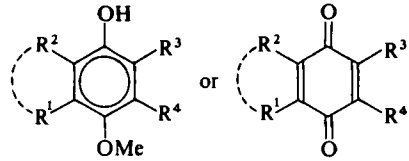
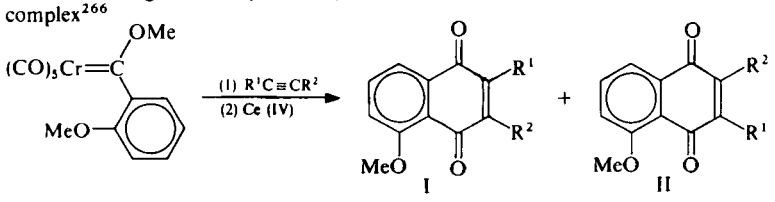
(388) R = Me R^1 R^2	R^3–C≡C–R^4 R^3	R^4	Product (% Yield)	Reference
				
–CH=CH–CH=CH–	Et	H	(35)	263
	Me	Me	(68)	263
	n-Pr	H	(45)	263
	n-Bu	H	(45)	263
	n-Pr	Me	(58)	263
	Et	Et	(62)	256
				
	Ph	Ph	X = Me (40)	265
	Ph	Ph	X = CF_3(25)	265
	Et	Et	 (70)[b]	266
	Ph	Ph	 (21.5)	265
	Ph	Ph	 (19)	265

TABLE 15 (continued)

(388) R = Me		R^3–C≡C–R^4		Product	
R^1	R^2	R^3	R^4	(% Yield)	Reference
					
–O–CH=CH–		Ph	Ph	X=O (19)	265
		n-Bu	H	X=O (23)	265
–S–CH=CH–		*n*-Bu	H	X=S (40)	265
		Ph	Ph	X=S (28)	265
					
$-(CH_2)_3-$		Ph	Ph	(36)[a]	264
		Ph	H	(76)[a]	264
		n-Pr	H	(54)[a]	264
		Et	Et	(37)[b]	264
$-(CH_2)_4-$		Et	Et	(64)[a] (65)[b]	264
		n-Pr	H	(61)[b]	264
		$SiMe_3$	H	(71)[c]	264
		(Z)-MeOCH=CH–	H	(68)[c]	264
		$AcOCH_2$	H	(33)[a]	264
		MeO_2C	H	(22)[d]	264
		PhCO	H	(17)[d]	264
		MeO_2C	MeO_2C	(8)[d]	264
$-(CH_2)_5-$		*n*-Pr		(66)[a]	264
		$CH_2=CHC(Me)$	H	(57)[a]	264
$-O(CH_2)_3-$		Et	Et	(71)[b]	264
		$(EtO_2C)_2(NHAc)CCH_2$	H	(67)[b]	264
		n-Pr	H	(38)[b]	264
EtO	Me	Ph	Ph	(67)[a]	264
		n-Pr	H	(40)[b]	264
EtO	H	$Me_2C=CHCH_2$	H	(23)[e]	264
Me	H	*n*-Pr	H	(51)[b]	264
H	Me	*n*-Pr	H	(75)[b]	264

[a] After oxidation with $FeCl_3$·DMF complex.
[b] After oxidation with CAN.
[c] After air oxidation.
[d] After oxidation with I_2.
[e] After treatment with tributylphosphine.

TABLE 16. Regioselectivity in the cyclization of a chromium carbene complex[266]

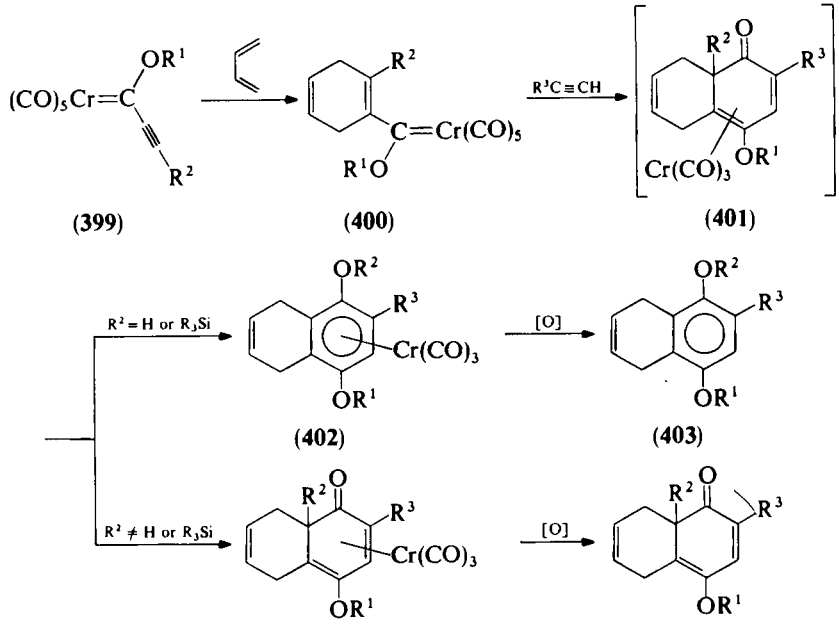


R^1	R^2	% Yield (I + II)	Product ratio I/II
Et	Me	81	1.5
n-Pr	Me	64	2.9
n-Pr	H	74	⩾ 111
i-Pr	Me	61	4.8
Ph	Me	78	*a*
$(CH_2)_3CO_2Bu$-*t*	H	66	*a*
$(CH_2)_3CONHBu$-*t*	H	70	*a*

[a] Only one isomer is obtained. The structure is not defined.

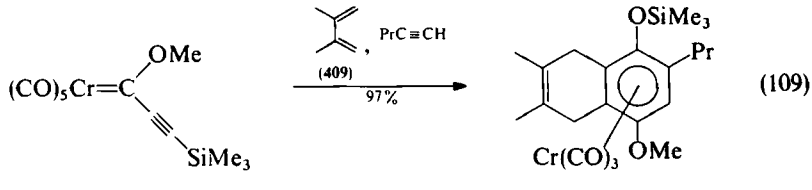
alkoxy group and the transition state geometry is restricted by this bonding of the two reactants. The single product (**397**) is expected from the metal complex and it is indeed obtained in moderate to good yield. This method is extraordinarily important for the synthesis of naturally occurring quinones, e.g. nanaomycin A and anthracyclinones.

As a variation and an extension of the above-mentioned reaction, a Diels–Alder reaction of an α,β-alkynyl carbene complex is developed to construct a new α,β-alkenyl complex[269].

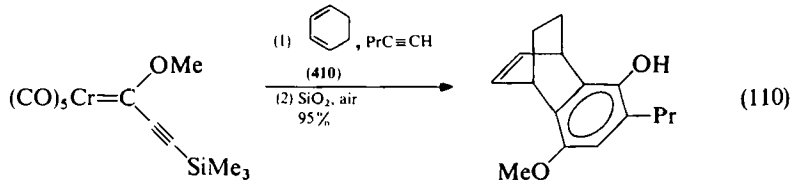


SCHEME 17

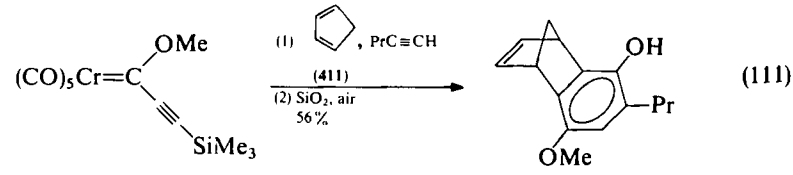
Due to the electron-withdrawing character of the metal carbene moiety, the alkynylcarbene complex (**399**) is a good dienophile, and annulation with a conjugated diene proceeds easily to afford the corresponding carbene adduct (**400**), which is a good precursor for the cyclization to give **401**. When the terminal substituent R^2 on the alkynyl carbene (**399**) is a hydrogen or a trialkylsilyl group, **401** easily undergoes a dienone–phenol rearrangement to the corresponding hydroquinone derivative (**402**), which by oxidation gives **403** (Scheme 17)[269]. As the applied dienes and alkynes do not interfere in the successive reactions, this tandem reaction can be conducted in a one-pot without isolation of the intermediary alkenyl carbene complex (**400**). Several examples of this component reaction are shown in equations 109–112.



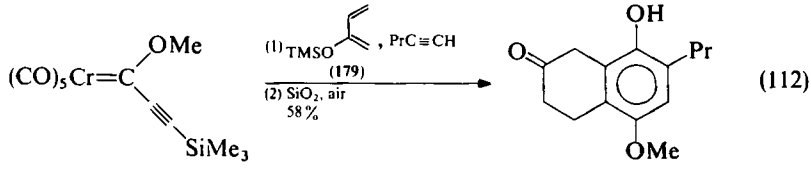
(404) (405) (109)



(404) (406) (110)



(404) (407) (111)



(404) (408) (112)

D. Stabilized Carbanions

1. Tandem directed metalation

A tertiary benzamido group on an aromatic nucleus promotes *ortho* metalation. Condensation of the *ortho*-lithiated product with α,β-unsaturated, especially aromatic, aldehyde affords the benzyl alkoxide intermediate (**412**). In the presence of additional

TABLE 17. Synthesis of polycyclic quinones by tandem directed metalation[270]

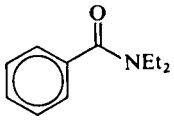
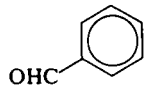
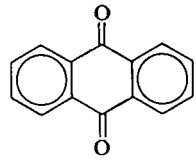
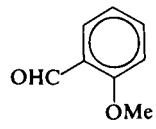
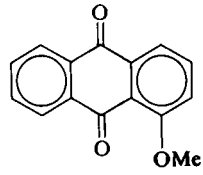
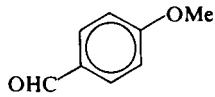
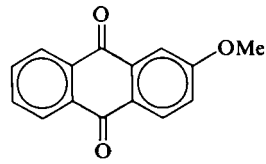
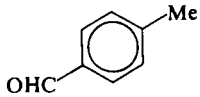
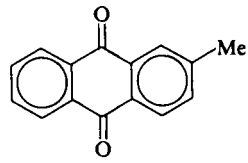
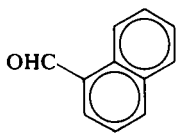
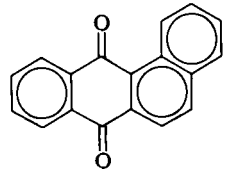
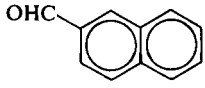
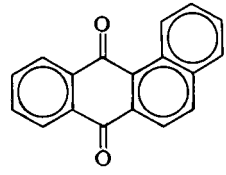
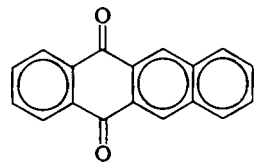
Amide	Aldehyde	Product	% Yield
			43
			10
			28
			15
			44[a]
			39[a]
			5[a]

TABLE 17 (continued)

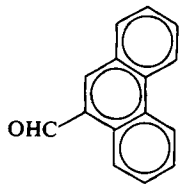
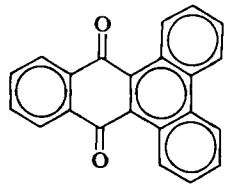
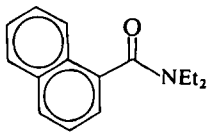
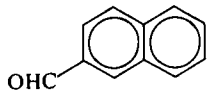
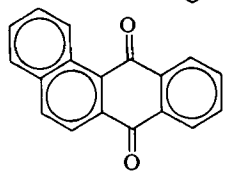
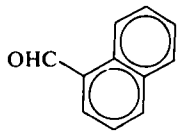
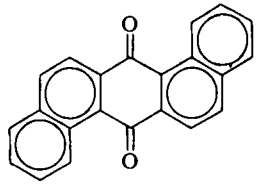
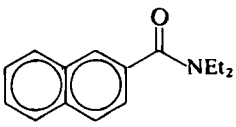
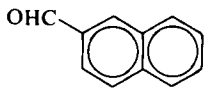
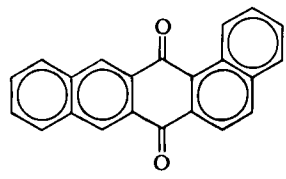
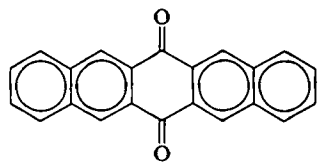
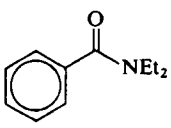
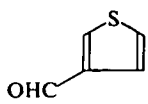
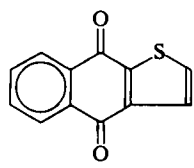
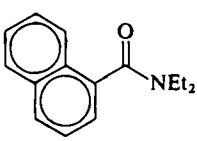
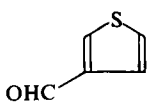
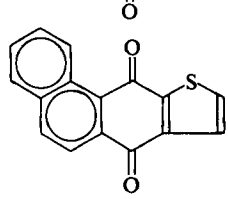
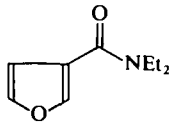
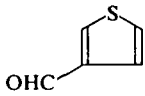
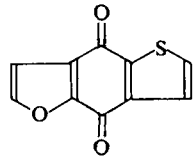
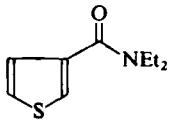
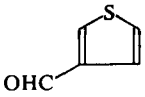
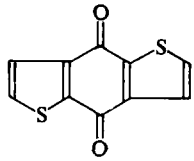
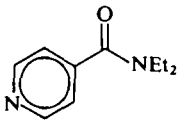
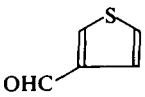
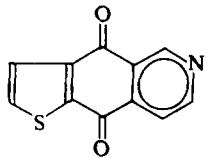
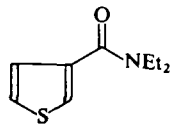
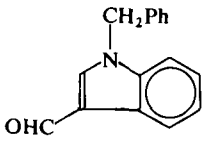
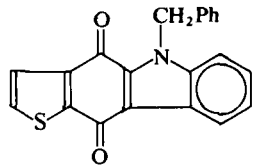
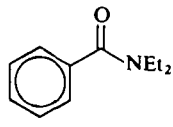
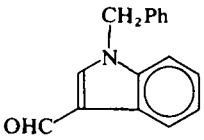
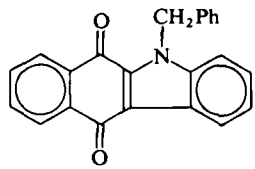
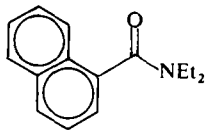
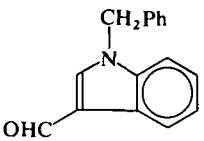
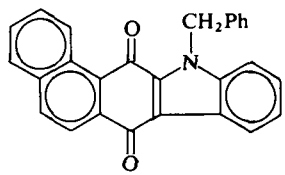
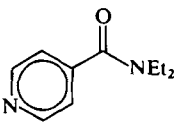
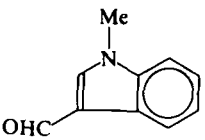
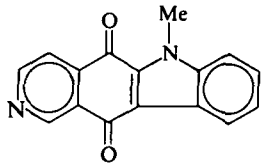
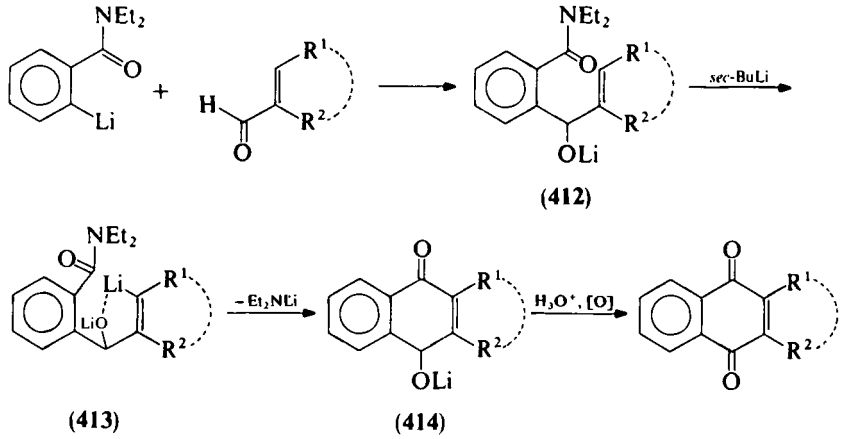
Amide	Aldehyde	Product	% Yield
			41[a]
			10[a]
			10[a]
			2
			2
			35
			37

TABLE 17 (continued)

Amide	Aldehyde	Product	% Yield
			24
			77
			20
			67
			44
			20
			76

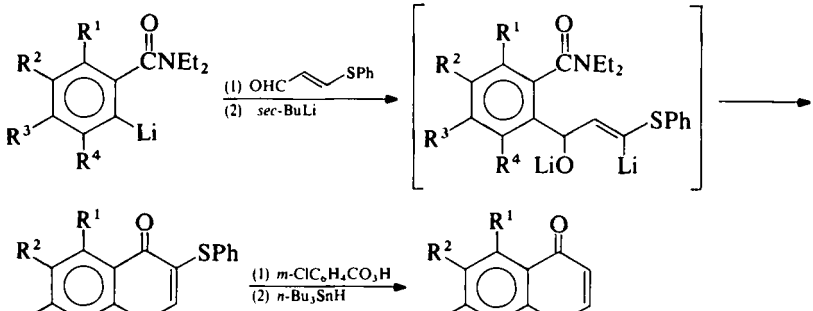
[a] The corresponding phthalide is obtained as a major product owing to the incomplete lithiation.



SCHEME 18

equivalent of alkyl lithium, **412** is further lithiated to **413**, which by intermolecular cyclization gives **414**, which in turn is converted to a quinone (Scheme 18)[270, 271]. This tandem reaction is useful for the preparation of polycyclic quinones, most of which are difficult to obtain selectively by other methods. The yields range from low to moderate (Table 17). The second lithiation is the key step in the reaction, as shown by the following facts. (1) Since the adduct from 2-naphthaldehyde possesses two positions capable of metalation, the corresponding two isomeric quinones are obtained. (2) Facile lithiation at the 2-position of furan, thiophene and pyrrole results in higher yields than in the other cases.

This methodology was extended to an α,β-unsaturated aldehyde which carries a β-thiophenyl group capable of stabilizing the formal vinyl anion (Scheme 19)[272]. Under these conditions, phenylthio-substituted quinones are obtained in fair yields. The auxiliary phenylthio group can be removed by oxidation of the sulfide by *m*-chloroperbenzoic acid followed by tin hydride reduction.

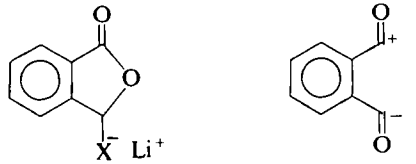


R^1, R^2, R^3, R^4 = H, Me, OMe

SCHEME 19

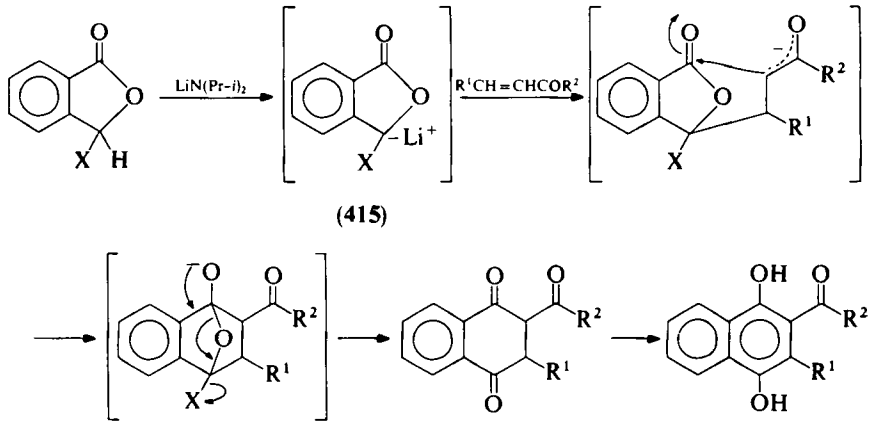
2. Annulation via isobenzofuran and related 1,4-dipole synthones

The carbanion derived from isophthalide (**415**) by treatment with lithium diisopropylamide (LDA) is considered to be a synthetic equivalent of **416** and reacts with α,β-unsaturated carbonyl compounds to give the corresponding acylnaphthoquinones



(**415**) (**416**)

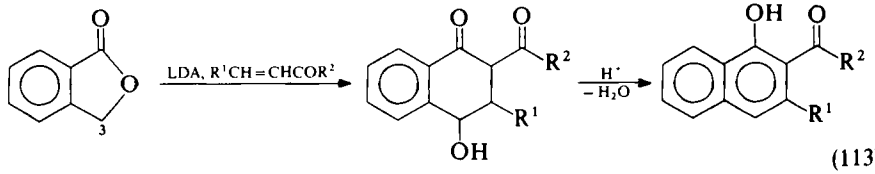
X = α-carbanion-stabilizing group



(**415**)

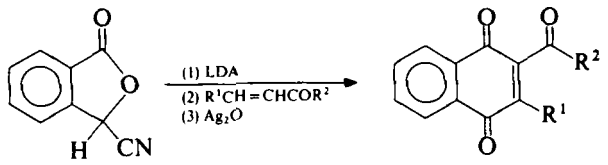
SCHEME 20

illustrated in Scheme 20. Although isophthalides (**417**) without any leaving group at the 3 position can be used in this cyclization[273], the obtained benzyl alcohol (**418**) is prone to dehydrate to the corresponding naphthol (**419**) under acidic conditions (equation 113).



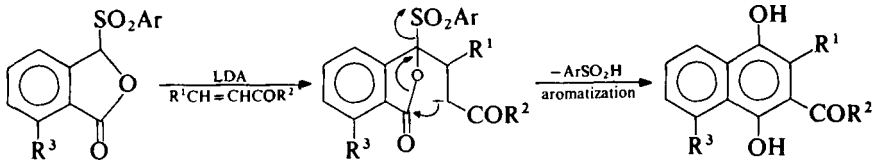
(**417**) (**418**) (**419**) (113)

Consequently, the introduction of a good leaving group at this position is necessary for the direct quinone synthesis. Since the use of cyanoisophthalide (**420**) was reported (equation 114)[274], many variations have been developed. Among related isophthalide derivatives, the sulfone (**422**) is extremely useful for this cyclization (equation 115), since the aryl sulfonyl group is both a good α-carbanion stabilizing group and a good leaving one[275, 276]. In most cases, acyl- or alkoxycarbonylhydroquinone is obtained in good yield.



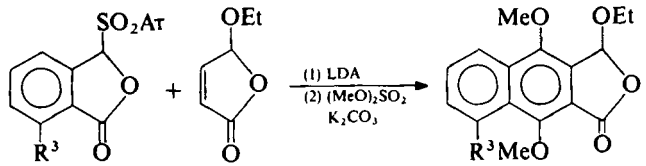
(420) (421) Ref. 274 (114)

$R^1 = R^2 = Me$, 85%
$R^1 = H$, $R^2 = OEt$, 61%

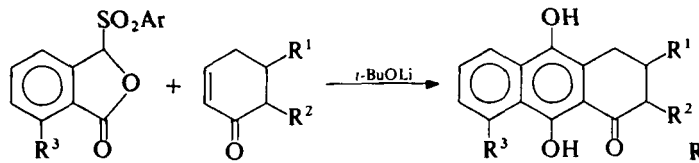


(422) (423) (424)

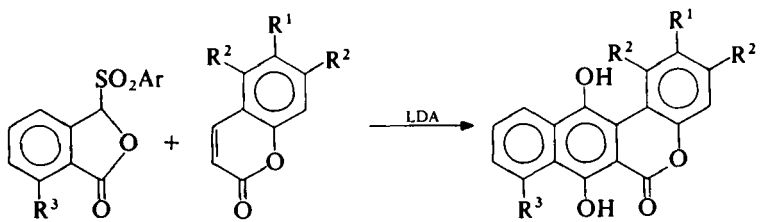
$R^1 = H$, Me, CH_2SMe, $R^2 = Me$, OEt, $R^3 = H$, OMe Refs 275, 276 (115)



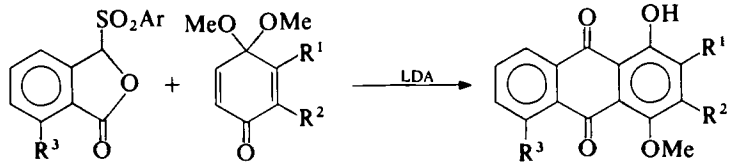
(422) (425) (426) Ref. 277 (116)



(422) (427) (428) Ref. 279 (117)



(422) (429) (430) Ref. 281 (118)

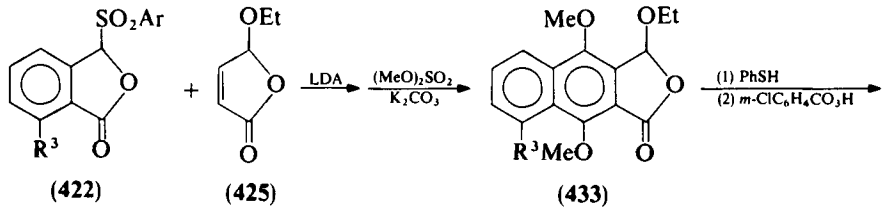


(422) (431) (432) (119)

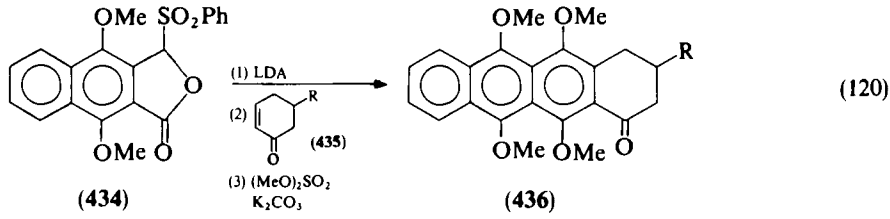
Refs 282, 283

This reaction was applied to the synthesis of various naphthoquinone and anthraquinone derivatives. Furanone (**425**)[277,278], cyclohexenone (**427**)[279,280], benzo-2-pyrone (**429**)[281] and quinone monoacetal (**431**)[282,283] were used as initial Michael acceptors, and gave **426**, **428**, **430** and **432**, respectively (equations 116–119). There are several impressive features in this reaction. (1) The regiochemistry of the annulation is predictable and there is no possibility of contamination with the regioisomers, which is frequently observed in the other annulations (i.e. a Diels–Alder reaction, metallacycle compounds, and metal carbene complexes). (2) A wide range of Michael acceptors can be applied in this reaction to afford the expected product in a satisfactory yield. (3) Versatile functional groups, which can survive under basic conditions, can be introduced in a regioselective manner to the produced aromatic compound.

As an extension of this method, the tetracyclic compound **436** was obtained by a repeated use of this reaction (equation 120)[275]. In addition to the α,β-unsaturated carbonyl



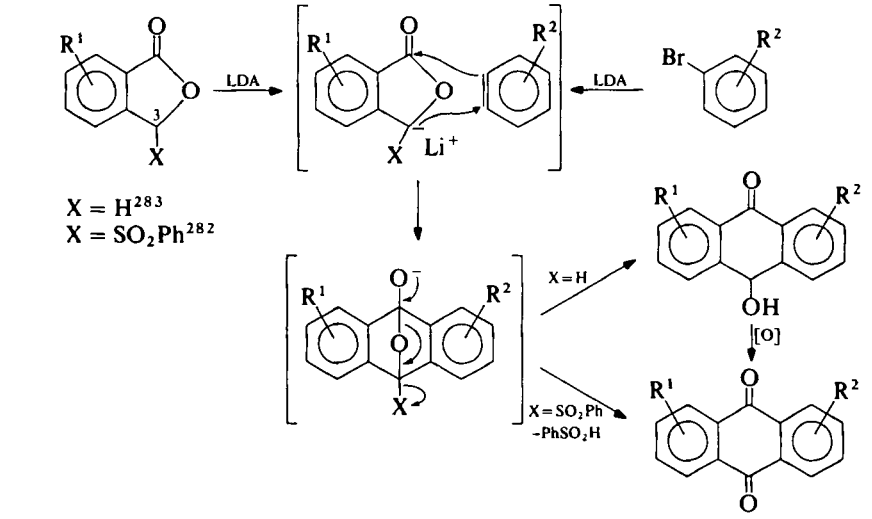
(422) (425) (433)



(434) (436) (120)

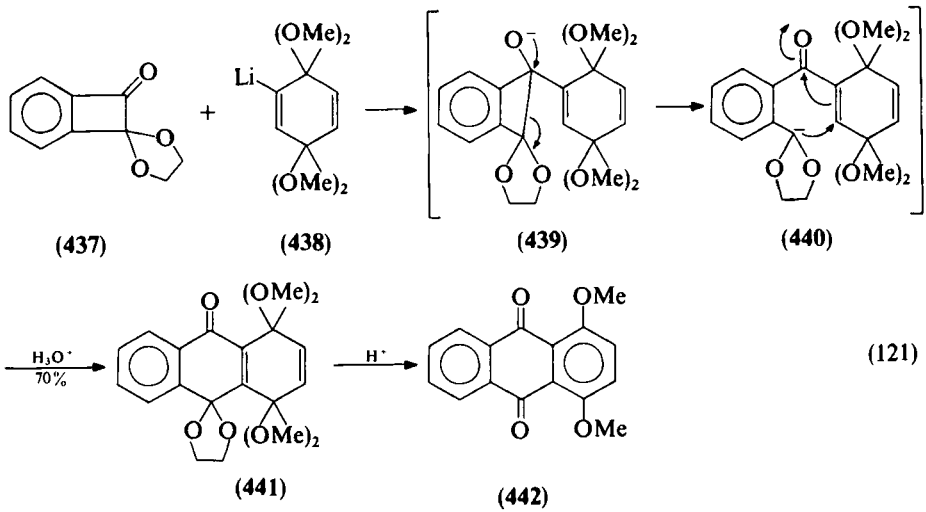
R = H, 68%
R = COMe, 68%
R = CO_2Me, 87%

compounds, benzyne was also used as a trapping agent of the initially formed anion[282–284]. When a phthalide and a substituted bromobenzene are treated together with two equivalents of LDA, a nucleophilic addition of lithium phthalide to benzyne which is generated *in situ*, is followed by an intramolecular cyclization. When a phenylsulfonyl group is at the 3 position, the anthraquinone is obtained directly in good yield, whereas the hydroxy derivative is obtained with 3-*H*-isophthalide (Scheme 21).



SCHEME 21

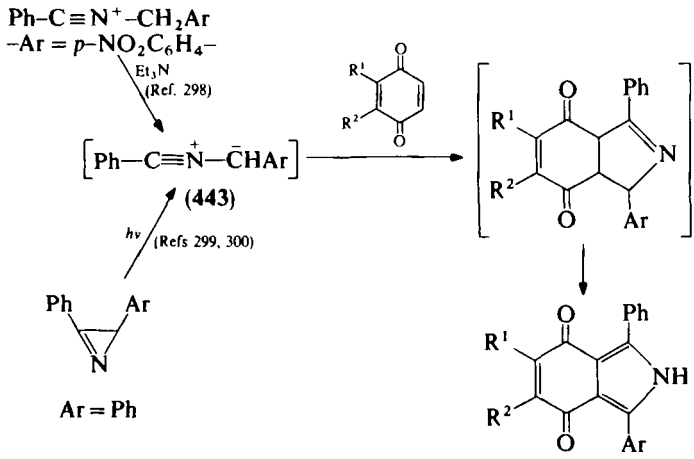
Relevant to this annulation, the benzocyclobutenedione monoacetal (**437**) is also considered as a synthon of **416**[285, 286]. The reaction of **437** with lithiated quinone bisacetal (**438**) proceeds by an initial nucleophilic attack of the lithiated reagent on the ketone. The intermediate acetal anion (**440**), considered to be the charge inverted equivalent of a formyl anion, then cyclizes intramolecularly to **441** through Michael type addition (equation 121).



(121)

E. Miscellaneous Reactions

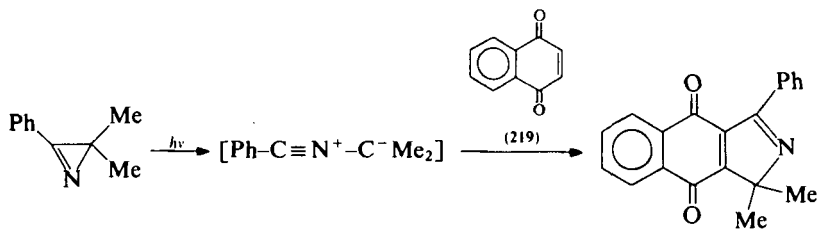
1,3-Dipolar cycloaddition is utilized for the synthesis of heterocyclic quinones. Reactions of nitrile ylides (**443**) with *p*-quinones possessing free 2 and 3 positions give the



R^1, R^2 = H, Me, MeO, –CH=CHCH=CH–

SCHEME 22

corresponding isoindoloquinone (Scheme 22)[287-289]. Benzonitrile benzylide (**443**, Ar = Ph) reacts with wide range of *p*-quinones[288], while benzonitrile-2-propanide (**445**) gives the corresponding isoindoloquinone **446** with only 1,4-naphthoquinone (equation 122).

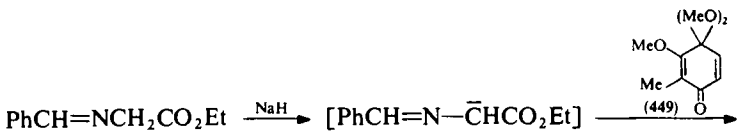


(444) **(445)** **(446)** (122)

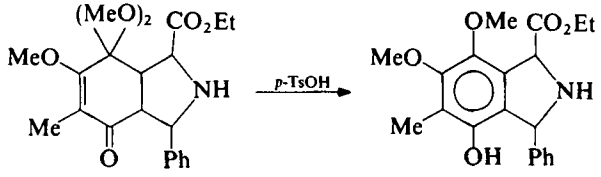
On the other hand, the reaction of **445** with benzoquinone arises at the quinone carbonyl group instead of the C–C double bond of the quinone. Since this reaction is very sensitive to the structure of the dipolarophiles, it does not have general applicability.

In the presence of sodium hydride, *N*-benzylidene glycine ester (**447**) forms *in situ* *N*-benzylidene imine (**448**), which cyclizes with a quinone monoacetal to give **451** after acid treatment (equation 123)[290]. **451** is also the promising precursor to the isoindoloquinone[290].

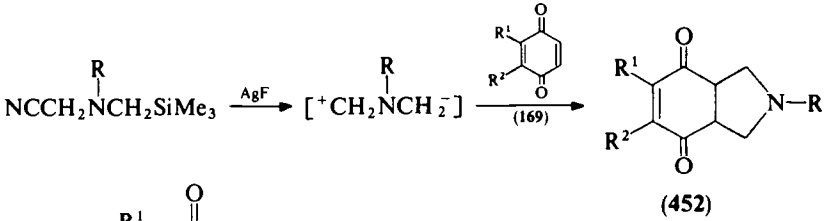
Recently, non-stabilized azomethine ylides, generated *in situ* by the treatment of cyanomethylaminosilanes with AgF, were found to cyclize with quinones to the corresponding isoindoloquinones (**453**) (equation 124)[291]. This reaction seems to have a rather wide applicability to various quinones and it gives the products in good yields. Another example is the 1,3-dipolar cycloaddition of quinones with oxazolium oxide (**455**), which is formed by dehydrative cyclization of the phenylglycine derivative (**454**) (Scheme 23)[292]. There is no regioselectivity in the reaction between an unsymmetrical quinone and



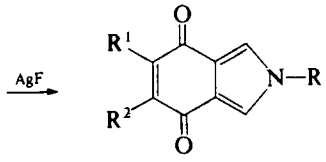
(447) (448)



(450) (451) (123)

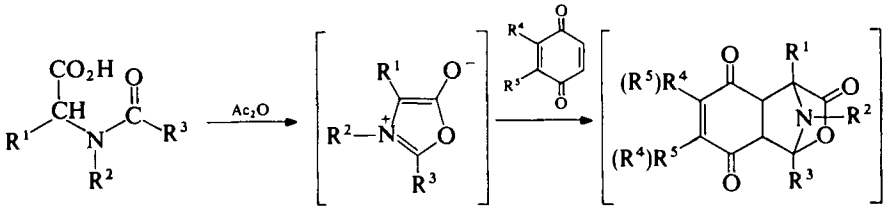


(452)



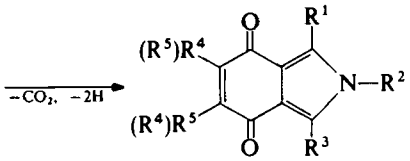
(453) (124)

R^1, R^2 = H, Me, MeO, 60–75%



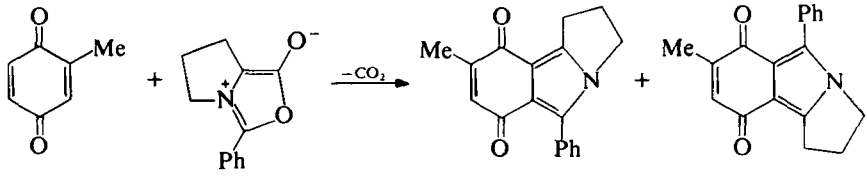
(454) (455)

R^1 or R^3 = Ph, R^2 = Alkyl



SCHEME 23

an oxazolium oxide when $R^1 \neq$ Ph. The reaction can be used to prepare the tricyclic systems **457** and **458** from the bicyclic oxazolium oxide **456** (equation 125).



(257) (456) (457) (458)

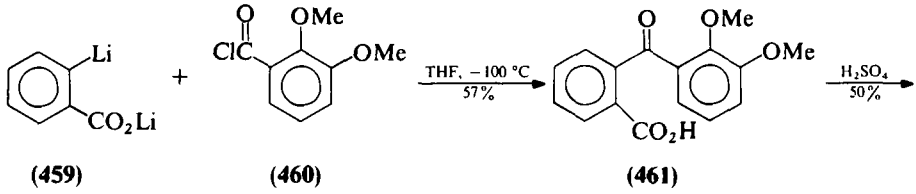
(125)

As seen above, the number of 1,3-dipoles applied to the cycloaddition reaction with quinone as a dienophile is so far limited. Further exploitation is necessary in order to extend the scope of the reaction with many other 1,3-dipoles[293].

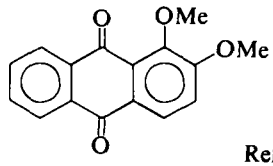
IV. CYCLIZATION AND CONDENSATION METHODS

A. The Friedel–Crafts Reaction

The Friedel–Crafts reaction is traditionally used for the synthesis of anthraquinone derivatives and has almost an equivalent value to that of the anionic annulation of a phthalide with α,β-unsaturated carbonyl compound (Section III.D.2). Several proton acids and Lewis acids, e.g. conc. H_2SO_4[294,295], $BF_3 \cdot OEt_2$[296], have been used for this reaction, but the yields are not always satisfactory. Trifluoroacetic anhydride (TFAA), trifluoromethanesulfonic acid and hydrofluoric acid are superior as acid catalysts and give cyclized products in good yields[121,297,298]. Several examples are compared in equations 126–130. As the carboxyl moiety, ester, acid chloride and acid anhydride as well as the free acid, are most commonly used, and are equally applied to this cyclization. Many other variations are known in the synthesis of anthracyclinones. As a special example, carbothioic acid derivative (**475**) is used as an alternative and the corresponding cyclized product (**476**) is obtained by using copper(I) trifrate (CuOTf) as the Lewis acid (equation 131)[299].



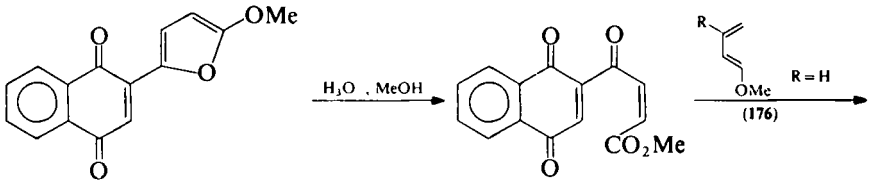
(459) (460) (461)



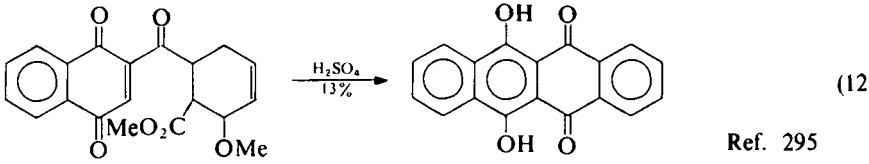
(222)

(126)

Ref. 294

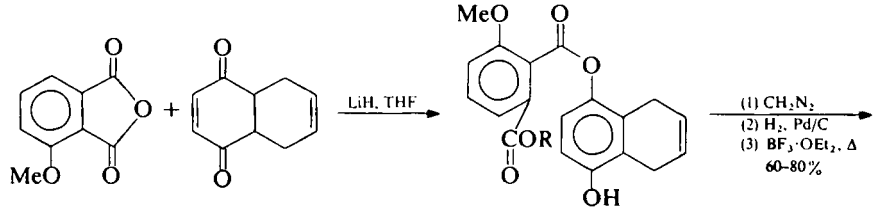


(462) (463)

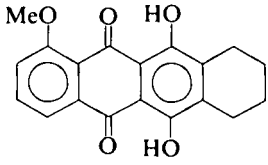


(464) (255) (127)

Ref. 295

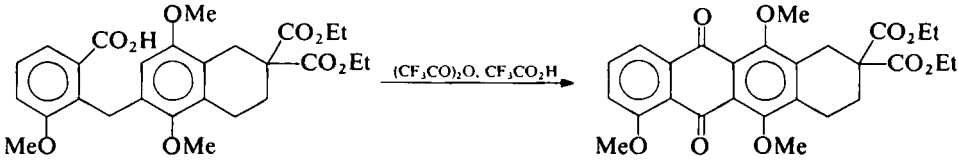


(465) (466) (467)
R = H



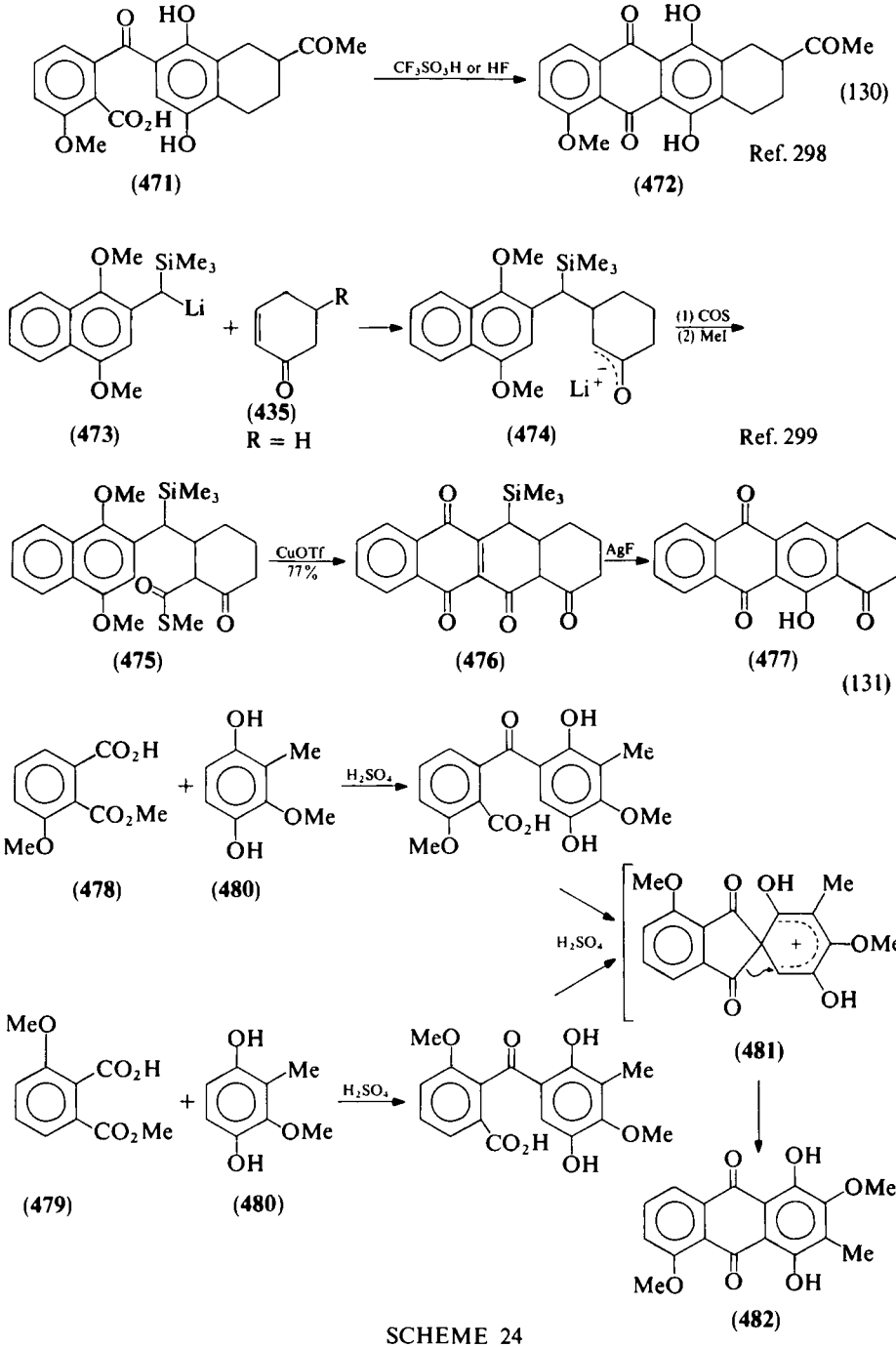
(468) (128)

Ref. 297



(469) (470) Ref. 297

(129)

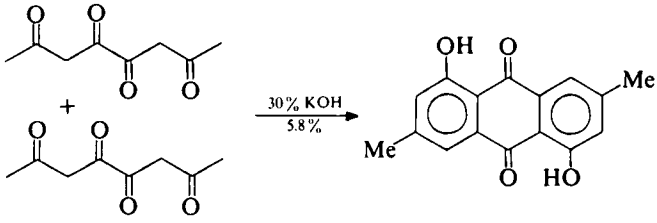

CF3SO3H or HF
(130)
Ref. 298
(471)
(472)
(1) COS
(2) MeI
(473)
(435)
R = H
(474)
Ref. 299
CuOTf
77%
AgF
(475)
(476)
(477)
(131)
H2SO4
(478)
(480)
(481)
(479)
(482)

SCHEME 24

When an intermolecular Friedel–Crafts cyclization to anthraquinone is conducted with a combination of both unsymmetrical phthalic acid monoesters, **478** or **479**, and the hydroquinone **480**, a single product (**482**) is obtained. It was speculated that the reaction proceeds via the spiro-type intermediate (**481**) (Scheme 24)[300,301].

B. Miscellaneous Reactions

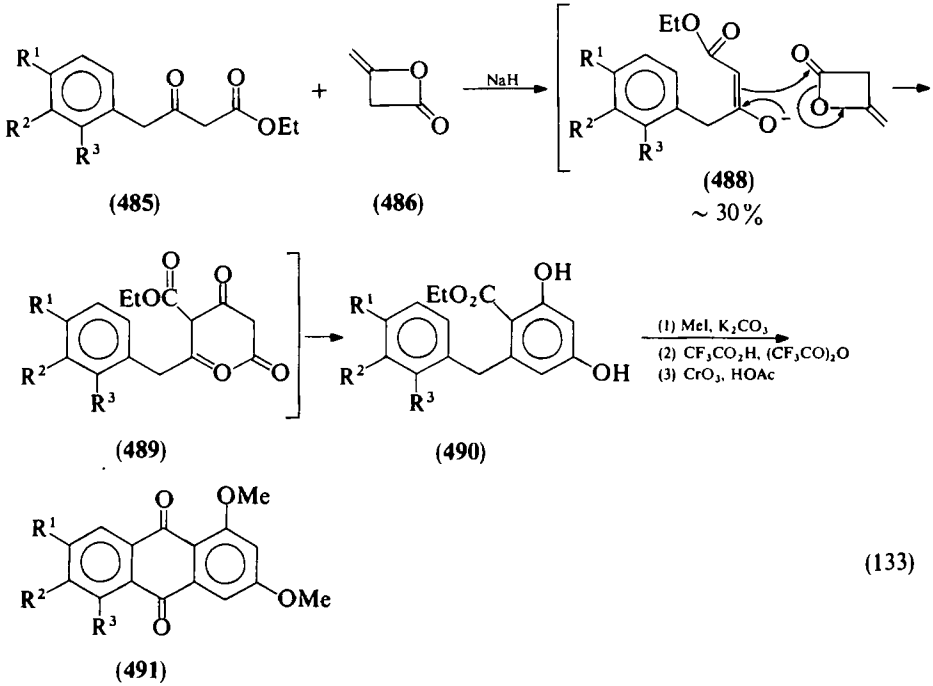
In the biosynthetic route to quinones, polyketide intermediates are postulated as the precursors of the aromatic nucleus. For a demonstration of this process, oxalyldiacetone (**483**) is treated with a concentrated base to afford the anthraquinone derivative **484** in 5.8% yield (equation 132)[302]. The low yield is attributed to the occurrence of random and unfavorable intermolecular condensation. Since diketene **486** is considered as a synthetic



(132)

(**483**) (**484**)

equivalent of the β-ketoacyl cation **487**, its condensation with the β-ketoacid ester **485** will give the polyketo intermediate **489**, which undergoes a Robinson type annulation to give **490** and then **491** (equation 133)[303].

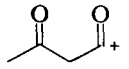


(**485**) (**486**) (**488**) ~ 30%

(**489**) (**490**)

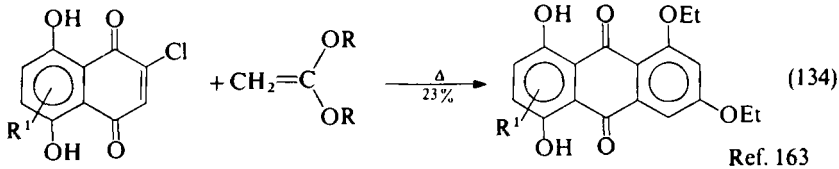
(133)

(**491**)



(487)

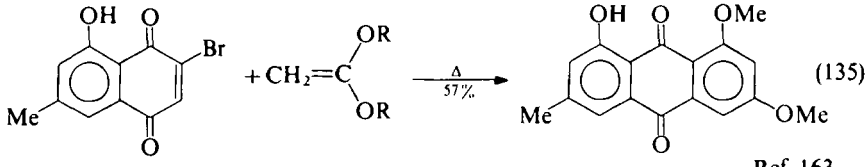
Nucleophilic attack of two moles of a ketene acetal on a haloquinone has been known to afford regiospecifically the corresponding 1,3-dialkoxyanthraquinone in varying yields[304]. This reaction was extensively examined with halonaphthazarines[163], 3-bromojuglones[163,305] and dihalo-*p*-benzoquinone (equations 134–136)[306]. Under optimized conditions, a moderate yield is obtained when five molar equivalents of the ketene acetal



(493) (492) (494) (134)

R = Et

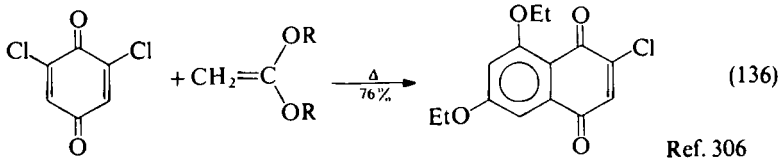
Ref. 163



(495) (492) (496) (135)

R = Me

Ref. 163



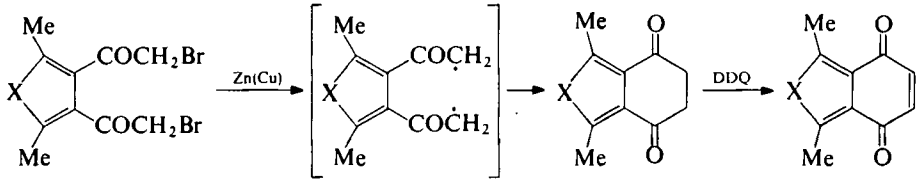
(228) (492) (497) (136)

R = Et

Ref. 306

to haloquinones are used. The requirement for such a large excess of the ketene acetal is due to its decomposition by the acid and alcohol, formed during the reaction, although the detailed reaction mechanism has not been fully revealed. This method is useful for the synthesis of several specific quinones in a one-step procedure. A similar product is obtained in the reaction of a vinyl ketene acetal with a haloquinone (Section II.A).

Heterocycles, such as furan, thiophene and indole, substituted by 3,4-bis(bromoacetyl) groups (**498**) afford the corresponding cyclized product (**500**) by their treatment with a Zn–Cu alloy[307]. The biradical **499** is postulated as an intermediate in the cyclization reaction. The quinone **501** is obtained by further oxidation (equation 137).

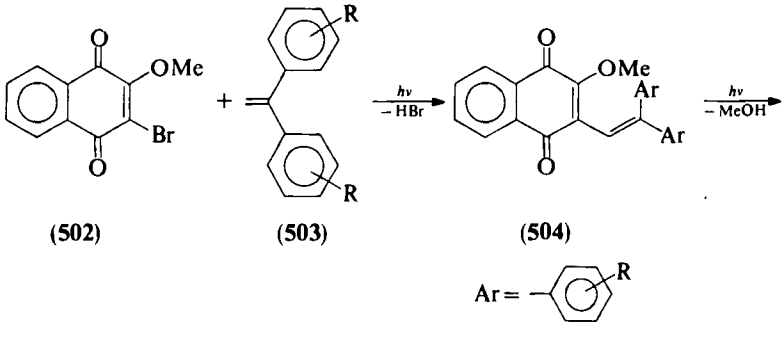


(**498**) (**499**) (**500**) (**501**)

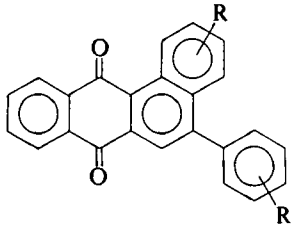
X = O, S, NMe

(137)

A photochemical reaction of the halogenated naphthoquinone **502** with 1,1-diarylethylenes (**503**) gives the benzanthraquinones (**505**) in one step presumably via the intermediacy of **504** as shown in equation 138. This reaction is extensively explored for the



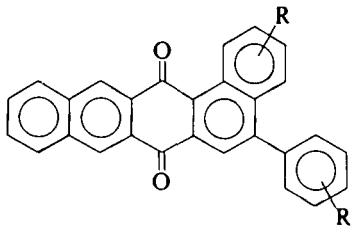
(**502**) (**503**) (**504**)



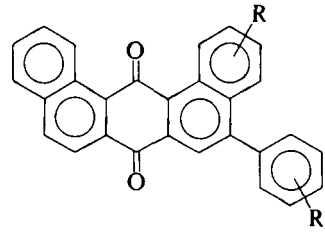
(**505**)

(138)

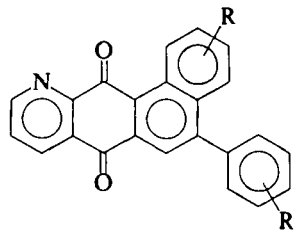
combination between various halogenated quinones and diarylethylenes[308–316]. The best results are obtained in the reaction of 2-bromo-3-methoxy-1,4-quinone derivatives and diarylethylenes (**503**) substituted by electron-donating group R, since the reaction is initiated by a photo-excited single electron transfer from the olefin to the quinone. The applicability of the reaction is shown by the synthesis of the polycyclic quinones **506–508**[316]. When the two R substituents on the aryl group are different, the cyclization occurs preferentially at the electron-rich aryl group.



(506)

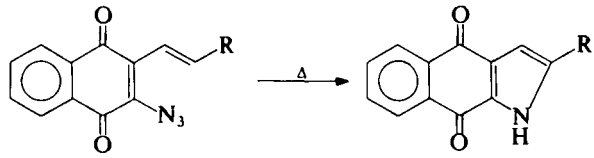


(507)



(508)

Azidoquinones show a versatile reactivity toward olefins and are considered to be good precursors for indoloquinones. Intramolecular cyclization of the 2-azido-3-alkenyl-1,4-naphthoquinone (**509**) upon heating gives the corresponding indoloquinone (**510**) in good yield (equation 139)[317]. A concerted mechanism rather than an intermediary formation of a nitrene was suggested in the reaction.

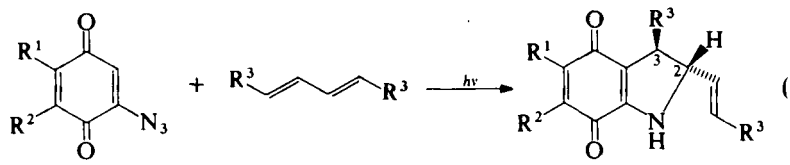


(509) (510) Ref. 317

R = Alkyl, Ph

(139)

On the other hand, the 2-azidoquinones (**511**) afford cyclized products (**513**) with conjugated dienes upon irradiation with near UV light (equation 140)[318-320]. The reaction proceeds in a completely stereoselective manner. The relative stereochemistry at

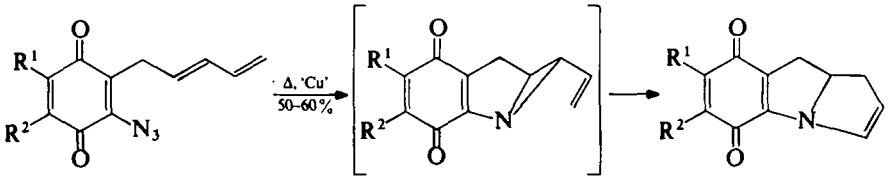


(511) (512) (513) Ref. 319

(140)

the 2 and 3 positions is *trans* and it is established that a vinylic group at the 2 position preserves completely its original stereochemistry[319,320].

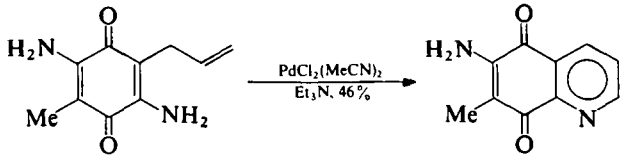
The 2-azido-3-pentadienylquinone (**514**) intramolecularly cyclizes upon heating with a copper catalyst directly to afford a tricyclic product (**516**) in reasonable yield[321,322]. This product is neither obtained under photochemical conditions nor without a copper catalyst. Mechanistically, it was proposed that an initial formation of unstable 1,2-addition product (**515**) is followed by a 1,3-rearrangement (equation 141).



(**514**) (**515**) (**516**)

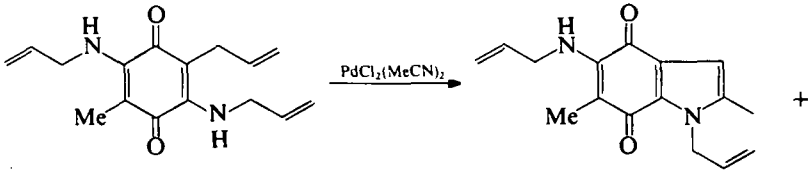
Refs 321, 322 (141)

Palladium-salt catalyzed cyclization of 2-allyl-3,6-diamino-5-methyl-1,4-benzoquinone (**517**) affords the quinolinoquinone **518** in a modest yield (equation 142), while 2-allyl-3,6-bis(allylamino)-5-methyl-1,4-benzoquinone (**519**) gives a mixture of the three indoloquinones **520–522** without selectivity (equation 143)[323].

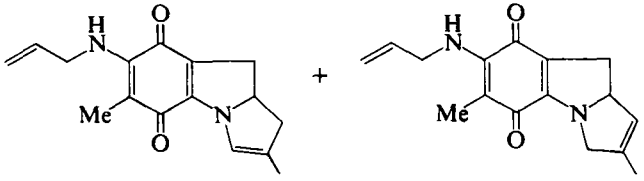


(142)

(**517**) (**518**)



(**519**) (**520**)
20%

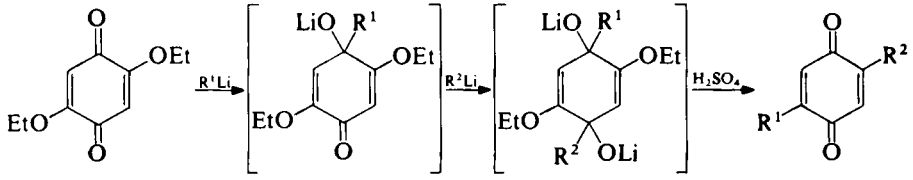


(143)

(**521**) (**522**)
15% 25%

V. MISCELLANEOUS METHODS

Nucleophilic addition of organometallic reagents to quinones have been extensively studied[324, 325]. At a lower temperature, these reactive carbon nucleophiles react with quinone to afford the 1,2-addition product under conditions where simple reduction of the quinone to the hydroquinone does not take place. When the alkylation with alkyllithium is applied to 2,5-dialkoxy-1,4-benzoquinone (**523**), the product is 2,5-dialkyl-1,4-benzoquinone (**149**), whose carbonyl groups are formally rearranged as shown in equation 144[326]. Addition of the first equivalent of a lithium reagent R^1Li affords an adduct (**524**), to



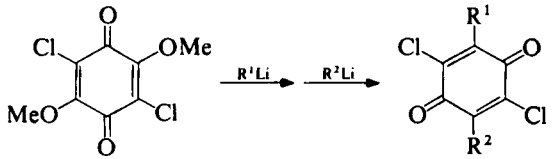
(523) (524) (525) (149)

52–62%

(144)

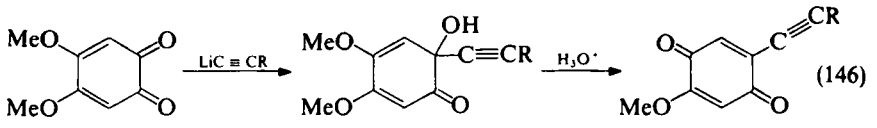
which the second lithium reagent R^2Li adds to give **525**. Hydrolysis and successive dehydration of **525** affords **149** in moderate yields. When R^1Li is a 'soft' nucleophile such as alkynyllithium, a selective monoalkylation is possible by control of the amount of the reagent, and successive treatment with the second R^2Li affords the quinone with two different carbon functionalities at the 2,5-positions. A limitation is that when R^1Li is an alkyl- or alkenyllithium they are too reactive to stop the reaction at the monoalkyl (or monoalkenyl) stage.

Similarly, 2,5-dichloro-3,6-dimethoxybenzoquinone (**526**) gives **527** by a similar reaction without loss of halogen atoms[326]. This methodology is also applicable to 4,5-dimethoxy-1,2-benzoquinone (**530**)[327], which gives 2-alkynyl-5-methoxy-1,4-benzoquinone (**530**) in good yield (equations 145 and 146).



(526) (527) (145)

Ref. 326



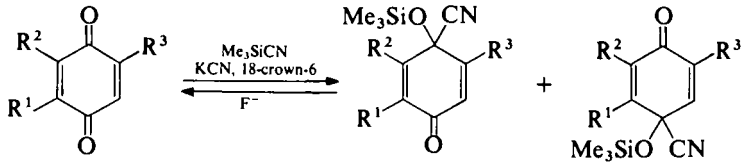
(528) (529) (530) (146)

Ref. 327

VI. PROTECTION OF QUINONES AND HYDROQUINONES

Since a quinone (or a hydroquinone) is a reactive species, it is frequently required to protect the carbonyl or the hydroxy groups against a reactive reagent or destructive reaction conditions. The criteria for the protecting method are (1) easy operation in the protection and the deprotection, (2) an excellent yield for both reactions, (3) high chemoselectivity, and (4) a wide applicability. Several protecting methods (or reagents) have been specifically developed for quinones.

Trimethylsilyl cyanide can give monocyanosilylation of quinones in the presence of a catalytic amount of a KCN–18-crown-6 complex (equation 147)[328, 329]. The site of the



(106) (531) (532) (147)

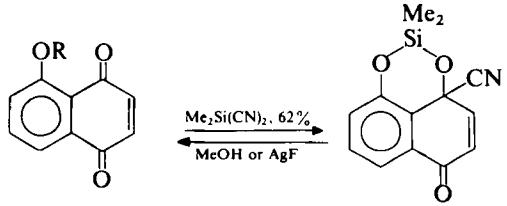
cyanosilylation is dominated by the relative electrophilicity of the carbonyl groups. For electron-donating substituents it occurs mainly at the highly substituted site, except in the presence of severe steric hindrance by a *t*-butyl group (Table 18). Since this protecting

TABLE 18. Regioselective trimethylsilyl cyanation of quinones[328]

R^1	R^2	R^3	Product ratio (531):(532)	% Yield[a]
H	H	H		80
H	H	Me	89: 11	92
H	H	MeO	100: 0	80
Me	H	MeO	100: 0	90
MeO	H	MeO	100: 0	65(100)
Me	H	Me	94: 6	(100)
H	*t*-Bu	*t*-Bu	0:100	(98)
–CH=CH–CH=CH–		H		75
–CH=CH–CH=CH–		Me	91: 9	96
–CH=CH–CH=CH–		MeO	100: 0	92
H	Br	Br	100: 0[b]	100[c]

[a] Yields in parentheses were determined by NMR; all others are yields of the purified adducts.
[b] The reaction was conducted in the presence of Ph_3P at 0°C in MeCN.
[c] Ref. 329a.

group is inherently unstable to both aqueous media and nucleophiles which easily react with the carbonyl group[329a], its use is rather limited. Deprotection of the cyanosilyl ether with AgF can regenerate the quinone in good yield. This reaction is applied before alkylation of a quinone with an organolithium[325] or a Grignard reagent[329b]. The related reaction with $Me_2Si(CN)_2$ is also effective for the regiospecific protection of juglone (**56**, R = H) (equation 148)[330].



(148)

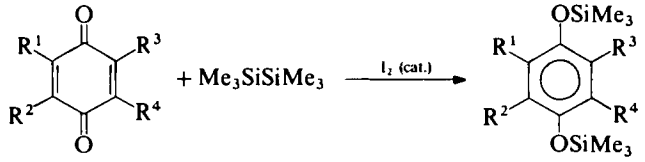
(56)
R = H

(533)

Quinone dialkyl acetals are extensively used as synthetic equivalents or as protected quinones. The details are given at Section II.D and Chapter 15. Since the quinone diacetals are obtained by electrolytic oxidation of the corresponding hydroquinone dialkyl ether, this method is not applicable to substrates carrying oxidizable functional group(s).

Protection of hydroquinones is much easier than that of the corresponding quinone, and in most cases, protecting groups which are applicable to phenols, are also suitable for this purpose[331, 332]. Typical groups are Me, $PhCH_2$, $MeOCH_2$ and trialkylsilyl groups, and the order of deprotectivity is $R_3Si > MeOCH_2 \simeq PhCH_2 > Me$. A trialkylsilyl group can be easily deblocked by aqueous protic acid when R = Me or by fluoride anion when $R_3 = t\text{-}BuMe_2$. Methoxymethyl and benzyl ethers are easily removed by a protic acid (typically *p*-TsOH) and by catalytic hydrogenation, respectively. Since hydroquinone dimethyl ether is very stable and can tolerate a wide range of reaction conditions, the only reliable method of its deprotection is oxidative demethylation by AgO or CAN (see Section II.D) and many applications are shown in Section VII. Both oxidizing reagents as well as the electrolytic acetal formation are reported to cause undesirable side reactions, when the substrate carries reactive functionalities.

Reductive silylation of quinones is also useful for the protection of hydroquinones (equation 149). Hexamethyldisilane is used as a silylating agent in the presence of a

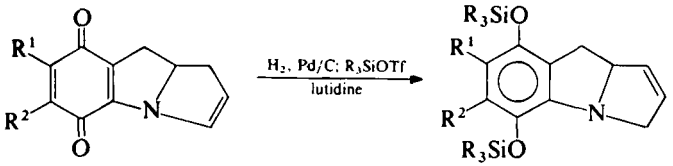


(149)

(534)

(535)

catalytic amount of iodine[333]. These conditions are applicable to a wide range of quinones and they provide hydroquinone disilyl ethers in better yields compared with the related reactions with chlorotrimethylsilane–alkali metal systems[334–337]. It is assumed that iodotrimethylsilane is formed in the course of this reaction. For the preparation of hydroquinone disilyl ethers from hydroquinones, conventional methods, such as the use of R_3SiCl-base or R_3SiOTf-base, are useful[331]. For example, after a hydrogenative reduction of a quinone in lutidine, the hydroquinone obtained is converted *in situ* to the corresponding silyl ether by addition of R_3SiOTf[338]. Even when a quinone is substituted by a double bond in the molecule, a reductive silylation can be conducted without hydrogenation of the double bond, presumably due to the much higher reduction rate of the quinone compared with that of the double bond in lutidine. This method was applied to the reductive silylation of **516** (equation 150), for which the reductive protection method is difficult due to its easy oxidizability.



(516) (536) (150)

In all these cases, the hydroquinone disilyl ether can be easily transferred either to the original hydroquinone by treatment with a protic acid or a fluoride anion, or to the corresponding quinone by an oxidative desilylation.

VII. SYNTHESIS OF NATURALLY OCCURRING QUINONES

A large number of quinones are found in pigments, bacterial metabolites, coenzymes and vitamins. A comprehensive coverage of the whole class of naturally occurring quinones is found in references 339 and 340, which treat their origin, distribution, structural determination and biological activities. Discussions in this review are concentrated on the synthesis of the title compounds which possess interesting biological activities. This field is considered especially as a *concours d'élégance* of recently developed new reactions and methodologies, where many 'state-of-art' syntheses were realized. Many applications of fundamental reactions which are discussed in Sections II–IV have also appeared.

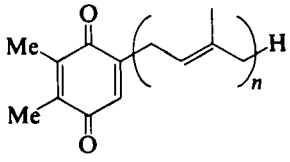
Anthracyclines are interesting due to their broad range of antitumor activities, and many of them are used in the practice of cancer chemotherapy. A large number of synthetic works on anthracyclinones, the aglycones of anthracyclines, have appeared in recent years. Since most of reported methodologies applied to anthracyclinone synthesis are summarized in several reviews[341a-k], this topic is not included in this section in order to avoid overlap with these reviews.

A. Polyprenylated Quinones

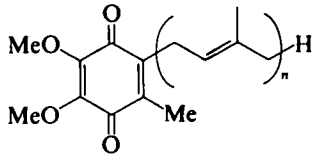
Quinones belonging to the title compounds are mainly found in electron transport systems of animals, plants and microorganisms. The typical prenylated quinones are shown in Chart 3.

The most characteristic feature of these quinones, except for tocopherols, is that they have a polyprenyl side chain with an all-*trans* configuration. These isomers of phylloquinone (**540**) and menaquinone (**539**) show higher physiological activities than their *cis* isomers. The synthetic interest is mainly in two problems: first, the introduction of a polyprenyl group to a quinone (or a hydroquinone) with high *trans* stereoselectivity at the Δ^2 position of the side chain; second, in prevention of chroman ring formation, side chain cyclization and other unfavorable reactions. Classically, Friedel–Crafts type reaction by an acid-catalyzed alkylation of the corresponding polyprenyl alcohol (or halide) with a hydroquinone or its protected form has been performed (equation 151). A large number of variations has appeared, mostly in patents, and they can be found in the leading references[342-348]. Discussions in this review are concentrated on new methodologies[349]. Since the synthesis of tocopherols by means of Lewis acid-catalyzed prenylation of trimethylhydroquinone and concurrent formation of chroman ring has been well established, the asymmetric synthesis of **541** is discussed here.

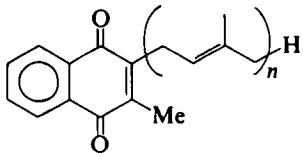
The many efforts in this field are classified into the following four categories: (1) coupling reactions between quinones (or their protected analogues) and several



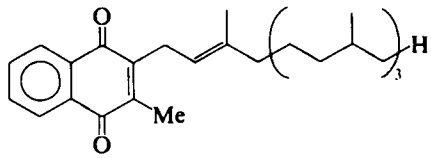
(537) plastoquinone-*n*



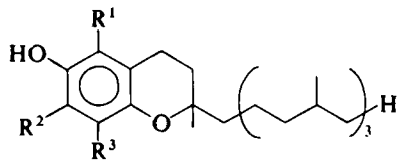
(538) ubiquinone-*n* (coenzyme Q_n)



(539) menaquinone-*n* (vitamin $K_{2(5n)}$)



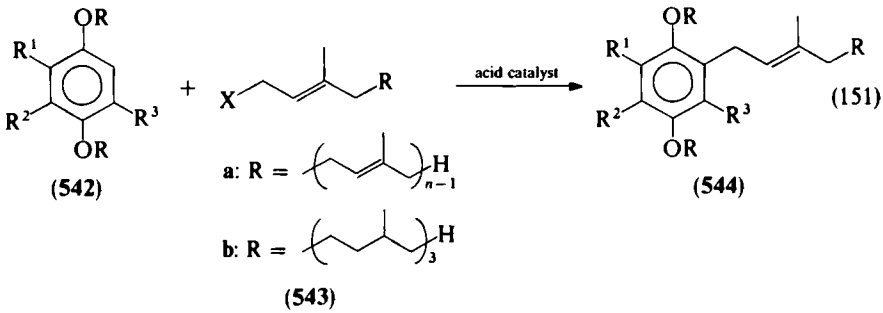
(540) phylloquinone (vitamin K_1)



(541) tocopherol (vitamin E)

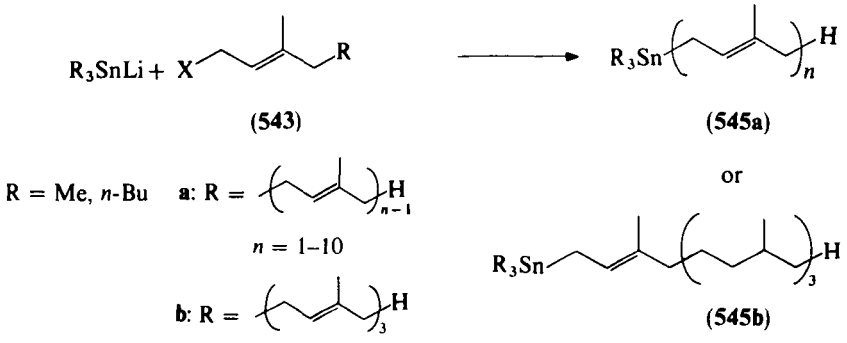
α: $R^1 = R^2 = R^3 = Me$
β: $R^1 = R^3 = Me$, $R^2 = H$
γ: $R^1 = R^3 = H$, $R^2 = Me$
δ: $R^1 = R^2 = H$, $R^3 = Me$

CHART 3



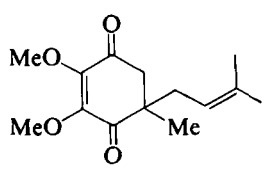
organometallic reagents; (2) coupling reactions between prenyl halide and an arylmetal, which is the synthetic equivalent of the quinone; (3) other methods including extension of polyprenyl side chain, rearrangement of the prenyl group to quinone nucleus, etc.; and (4) construction of the quinone nucleus itself from a non-aromatic precursor with a prenyl side chain.

We will first discuss the coupling reaction of quinones of the corresponding hydroquinone diethyl ethers with allylic organometallics. A direct introduction of prenyl group to quinone seems to be the best method for maximizing the synthetic efficiency. The most successful method is a Lewis acid-catalyzed prenylation of a quinone with polyprenyltrialkylstannanes (**545a, b**)[350 - 354]. These substrates can be prepared by the coupling reaction of polyprenyl halide with R_3SnLi without loss of the stereoisomeric purity. Consequently, the reaction affords prenylated quinones in good to excellent yields with preservation of the original *trans* stereochemistry at Δ^2 (equation 152). The



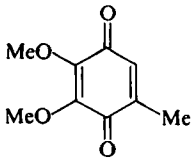
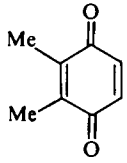
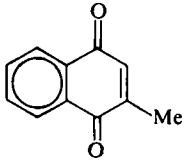
(152)

undesirable side reactions mentioned above are not observed in ubiquinone-*n* synthesis by this method. This method is also applicable to the synthesis of a wide range of other polyprenylated quinones **537–540** (Table 19)[350–354]. π-Allylnickel complex (**547**, R = H) is another reagent used for this conversion. However, a direct reaction of this complex with quinone (**80**) gives preferentially the undesirable *ipso*-substituted product (**548**)[355–358]. In



(548)

TABLE 19. Synthesis of polyprenylated quinones by the Lewis acid catalyzed allylation of quinones with polyprenylated stannanes[350, 351, 353]

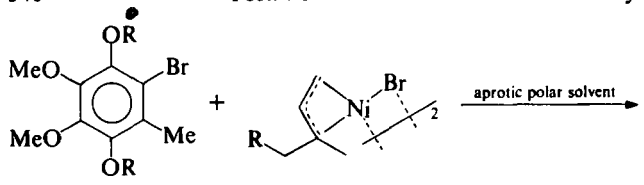
Quinone	Polyprenylstannane (**545a**) R = Me, n	Product[a]	% yield	Stereochemistry at $\Delta^{2'}$, *trans/cis*
	1	(**538**)	(75)	—
	2		90(65)	> 99/1
	2 ($\Delta^{2'}$ = *cis*)		79(70)	12/88[b]
	3		100(93)	99/1
	4		88(70)	99/1
	5		100(94)	99/1
	6		60(59)	98/2
	7		(40)	99/1
	8		(25)	98/2
	9		(51)	100/0
	10		(51)	86/14[c]
	2	(**537**)	(23)	95/5
	2	(**539**)	(48)	96/4
	2 (**545b**)	(**540**)	46(30)	95/5

[a] Yield in parentheses is of isolated material. All other yields were determined by ^{1}H-NMR.
[b] A 94:6 *cis/trans* mixture of nerylstannanes was used.
[c] The isomeric purity of the applied decaprenyl bromide is *trans/cis* = 82/18.

contrast, the coupling reaction of **547** with protected bromohydroquinone **546** gives the corresponding prenylated product **549** (equation 153), but the control of the stereochemistry at Δ^2 is difficult due to the inherent character of the complex **547**[359, 360].

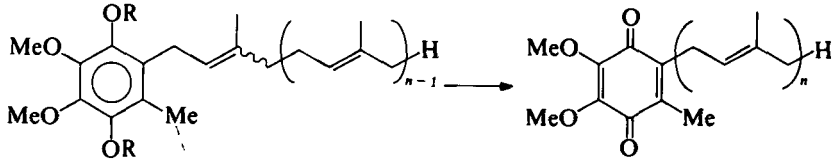
The coupling reaction of an arylmetal derivative and polyprenyl halide was used successfully in several syntheses (equations 154 and 155). Both the hydroquinone monopotassium salt (**559**) and the arylmetal derivative (**552**) undergo a coupling reaction with polyprenyl halide (**543**, X = halogen) or polyprenyl phosphates to afford the desirable product with complete retention of the stereochemistry[361].

The arylstannyl derivative (**555**) causes coupling reaction with phytyl halide (**543b**, X = Br) in the presence of $ZnCl_2$ as a Lewis acid catalyst (equation 156)[362], but the

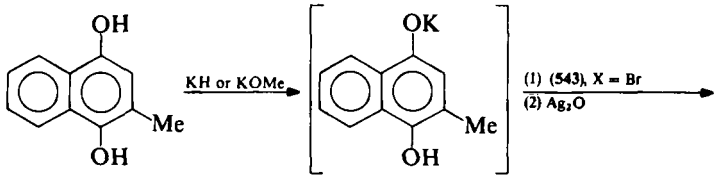


(546) (547) (153)

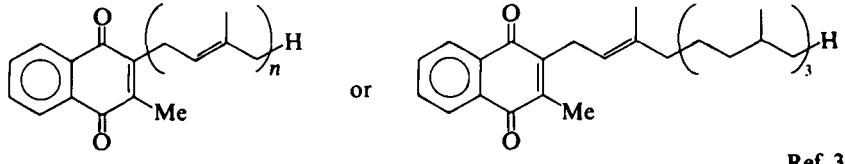
R = Ac, CH_2OMe



(549) (538)



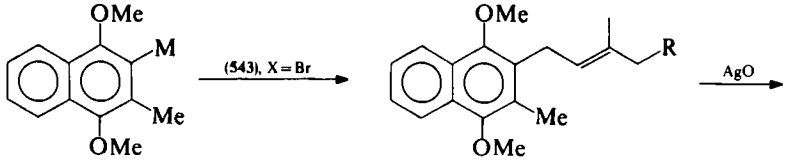
(550) (551) (154)



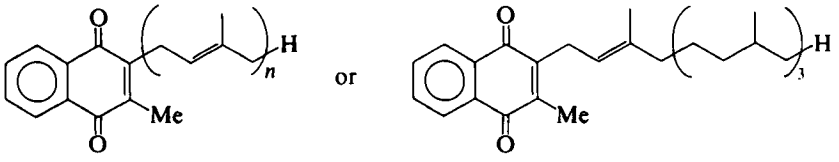
(539) (540) Ref. 361

stereoselectivity of the reaction is unclear. A quinone bisacetal, e.g. **566**, is considered to be a synthetic equivalent of a quinone with inverted charge affinity, and is easily converted to the corresponding cuprate (**557**) by successive treatment with BuLi/CuI. Nucleophilic substitution of **543b** (X = Br) by **557** gives phylloquinone (**540**) in good yield after deprotection of the bisacetal group (equation 157)[126]. This methodology was also applied to the synthesis of cymopol (**558**), a marine antibiotic with hydroquinone nucleus[363, 364].

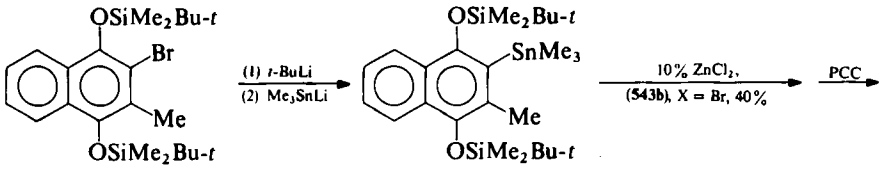
A coupling reaction of a quinone or a hydroquinone with polyprenyl halides is conducted in the presence of Zn-amalgam[365] or metallic Zn[366]. The Zn-amalgam method gives ubiquinones and related polyprenylquinones in good *trans* stereoselectivity (E/Z = 8/1–11/1). Mechanistically, these reactions proceed by the formation of an



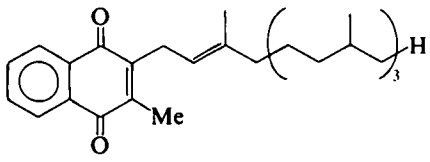
(552) M = Li, $\frac{1}{2}$ CuLi, MgBr (553) (155)



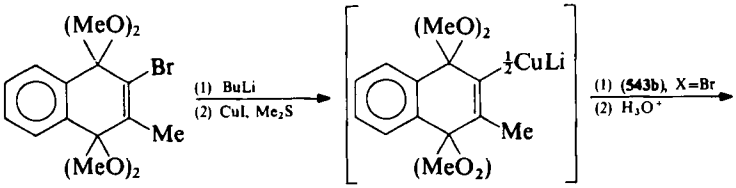
(539) (540) Ref. 361



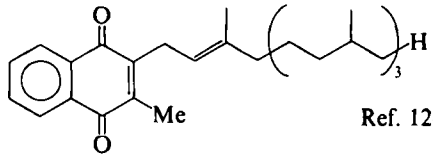
(554) (555)



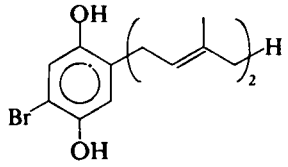
(540) Ref. 362 (156)



(556) (557)



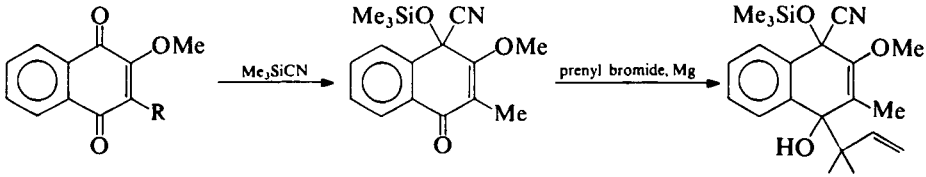
(540) Ref. 124 (157)



(558)

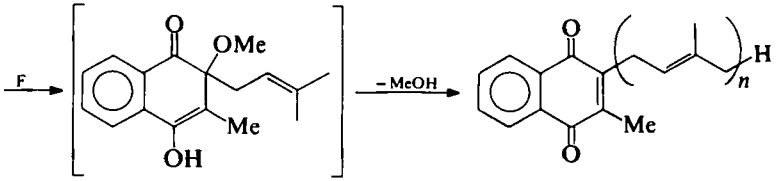
intermediate Zn-phenoxide derived from reduction of the quinone, followed by nucleophilic attack on the prenyl halide.

Several miscellaneous reactions belonging to the third category are shown below. A prenyl group can be selectively introduced to a trimethylsilyl cyanide protected quinone (**560**) by means of a Grignard reagent generated *in situ*. In the course of deprotection, the prenyl group rearranges in [3, 3] fashion to afford menaquinone-1 (**539**, $n = 1$) with concomitant elimination of MeOH (equation 158)[329b]. Since this reaction was only conducted with the simple prenyl group, the possibility of a stereoselective introduction of a polyprenyl group is unclear.



(559) (560) (561)

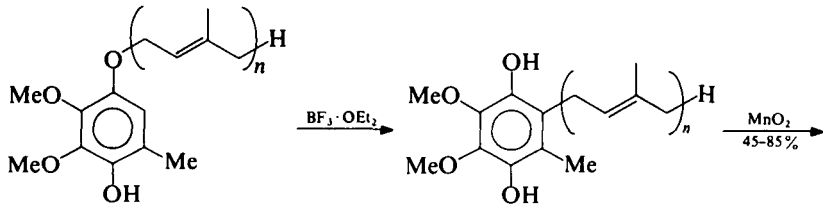
R = Me



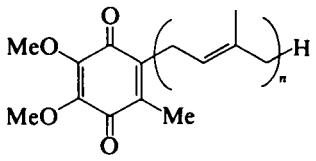
(562) (539) $n = 1$ (158)

A Lewis acid mediated Claisen-type [1, 3]-sigmatropic rearrangement of an aryl polyprenyl ether (**563**) is applied in the ubiquinone-*n* synthesis (equation 159)[367]. The rearrangement proceeds with complete retention of the stereochemistry for the *trans* isomer of **563**, but with the *cis* isomer, a slight contamination with the *trans* form is observed in this stage. This procedure was also applied for the synthesis of plastoquinone-*n*, and a similar high stereoselectivity was attained.

Many catalytic condensation reactions and their modification between hydroquinone and polyprenyl halide have been reported. Inclusion of 2-methylnaphthohydroquinone in a β-cyclodextrin cavity is applied for the selective coupling with prenyl bromide[368,369]. The reaction probably proceeds via nucleophilic attack of the monoanion of the

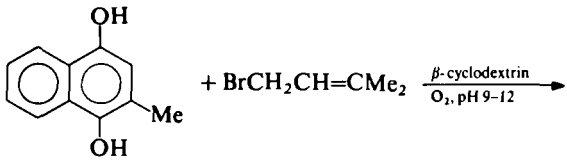


(563) (564)

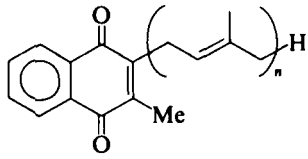


(538) (159)

hydroquinone on the bromide followed by aerial oxidation to prenylated quinone. β-Cyclodextrin plays a key role in controlling the regiochemistry of the nucleophilic attack and in prevention of successive side reactions of the prenylated product (equation 160).



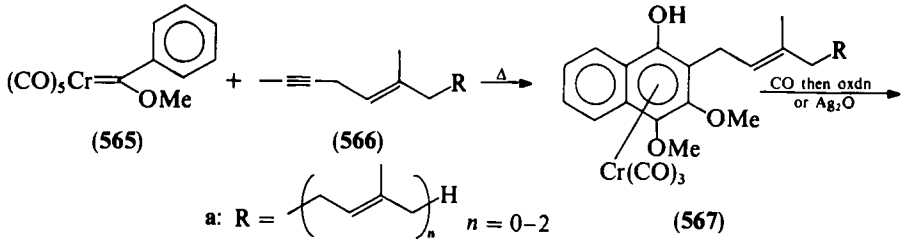
(550)

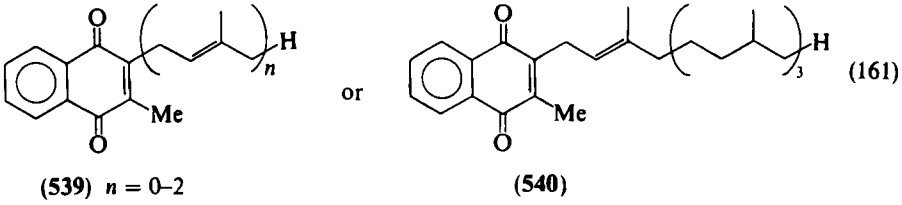


(539) $n = 1$ (160)

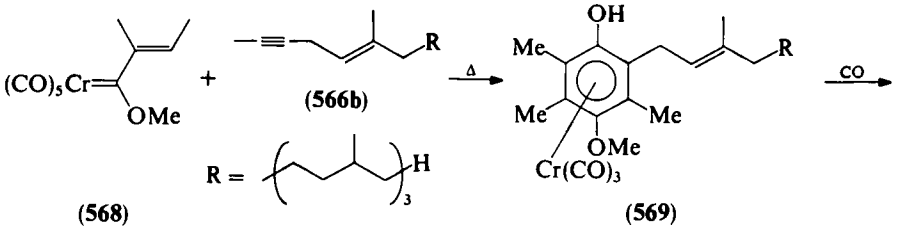
Quaternary ammonium and phosphonium salts are used as phase transfer catalysts in the synthesis of phylloquinone and menaquinones[370]. The phase transfer system as well as the cyclodextrin one plays a protection role of the lipophilic product from undesirable side reactions.

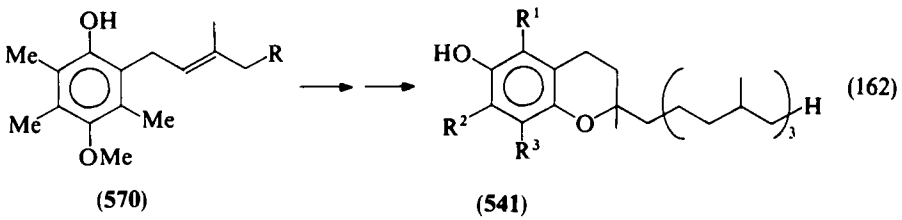
A chromium carbene complex is known to be an excellent reagent for construction of the prenylated quinone ring itself from these compounds (equation 161) (see Section II.C). The method is utilized for the synthesis of phylloquinone, menaquinones and tocopherol from alkynes substituted with the corresponding polyprenyl group[354,371,372]. Under these





(161)

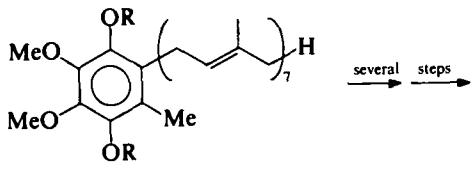




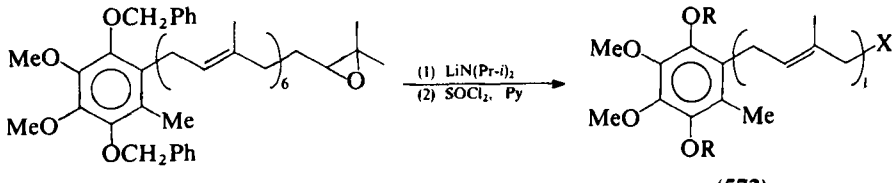
(162)

conditions, the olefinic double bond is immune to isomerization and its *trans* stereochemistry at Δ^2 is completely preserved in the produced quinone.

Since some bacteria, e.g. *Candida utilis*, produce ubiquinone, e.g. **538** ($n = 7$), with a rather short polyprenyl chain, elongation of this unit is examined for the preparation of its higher homolog, which is more useful for therapeutic treatment (equations 163 and 164)[373-376].

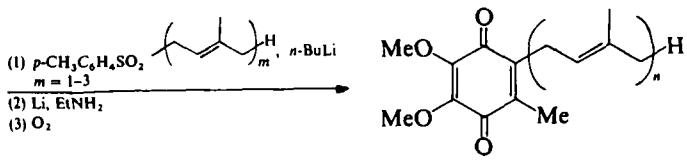


R = CH_2Ph



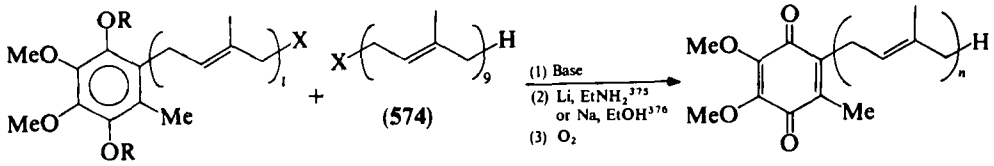
(571) (572)

l = 7, R = $PhCH_2$, X = Cl



(163)

(573) (538) $n = l + m$ = 8–10 Ref. 374



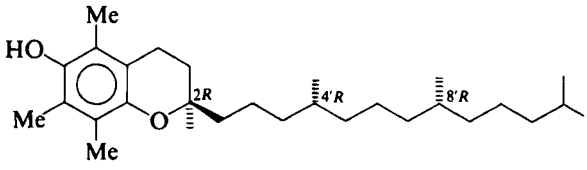
(572) (538) n = 10

$\left\{\begin{array}{l} R = PhCH_2, \\ l = 1,\ X = PhSO_2{}^{375} \end{array}\right.$ X = Br

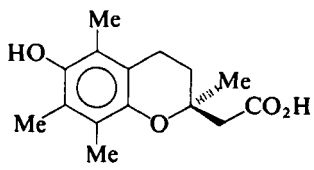
$\left\{\begin{array}{l} R = MeOCH_2 \\ l = 1,\ X = Br^{376} \end{array}\right.$ $X = PhSO_2$ (164)

Synthesis of tocopherol itself is rather easy, since after the introduction of a phytyl group to trimethylhydroquinone in the presence of a strong (Lewis) acid it spontaneously cyclizes to the chromane ring. *d*-α-Tocopherol, with a 2*R*, 4′*R*, 8′*R* stereochemistry, has the highest

physiological activity in the group. Consequently, many attempts for the enantioselective synthesis of *d*-α-tocopherol (**575**) have been made. The central problem in the synthesis is the control of the *R*-stereochemistry at the 2 position of **575**, since the absolute

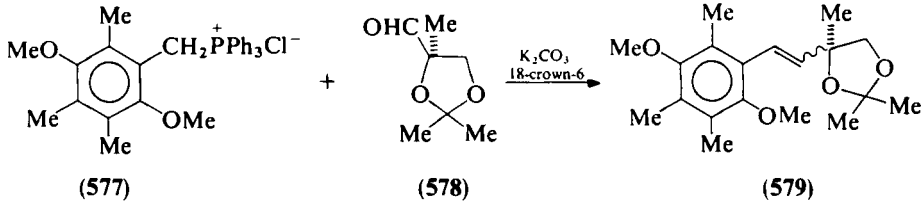


(**575**)

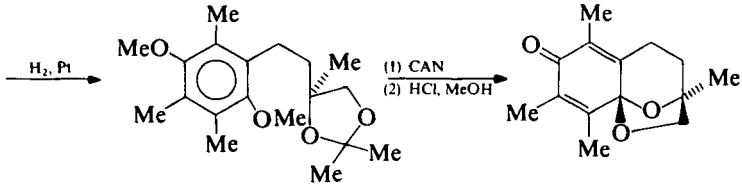


(**576**)

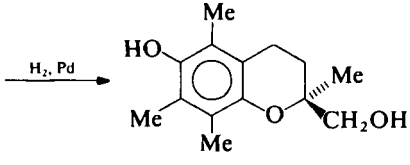
configuration at this position should affect biological activity. Most of the reported methods use (*S*)-2-chromanacetic acid (**576**) as a chiral chroman precursor which is obtained by optical resolution[377]. Two other methods toward synthesis of the chiral alcohol (**582**) related to the chiral acid (**576**) have been reported so far. In the first one, an optically active C_4 synthon (**578**) is coupled with Wittig reagent (**577**) and successive hydrogenation affords **580**. After several steps, (*S*)-chroman ethanol (**582**) is obtained exclusively (Scheme 25)[378]. An almost similar approach uses a different chiral synthon, i.e. (*S*)-(−)-2-methyl-5-oxotetrahydro-2-furoic acid (**583**), which can be derived as a racemic lactone acid from levulinic acid and successively resolved to its enantiomers[379]. The (*S*)-(−)-lactone acid (**583**) can be transferred to **586** in several steps, and annulation of **586** with dimethyl acetonedicarboxylate under basic conditions affords the phenol (**588**), which is



(**577**) (**578**) (**579**)

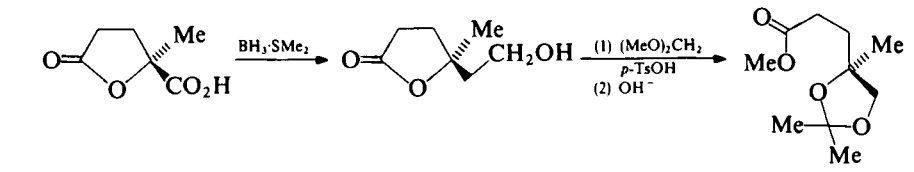


(**580**) (**581**)

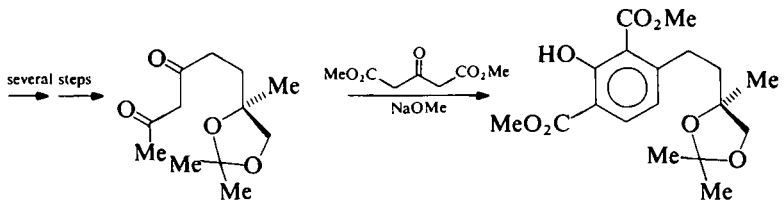


(**582**)

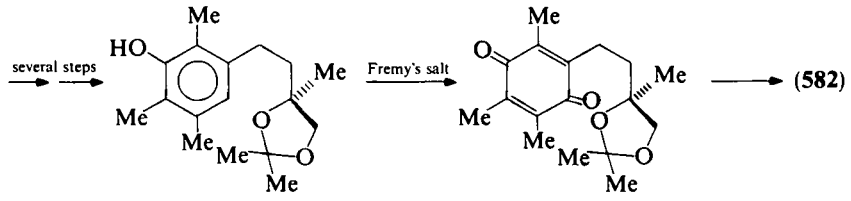
SCHEME 25



(583) (584) (585)

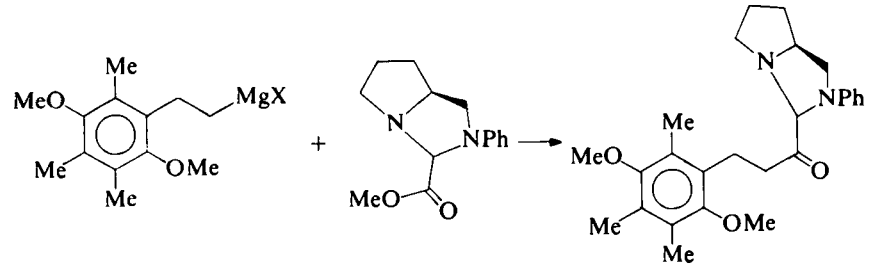


(586) (587)

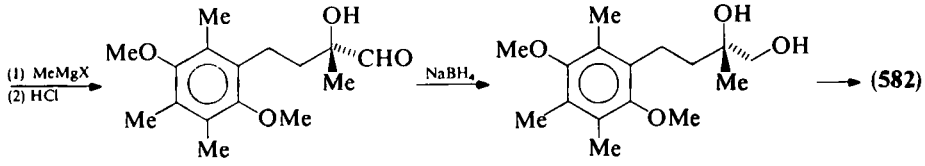


(588) (589)

SCHEME 26



(590) (591) (592)



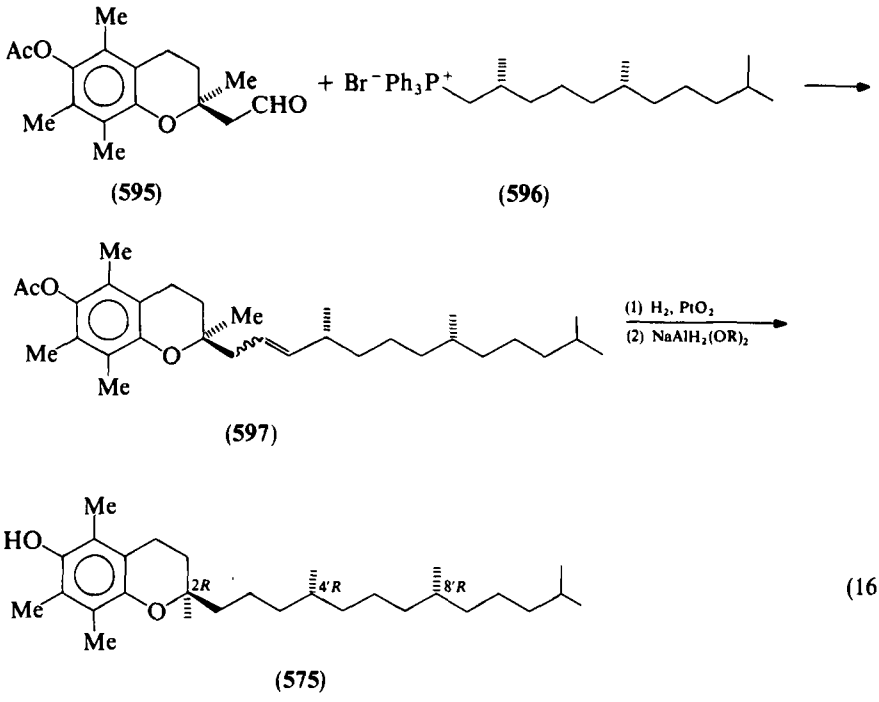
(593) (594)

SCHEME 27

converted to **582** in a similar way (Scheme 26)[379]. This method is completely different from other methods, since it involves construction of the phenol ring from non-aromatic chiral starting material.

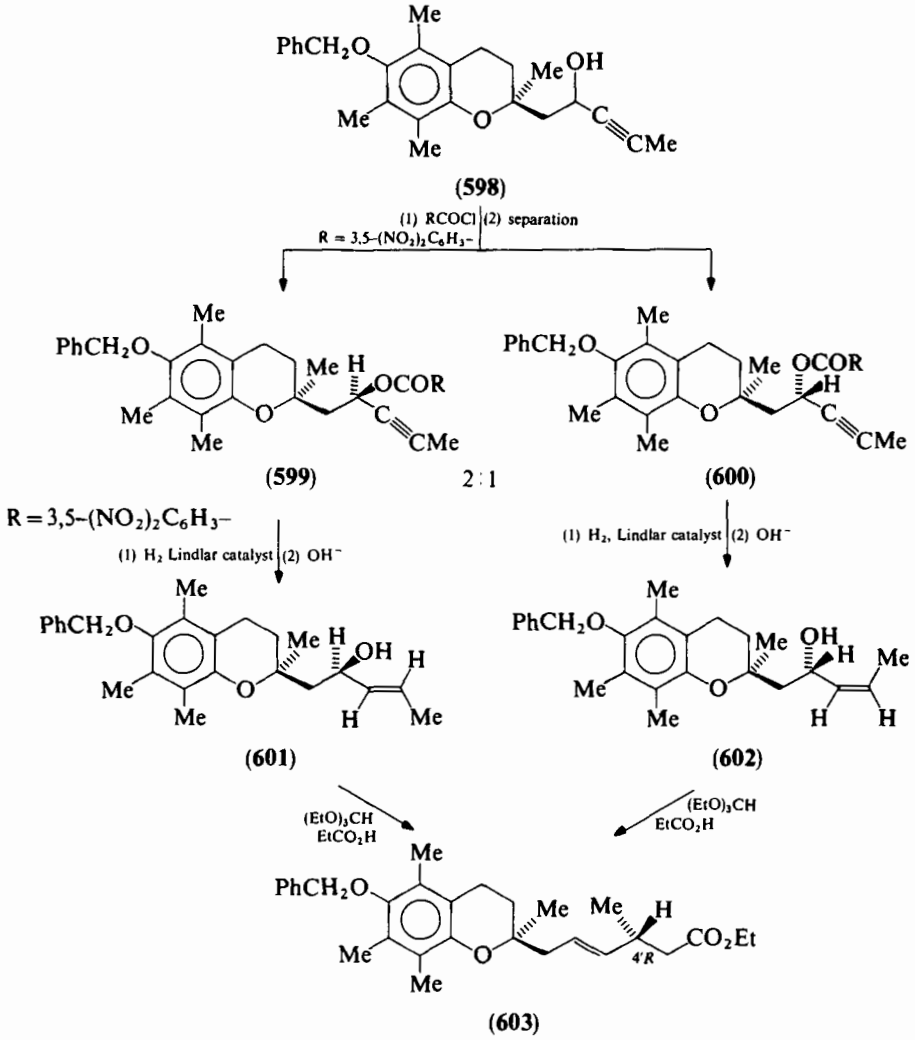
The second method involves an enantioselective methylation of the keto aminal (**592**) as the key step of asymmetric induction leading to the chiral diol (**594**) in > 95% optical purity (Scheme 27)[380]. The obtained chiral diol (**594**) is converted to (**582**) in a similar way.

The second major problem is to extend the side chain of the optically active chromanacetic acid **576**. The most straightforward approach is a coupling between the requisite optically active side chain and **595**, which is derived from either **576** or **582** (equation 165)[377]. The optically active C_{14} unit of **596** is derived from 7*R*,11*R*-phytol by a series of degradative reactions.



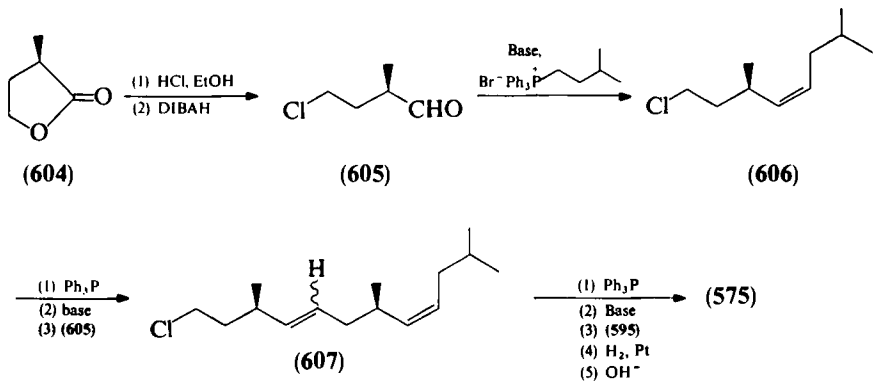
(165)

The sequential synthesis of optically active side chain is examined in several ways. After the diastereoisomers of the propynyl alcohol (**598**), derived from the key intermediate (**576**) in a few steps, are separated as the corresponding 3,5-dinitrobenzoates **599** and **600**, each diastereomer is subjected to partial hydrogenation, followed by orthoester Claisen rearrangement to afford a single diastereomer of the acid ester **603** with 4'*R* configuration. Very interestingly, the chirality transfer from both **601** and **602** proceeds stereospecifically with almost 99% efficiency, allowing the synthesis of optically pure **603** from the mixture of diastereoisomers **601** and **602** (R = H) (Scheme 28). The optically active tocopherol (**575**) can be easily prepared from **603**[381]. The stereochemical course of this Claisen rearrangement is well established in the study of model systems and this method is also utilized for the synthesis of the optically active side chain fragment[382,383].



SCHEME 28

As another chiral source, (−)-(*S*)-3-methyl-γ-butyrolactone (**604**) is used for the synthesis of the optically active side chain. The chiral aldehyde (**605**) derived from **604** is repeatedly used as a chiral fragment, and elongation of the chain by means of Wittig reaction furnishes C_{15} chloride (**607**). Another Wittig reaction with **595** and successive hydrogenation affords (−)-(*S*)-tocopherol acetate (Scheme 29)[384]. Variations of the synthesis of the optically active 2-chromanacetic acid (**576**)[385] and of the coupling of a side chain with **576**[386] were also reported.

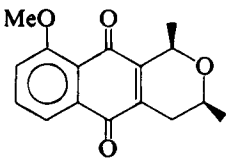


SCHEME 29

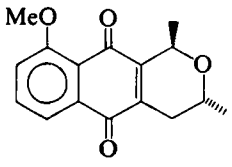
B. Pyranoquinones

Pyranoquinones are found in plants and in microbial metabolites. Since most of them have broad biological activities, many synthetic efforts have been made toward their preparation. The following compounds attracted special attention due to their strong biological activities; eleutherin (**608**)[387], isoeleutherin (**609**)[387], nanaomycin A (**610**)[388–390], nanaomycin D (**611**)[391], deoxyfrenolicin (**612**)[394], frenolicin (**613**)[395], kalafungin (**614**)[392], granaticin (**615**)[393,396], griceusin A (**616**)[397] and griceusin B (**617**)[397] (Chart 4). Many other quinones classified to this family have been found and they are listed in reference 340.

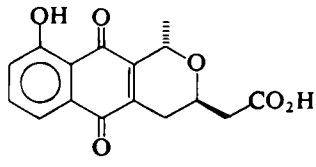
Eleutherin (**608**) and isoeleutherin (**609**) are the compounds with the simplest structure in this family. Since the first synthesis[398], allylation followed by benzopyran ring formation are the key steps in the synthesis. The acylquinone (**618**) is a good precursor for these quinones because the acyl group first activates the vicinal position toward nucleophilic Michael addition, and then it is utilized as an oxygen source for the pyran ring formation[399]. Allylation of the acylquinone **618** with allylstannane (**619**) in the presence of



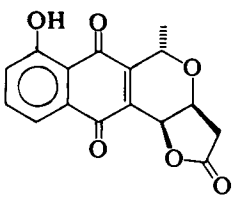
(608)



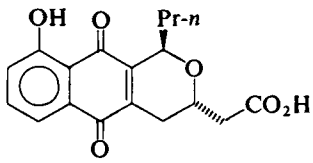
(609)



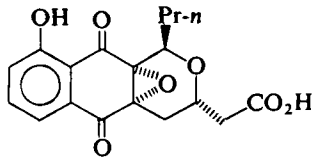
(610)



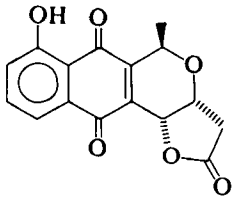
(611)



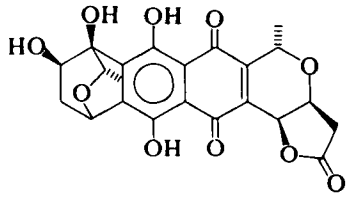
(612)



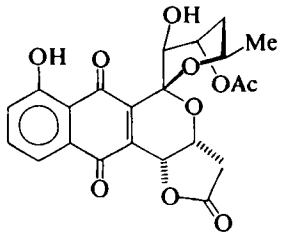
(613)



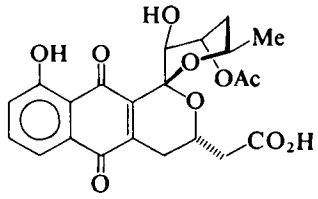
(614)



(615)



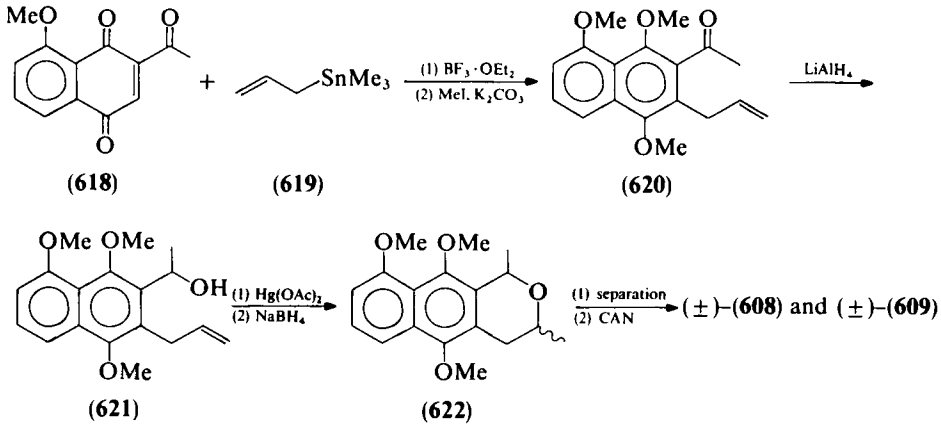
(616)



(617)

CHART 4

a Lewis acid affords allylated product (**620**) in 92% yield after etherification of the obtained hydroquinone. The successive reduction and pyran ring formation give racemic eleutherin (**608**) and isoeleutherin (**609**) (Scheme 30)[399]. According to an almost similar strategy to use **621** as the key compound, racemic **608** and **609** were prepared[110,400-402]. After treatment of **620** with potassium *t*-butoxide in DMF, the *trans* isomer of **622**, which can be oxidized to (±)-isoeleutherin (**609**), is obtained in high stereoselectivity[110].

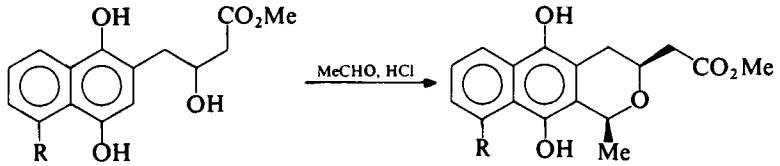


(618) (619) (620) (621) (622)

isomeric ratio = ca. 1:1

SCHEME 30

Nanaomycin A (**610**) and deoxyfrenolicin (**612**) were prepared through versatile synthetic routes due to the interest in their strong and characteristic biological activity against mycoplasms, fungi and Gram-positive bacteria. The demethoxy analogs of (±)-nanaomycin A[403] and (±)kalafungin[404] were synthesized. In the former synthesis[403], the pathway similar to the previously described eleutherin synthesis[398] is utilized for the construction of the pyran ring, i.e. condensation of acetaldehyde with the hydroquinone (**623**, R = H) in the presence of HCl generates only the *cis* isomer (**624**, R = H) (equation 166). In spite of its thermodynamic instability compared with the *trans* isomer[404] this

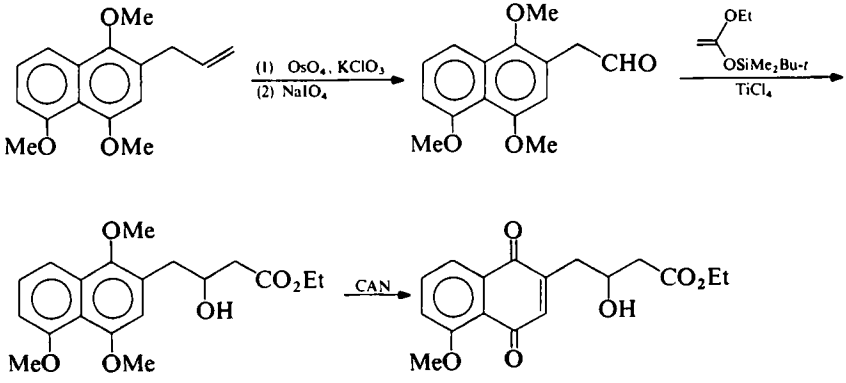


(166)

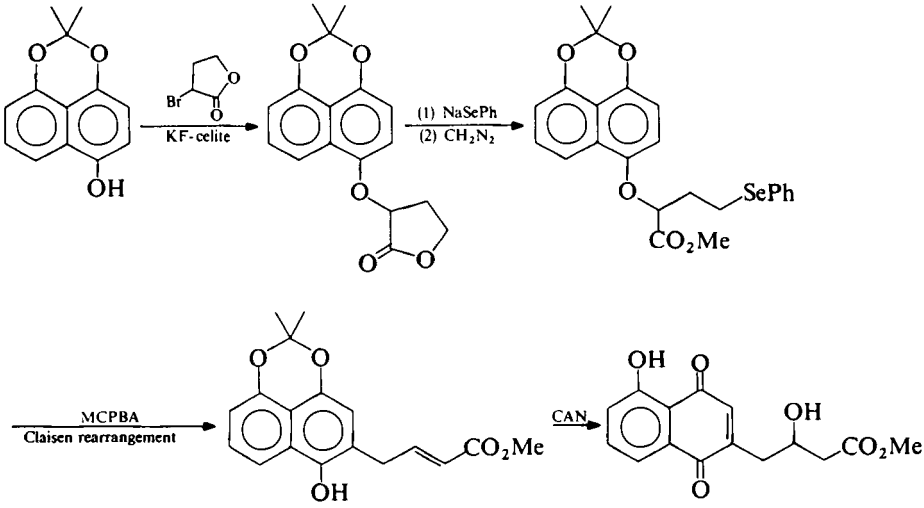
(**623**) (**624**)

method is extended to the synthesis of (±)-nanaomycin A (**610**)[405,406] and (±)-kalafungin (**614**)[405], using **623** (R = OMe,[404] OH[406]) as the key intermediate. Both approaches to **623** or its oxidized form are illustrated in Schemes 31[405] and 32[406].

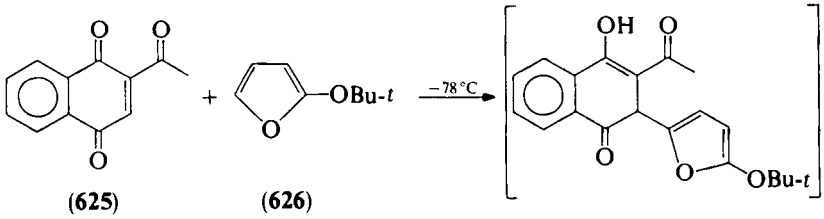
Another interesting approach to 9-deoxykalafungin includes Michael addition of the furan (**626**) (as the butenolide anion equivalent) to the acylquinone (**625**) (Scheme 33)[404]. The reduction of the acyl group in **627** followed by cyclization affords the pyranolactone (**628**) as the stereoisomeric mixture. A stepwise synthetic approach to **610** and **612** uses an intramolecular hemiacetal formation and a successive Wittig reaction as a key step (Scheme 34)[407]. The Wittig reaction generates two diastereoisomers of **630**, but at the final deprotection stage the acid treatment completely converts the isomeric mixture to the *trans* form. Attempted epoxidation of (±)-deoxyfrenolicin methyl ester (**612**) with *t*-BuOOH gives (±)-frenolicin (**613**) and (±)-epifrenolicin (**629**) in 1:1 ratio. This is the only example of the synthesis of (±)-frenolicin[407]. In an alternative approach to formation of the pyran ring, an intramolecular Michael addition of **631** is considered to be an efficient pathway, since the α,β-unsaturated acid ester side chain can play two roles as a Michael acceptor and



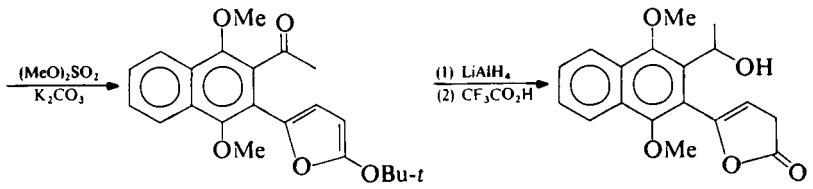
SCHEME 31



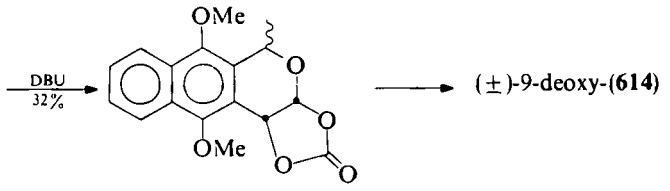
SCHEME 32



(625) (626)



(627)

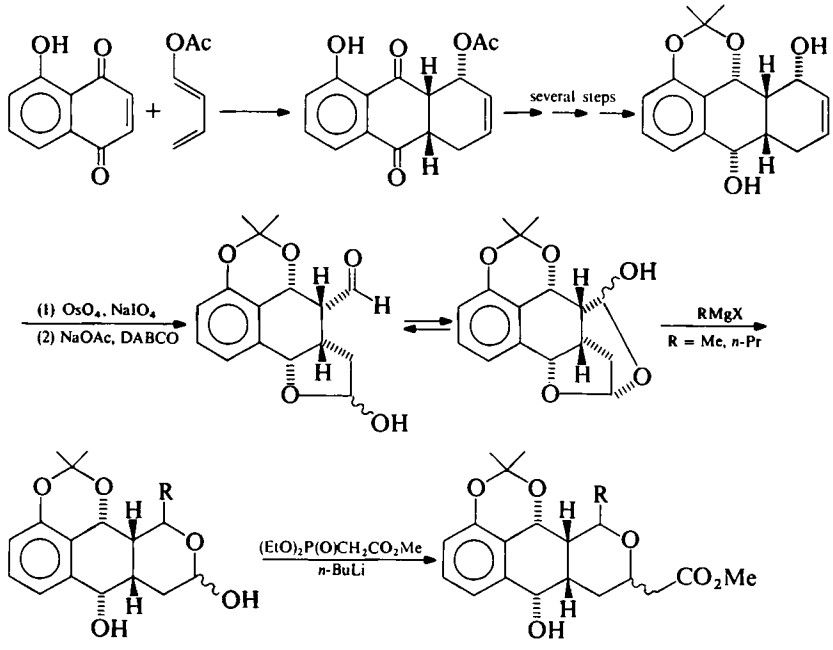


(±)-9-deoxy-(**614**)

(628)

isometric ratio = 2.7:1

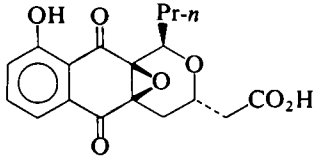
SCHEME 33



(630)

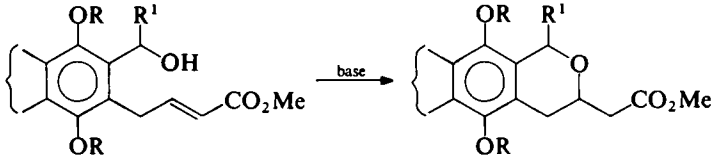
(1) PCC
(2) DDQ; p-TsOH
→ (±)-(610) and (±)-(612)

SCHEME 34



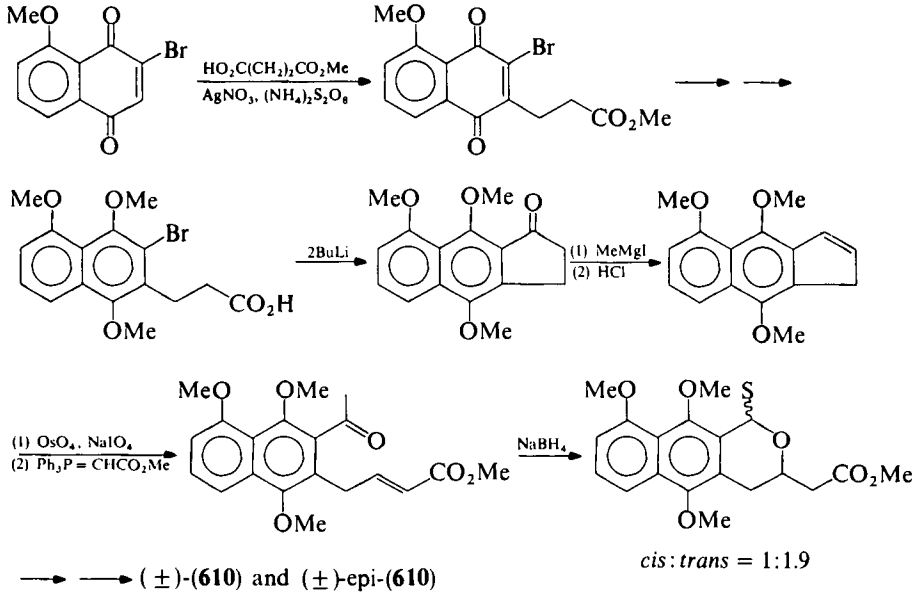
(629)

as an essential functionality for ring-closure to pyranonaphthoquinones (equation 167). The key intermediate (631) is synthesized by a combination of conventional reactions (Scheme 35)[400,401]. A more direct approach was found to give a higher overall yield. As

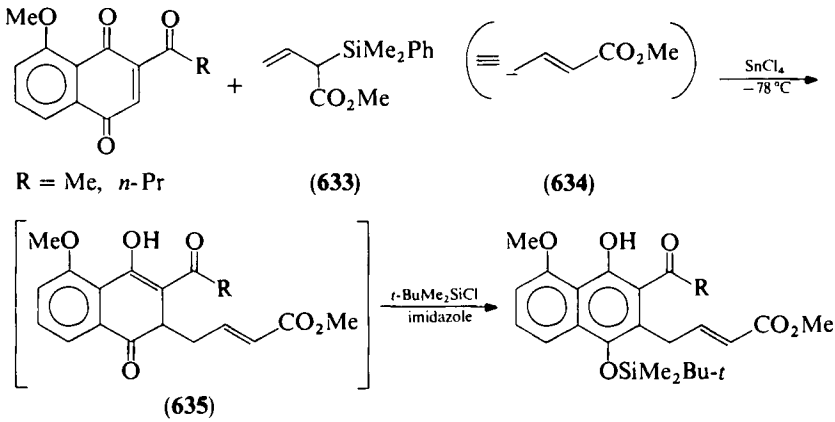


(167)

(631) (632)



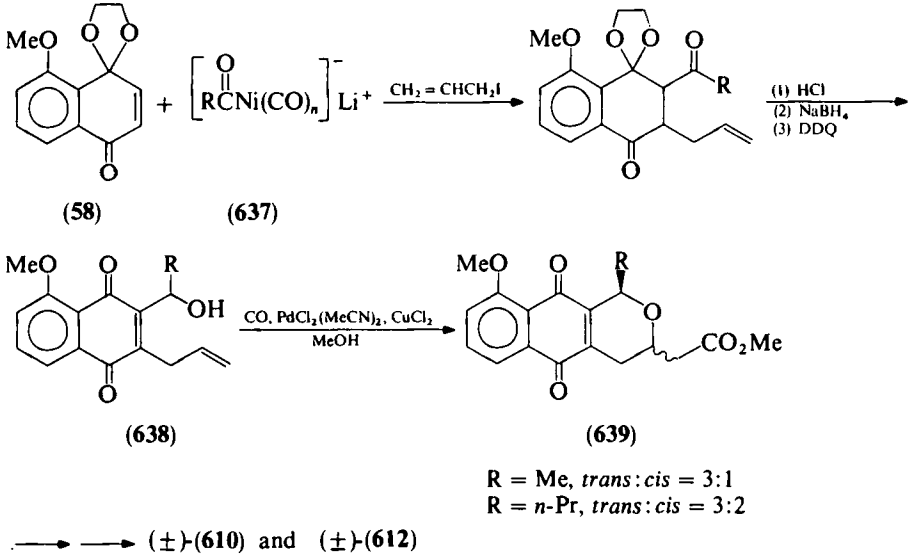
SCHEME 35



SCHEME 36

shown in the eleutherin synthesis (Scheme 30), an acylquinone is an extremely good Michael acceptor, and its Lewis acid mediated reaction with methyl 1-dimethylphenylsilyl-2-butenoate (**633**) (a synthetic equivalent of methyl 2-butenoate anion, **634**) successfully affords a desired intermediate (**635**) in a quantitative yield. After protection of the hydroxy group in order to avoid reaction with the α,β-unsaturated ester moiety, successive reduction and cyclization furnish an equimolar mixture of two diastereoisomers (**636**). By this methodology, (±)-(**610**) and (±)-(**611**) are obtained in excellent overall yield (Scheme 36)[408-410].

The key intermediate (**631**) mentioned above is prepared in two different ways. One method for the required functionalization involves a Michael type addition of the lithium acylnickel carbonyl complex (**637**) to juglone monoacetal (**58**) and successive trapping of the generated enolate anion with allyl iodide. After reduction of the alkanoyl group and then oxidation, the key intermediate quinone (**638**), which is obtained more directly and conventionally by allylation of acylquinones with allylstannane[399,414] is prepared. Further reaction gives **639** (Scheme 37)[411].



(**58**) (**637**)

(**638**) (**639**)

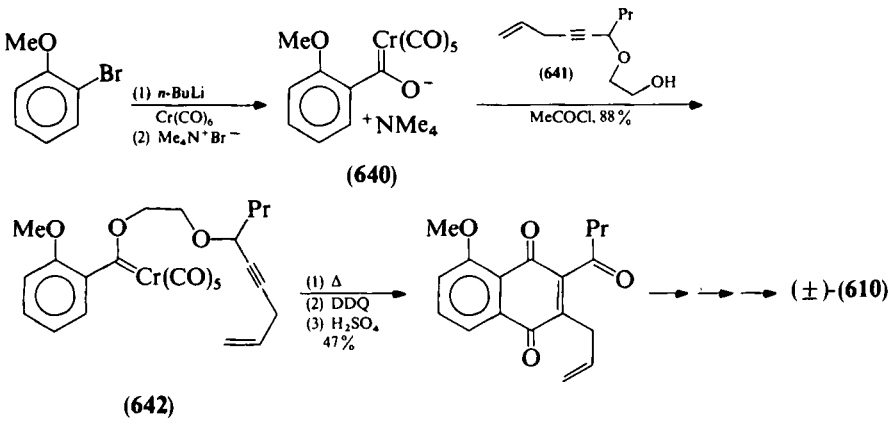
R = Me, *trans*:*cis* = 3:1
R = *n*-Pr, *trans*:*cis* = 3:2

——→ ——→ (±)-(**610**) and (±)-(**612**)

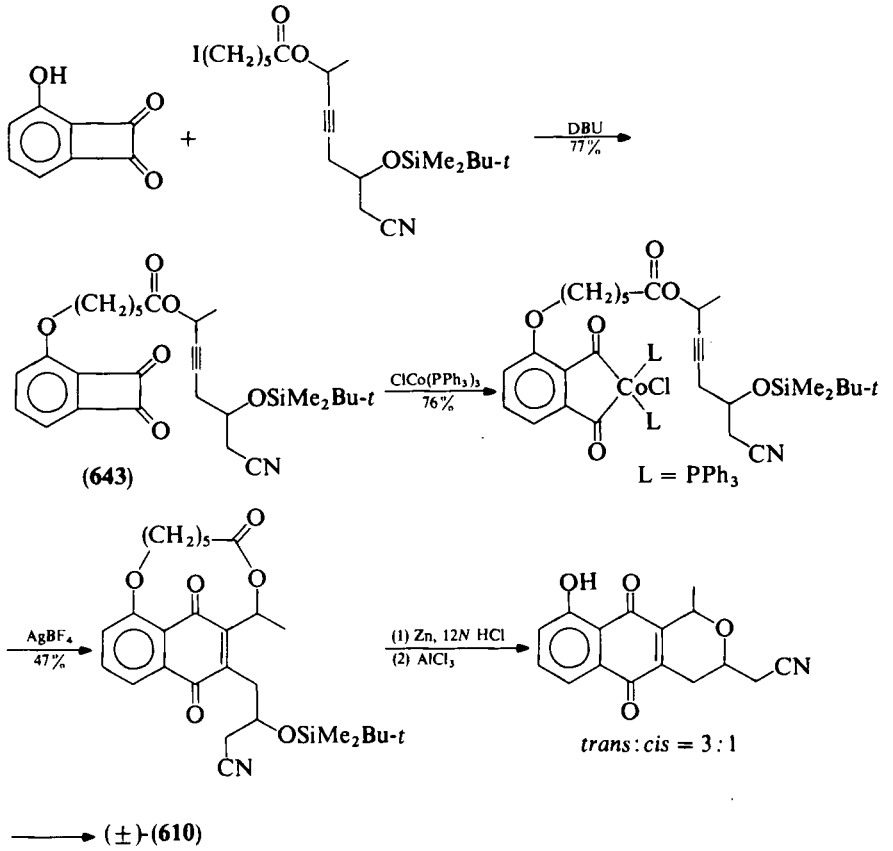
SCHEME 37

Annulation reaction of the chromium carbene complex (**640**) with an appropriate alkyl chain is applied to the synthesis of the similar key intermediate (Scheme 38)[412,413]. This synthetic strategy is based on a non-quinonoid compound as a precursor. From the standpoint of the total synthetic efficiency, there is no advantage in this procedure compared with other methods, but it demonstrates a regioselective intramolecular annulation of the chromium carbene complex.

The regiocontrolled intramolecular annulation of a phthaloylcobalt complex applies the same synthetic strategy (Scheme 39)[254]. The covalently bound precursor (**643**) is necessary for control of the regiochemistry in the annulation, as was the case with the chromium carbene complex.

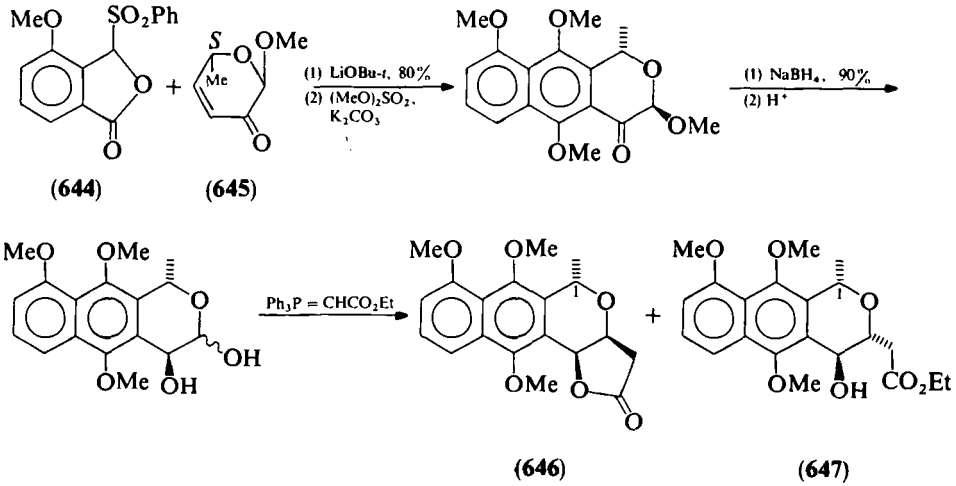


SCHEME 38



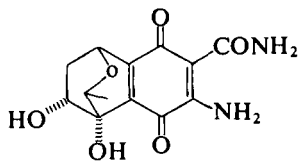
SCHEME 39

Enantiospecific synthesis of nanaomycins and related compounds is performed by using a chiral compound (**645**) derived from a carbohydrate source (Scheme 40)[415]. The requisite naphthopyran structure is constructed by the tandem cyclization between phthalide (**644**) and the optically active α,β-unsaturated ketone (**645**) (see Section III.D.2). The intermediates **646** and **647** are converted to enantiomerically pure nanaomycin D (**611**) and kalafungin (**614**), respectively. Consequently, one asymmetric center is transferred from **645** and the successive Wittig reaction gives two isomeric products, **646** and **647**.



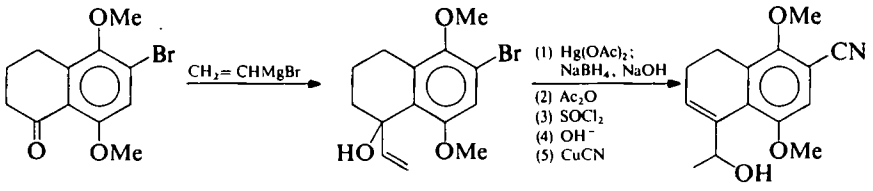
SCHEME 40

Several partial syntheses toward granaticin have been reported so far. Its oxabicyclo[2.2.2]octene portion is a characteristic moiety in this family, and a similar one is found in sarubicin A (or antibiotic U-58,431) (**648**)[416]. As the initial attempt in the

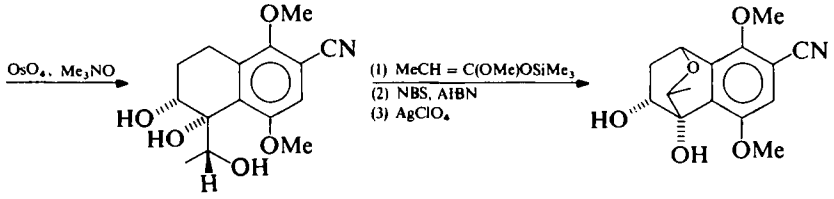


(**648**)

direction, sarubicin A was synthesized. The method used for construction of the common oxabicyclooctane ring system is potentially applicable to the synthesis of granaticin. It includes two key reactions: (1) preparation of a triol (**652**) by means of stereoselective diol formation by OsO_4, and (2) an oxabicyclooctane ring formation by an intramolecular cyclization of the triol to **652** (Scheme 41)[417,418]. The key intermediate (**655**) analogous to **651** is prepared in an alternative method[419]. The aldehyde (**653**) reacts with $TiMe(OPr\text{-}i)_3$ to give **655** in a very high stereoselectivity (equation 168). The Ti(IV) probably coordinates tridentatively to three oxygen functionalities in **653** and as in **654** methylation therefore occurs from the least hindered site.



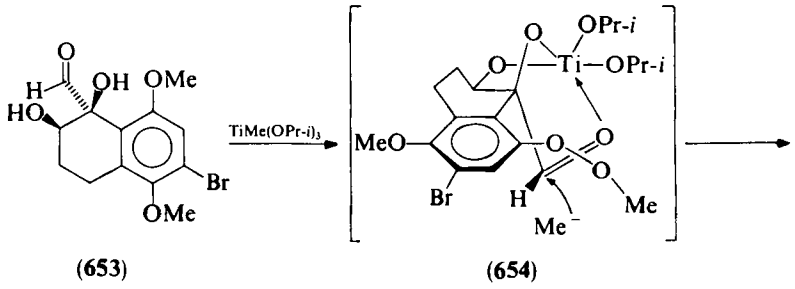
(649) (650)



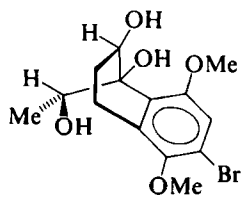
(651) (652)

⟶ ⟶ (±)-(**648**)

SCHEME 41

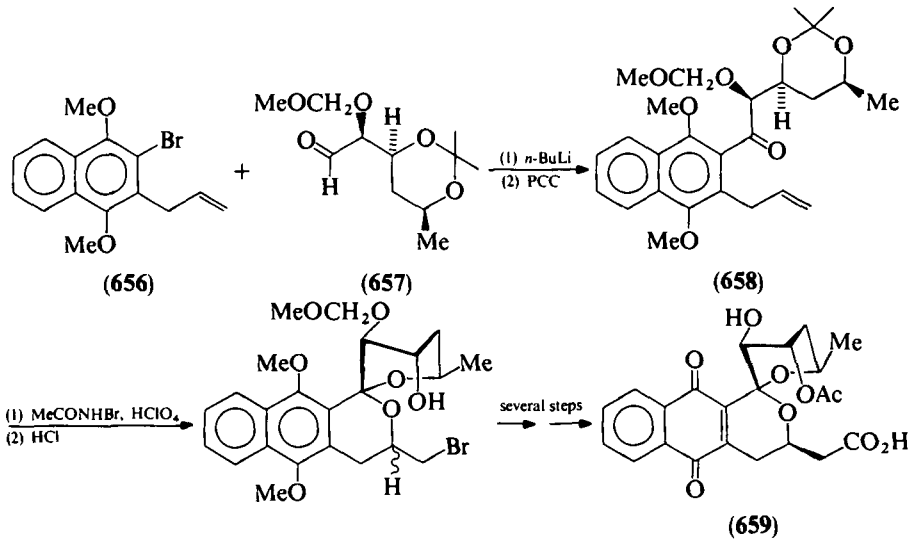


(653) (654)



(655) (168)

Griseusin A and B have a spiroketal moiety together with two pyran rings. Enantioselective synthesis of these compounds is achieved by using **658** as a chiral source, derived from sugar (Scheme 42)[420]. The nucleophilic coupling reaction of **656** with **657** and successive PCC oxidation afforded **658**. The requisite spiro ketal structure of **659** is accomplished by acid treatment of a triol (**658**). Since the final product in this synthetic

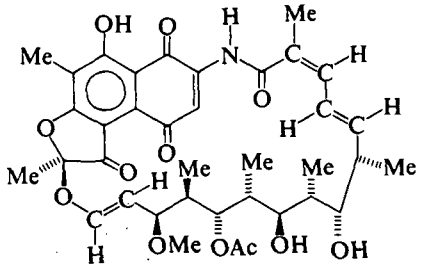


SCHEME 42

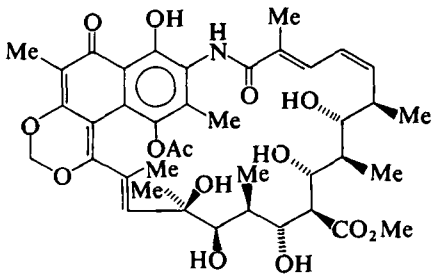
scheme is the antipode of the expected griseusin B, the correct absolute configuration of natural griseusin A and B was determined to be **616** and **617**, respectively, by comparison of the CD spectrum with those of the synthetic griseusins.

C. Ansamycins

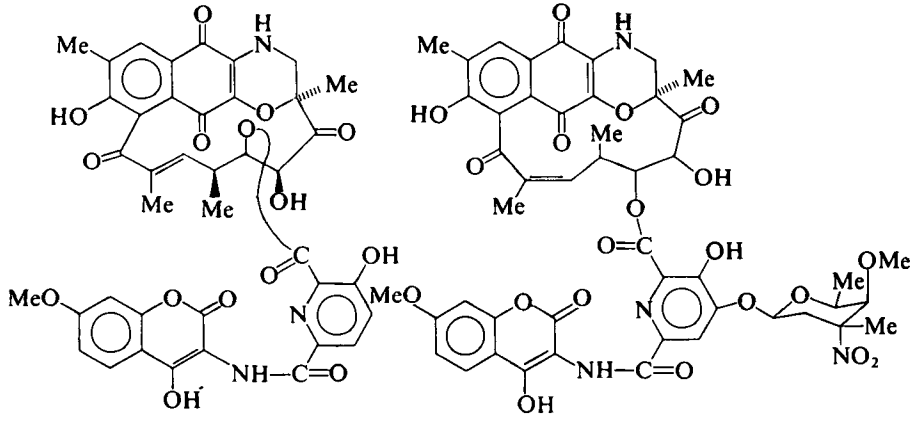
A large number of ansamycin antibiotics have been found so far, and their structures are characterized by the presence of an *ansa* chain bridge attached to a naphthoquinone (or naphthohydroquinone) or to a benzoquinone nuclei. Examples are structures **660–663** given in Chart 5. The detailed chemistry of ansamycins is treated in leading reviews[421-424]. Due to the complexity of their structure, a limited number of ansamycin antibiotics have been synthesized. In this review, the synthesis of the quinonoid moiety is discussed, whereas for the preparation of *ansa* chains, several successful approaches have appeared in the literature[425-430].



(660)



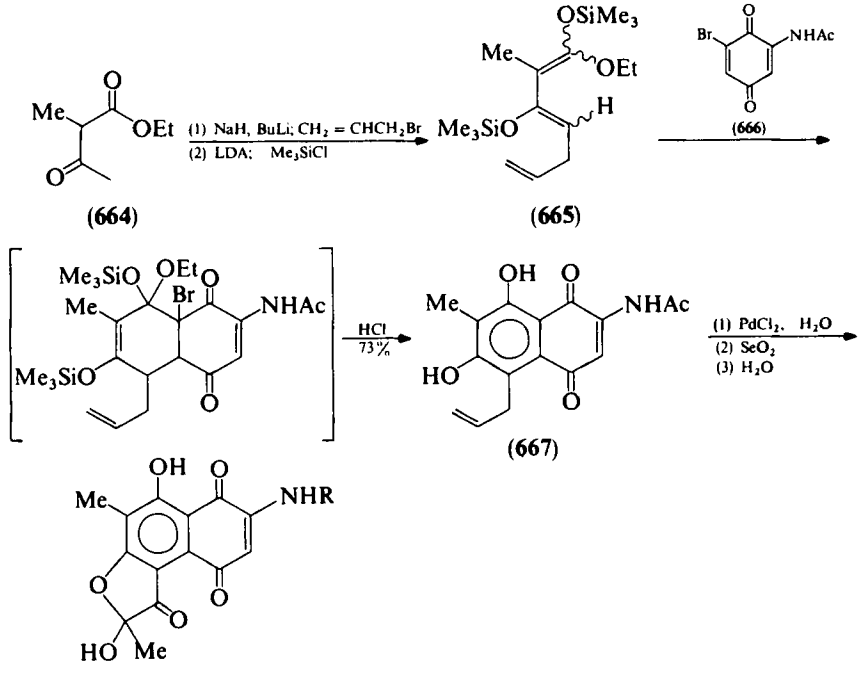
(661)



(662) (663)

CHART 5

For construction of required polyfunctionalized quinone (**668**), which is common to all the structures, the Diels–Alder approach seemed to be most efficient. Thus, the vinyl ketene acetal (**665**), derived from **664**, reacts with the bromoquinone (**666**) to afford **667** in 73%



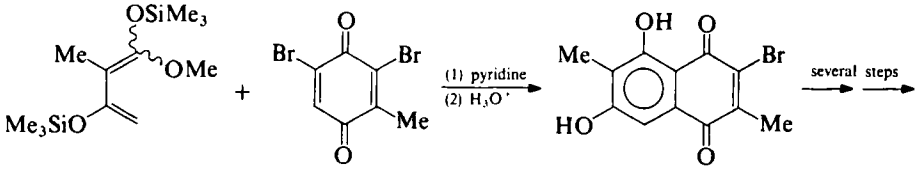
(664) (665) (666) (667) (668)

R = Ac

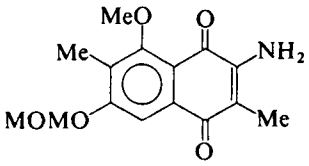
SCHEME 43

yield after aromatization with acid (Scheme 43)[431]. This annulation proceeds in a regioselective manner as in the related reactions discussed in Section III.A.4. **667** can be converted to **668** in three steps including Wacker type and selenium dioxide oxidation.

A similar method is utilized for the synthesis of the aromatic segment of streptovaricin D as shown in equation 169[432]. The difference in the electron-donating ability between the

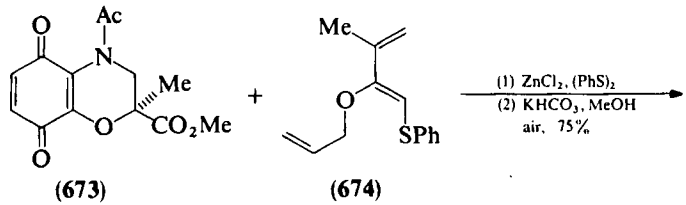


(669) (670) (671)

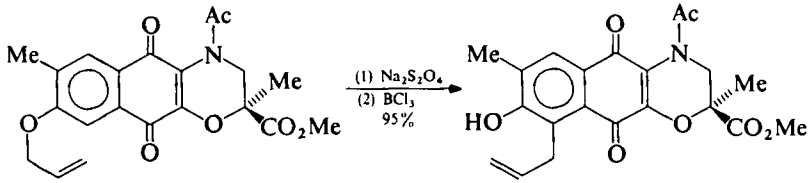


(672) MOM = $MeOCH_2$ (169)

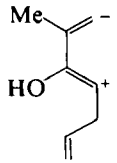
ethereal oxygen and the amido nitrogen in **673**[224] is utilized for a regioselective Diels–Alder reaction with **674**, which is considered as a synthetic equivalent of **675** (Scheme 44)[433]. A Lewis acid mediated Claisen-type rearrangement from a leuco form of



(673) (674)



(676) (677)

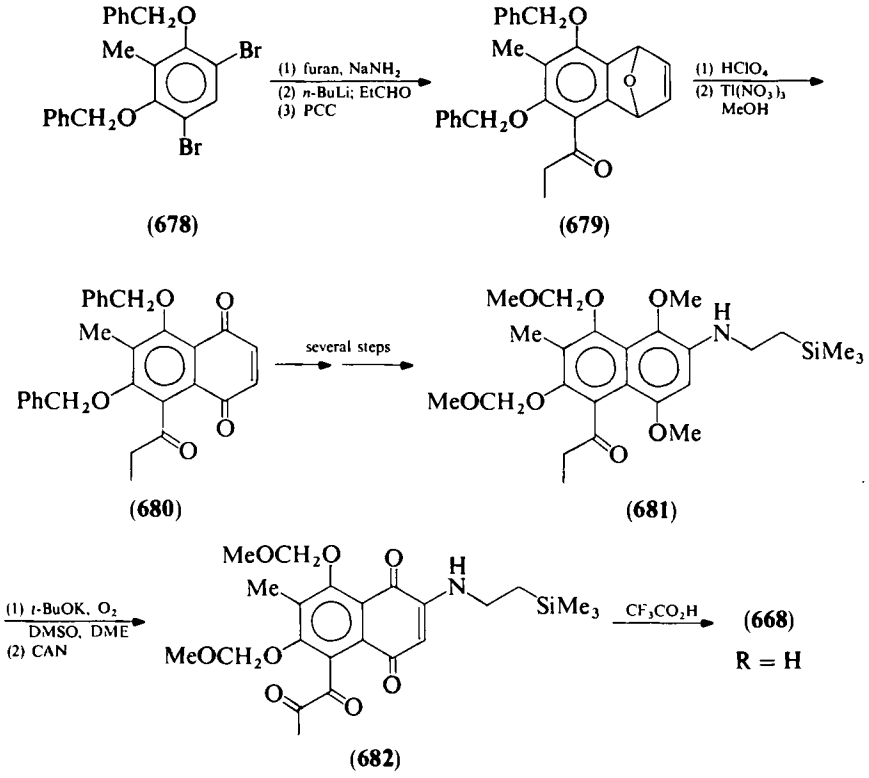


(675)

SCHEME 44

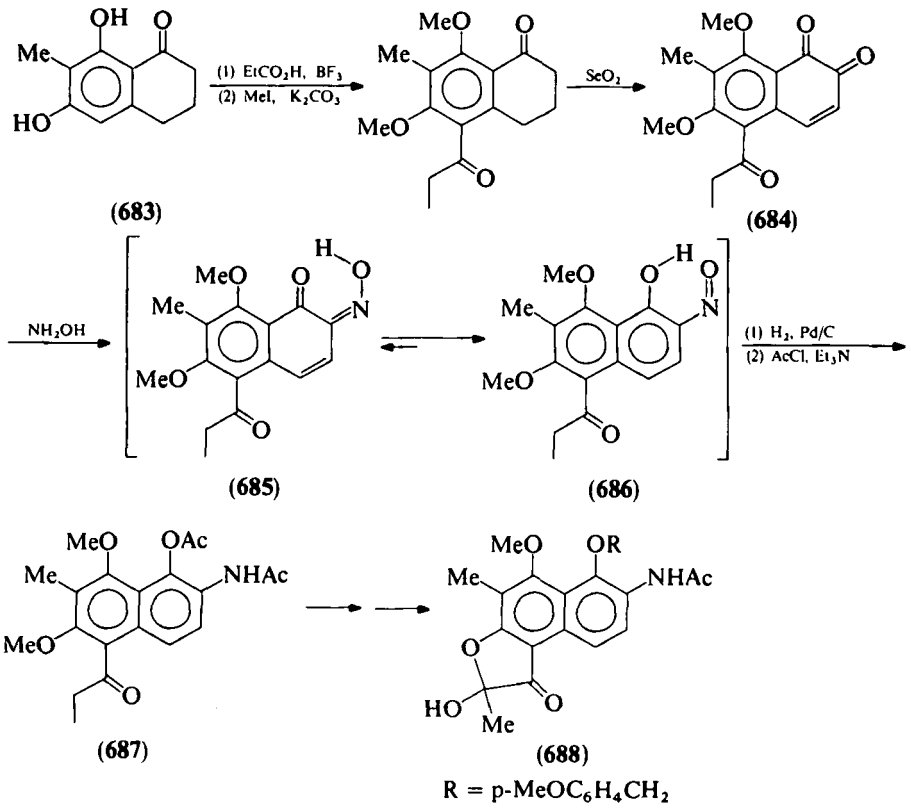
676 affords **677**, which is a promising precursor to build the aromatic segment of rubradirins **662** and **663**.

The aromatic segment (**668**, R = H) is prepared in a rather indirect pathway. Diels–Alder reaction of furan with the benzyne, generated from **678**, affords **679** after successive acylation with EtCHO and oxidation. The oxabicyclo[2.2.1]heptene (**679**) is oxidized to **680** and then to **682** after following several steps including the intermediacy of **681**. Deprotection of the latter affords **668** in a good yield (Scheme 45)[434].



SCHEME 45

An alternative route, not including a Diels–Alder reaction, is achieved by two groups. One approach is a route which mainly involves a modification of the benzocyclohexane ring of **683**. In this synthesis, an orthoquinone (**684**) is transferred to **688** via the corresponding quinone imine (**685**) and its tautomer (**686**) (Scheme 46)[435]. This aromatic segment (**688**) is successfully coupled with an *ansa* chain. For this coupling, the chlorothio ether (**689**) is used due to the low reactivity of the hydroxyl group of **688**. The coupling gives a mixture of four diastereoisomers with respect to the C(12), C(27) and C(29) positions. Two of them, which possess the same stereochemistry as the natural compound, were separated, and converted to the precursor quinone by a multi-step treatment: deblocking of the phenolic protection at C(1), olefination at C(28) and C(29) position, and



SCHEME 46

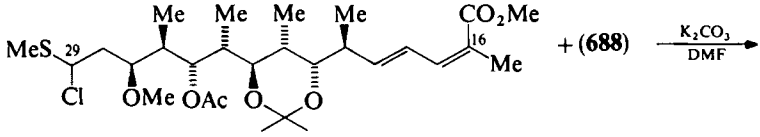
oxidation of the aromatic ring by Fremy's salt. Finally, the total synthesis of rifamycin S (**660**) is completed by forming the amide linkage in several steps (Scheme 47)[436].

The related quinone (**695**) used for the rifamycin synthesis is prepared by a sequence of nucleophilic Michael addition of a β-keto ester to quinone (**691**) followed by an intramolecular Claisen condensation of **693** to **694** and final oxidation by cerium ammonium nitrate (Scheme 48)[437].

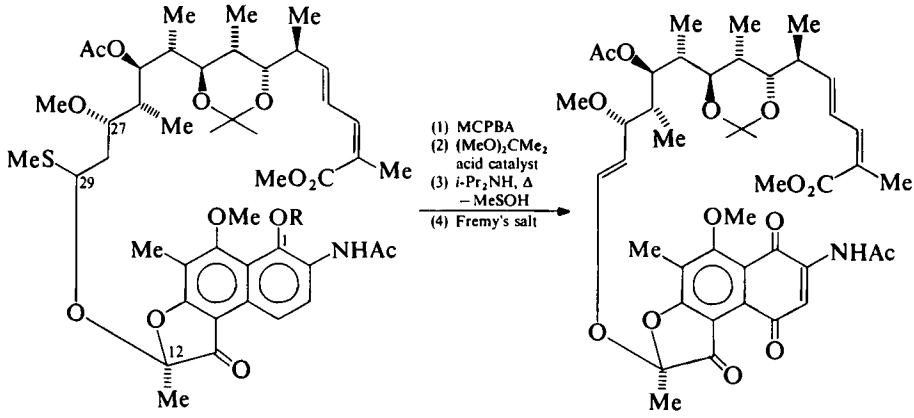
D. Mitomycins

Since mitomycin A[438], B[438], C[439] and porfiromycin[440] are isolated from *Streptomyces* strains, they are recognized to be active against Gram-positive and Gram-negative bacteria. Mitomycin C, especially, has the broadest and strongest activity against a wide range of tumors. The whole range of chemistry and biological and clinical activities are treated in many reviews[441-448].

Recently, the absolute configurations were corrected and they are depicted in **696** and **697**[449,450]. They are reasonable and in agreement with the biosynthetic studies. Mitosenes (**698**, R^1, R^2 = ⩾NR), which can be generated by the elimination of either methanol or

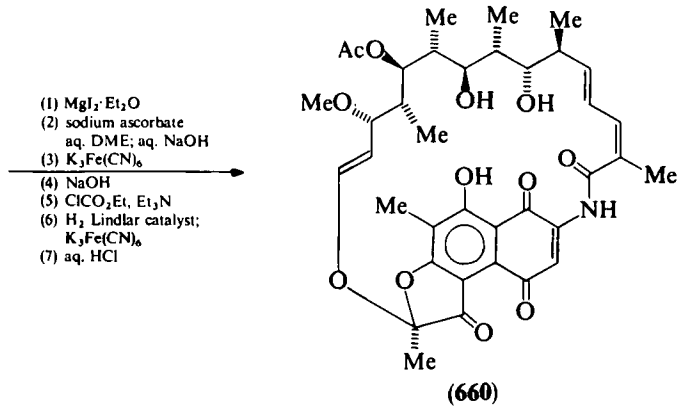


(689)



(690)

R = *p*-$MeOC_6H_4CH_2$

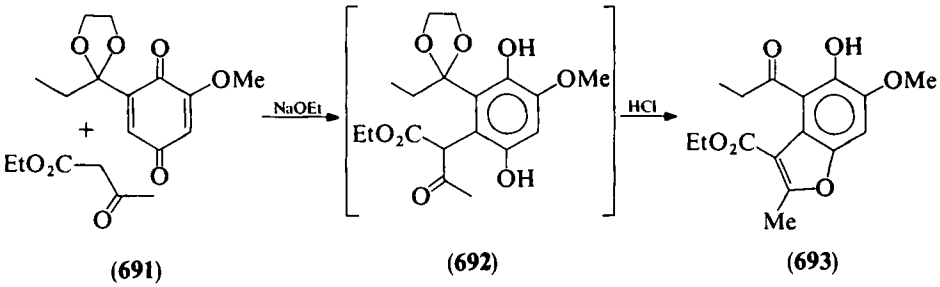


(660)

SCHEME 47

water from mitomycins, possess an almost similar activity toward bacteria and tumors as the parent mitomycins, and also are the target compounds in the synthetic studies.

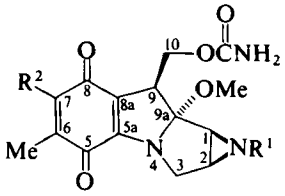
Since synthesis of these compounds involves many interesting points and challenges, many attempts have been reported so far. The earlier results are summarized in references



(691) (692) (693)

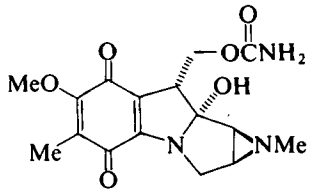
(694) (695)

SCHEME 48



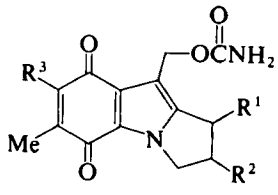
(696)

Mitomycin A, $R^1 = H$, $R^2 = OMe$
C, $R^1 = H$, $R^2 = NH_2$
Porfiromycin, $R^1 = Me$, $R^2 = NH_2$



(697)

Mitomycin B

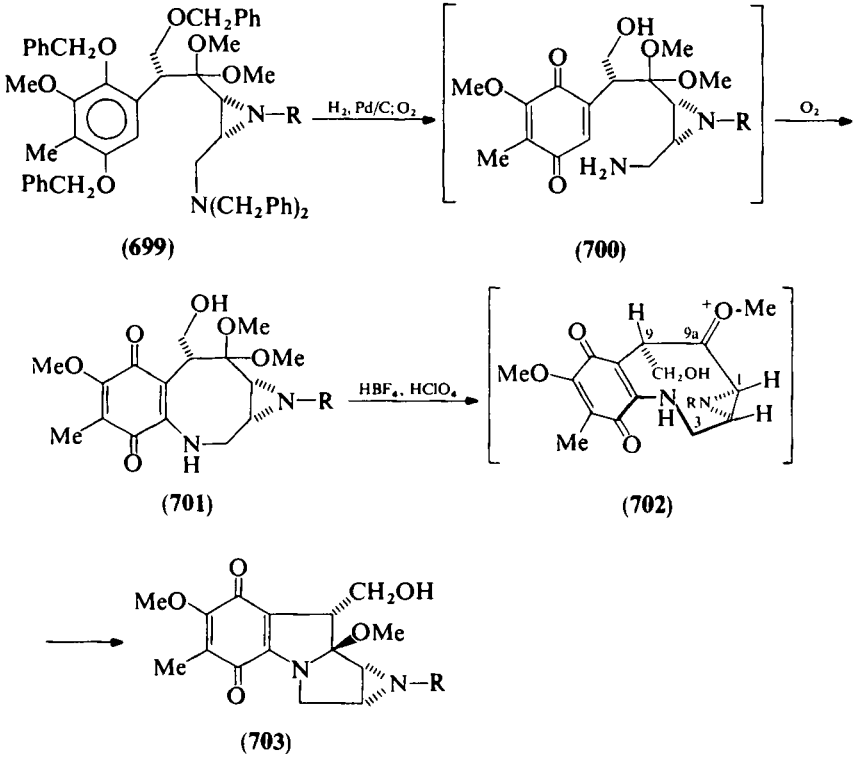


(698)

Mitosene

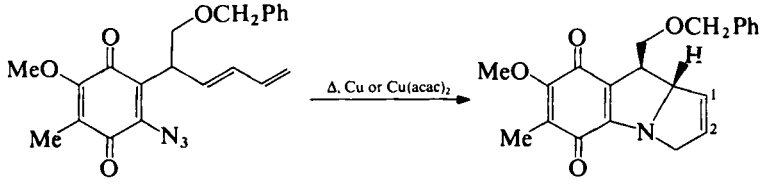
441–444, 446, 447 and here we treat the progress in this field after 1980. A total synthesis of the racemic forms of mitomycins A, C and porfiromycin was accomplished in 1977, by means of intramolecular amino cyclization. The central part of this methodology is briefly shown in Scheme 49 as a typical example for a series of related syntheses[451,452].

The most serious problem in the synthesis of mitomycins is how to preserve the fragile alkoxy group at the C(9a) position. This is solved by a transannular aminocyclization of **701** under acidic conditions to give **703** with a favorable stereochemistry (Scheme 49)[451,452].



SCHEME 49

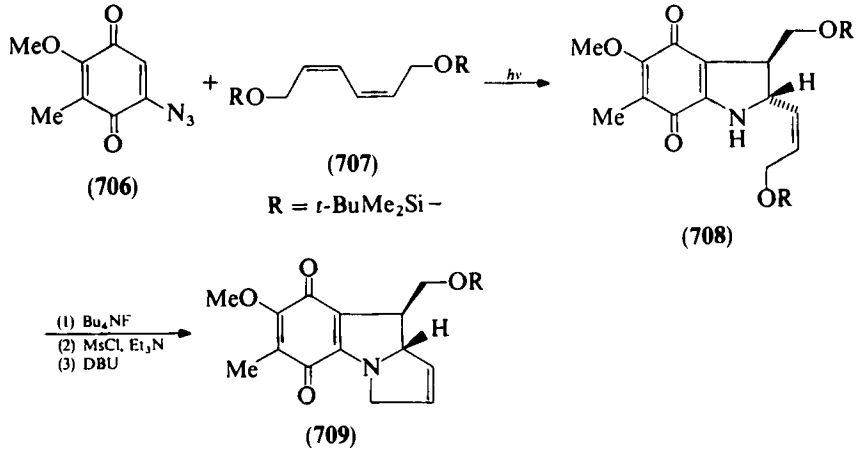
Most of the reported methods are concerned with the synthesis of the pyrrolo[1,2-*a*] indole ring and of mitosene (**698**). The simplest synthesis of this ring system is accomplished by a copper catalyzed intramolecular double cyclization of 2-(2′,4′-



(170)

pentadienyl)-3-azidoquinone (**704**) to **705** (equation 170)[321,322]. This method preserves the double bond at C(1)–C(2), which can be converted to an aziridine ring at a later stage.

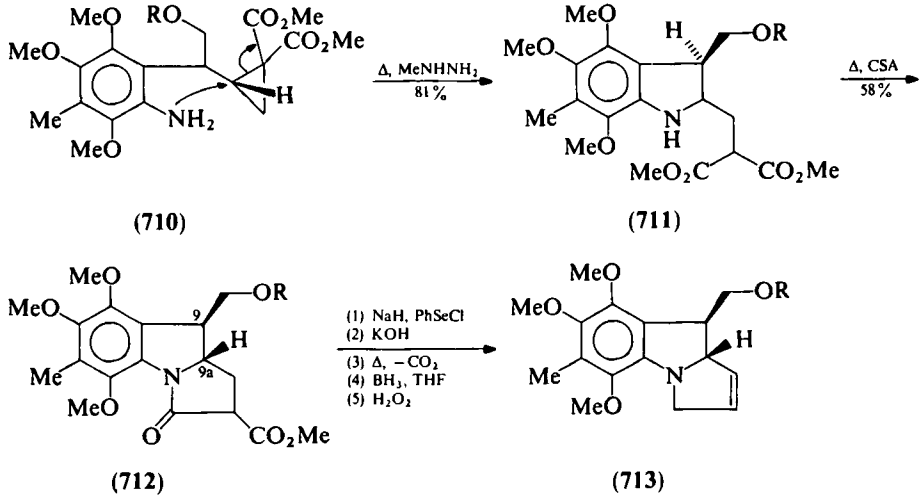
Intermolecular photochemical reaction of the azidoquinone (**706**) with a symmetrically functionalized *Z,Z*-diene (**707**) gives stereospecifically the indole derivative (**708**), which can be easily cyclized to **709**[320]. The stereochemistry of the olefinic double bond of the diene (**707**) is completely preserved in the *cis* configuration in **708** and this is a great advantage for the following cyclization to **709** (Scheme 50)[320].



(**706**) (**707**) R = *t*-BuMe$_2$Si– (**708**) (**709**)

SCHEME 50

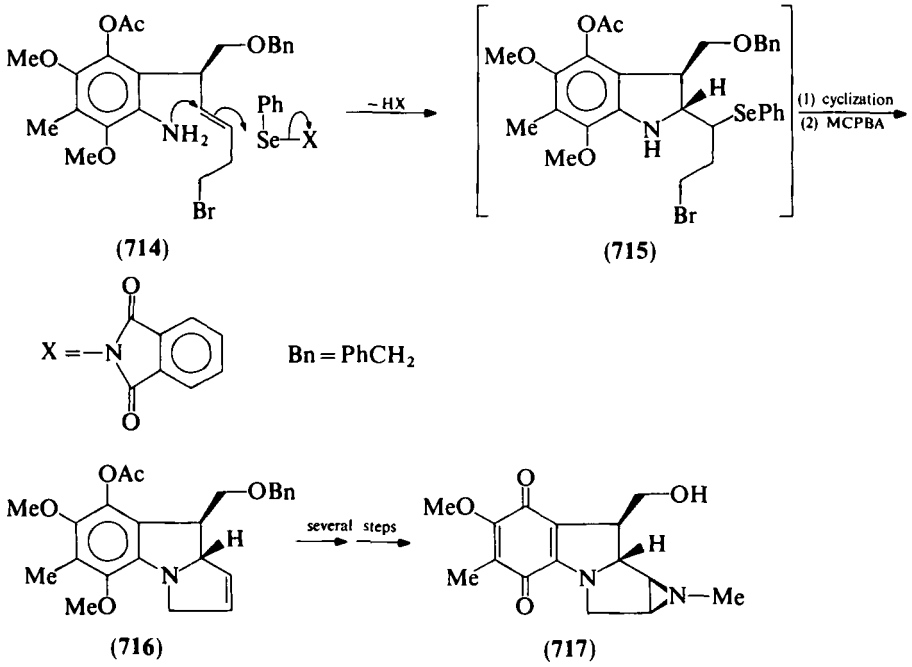
A similar target compound (**713**) is synthesized by several alternative ways. A stepwise preparation of the dihydroindole (**711**) is synthesized by means of intramolecular nucleophilic ring-opening of an activated cyclopropane ring. The conversion of the functionalities on the pyrrole ring from **712** to **713** is conducted in a five steps sequence (Scheme 51)[453].



(**710**) (**711**) (**712**) (**713**)

SCHEME 51

Intramolecular aminoselenation is one of the important methods to form dihydroindoloquinone and the related compound, **716**. In the cyclization of **714**, participation by the *N*-phenylselenophthalimide gives **716** in 31 % yield after oxidative elimination. The latter can be converted to **717** (Scheme 52)[454]. Interestingly, all the doubly cyclized products,



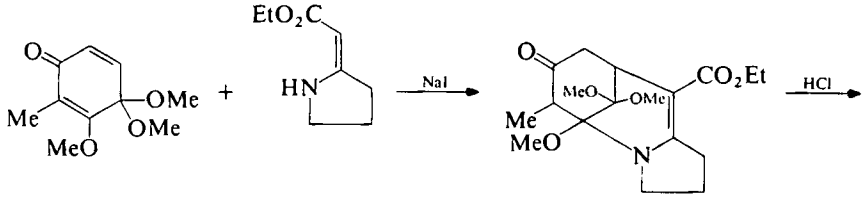
SCHEME 52

705, **709**, **712** and **716**, obtained according to the schemes as shown above possess *trans* configuration at C(9)–C(9a), irrespective of the applied methodologies.

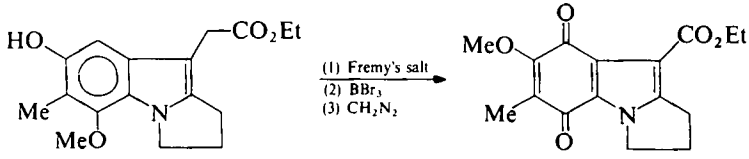
In a similar strategy, an intramolecular amino mercuration is used for the same purpose[455].

A double Michael addition of the exocyclic enamino ester (**719**) to the quinone monoacetal (**718**) gives the bicyclic product (**720**), which when subjected to acid catalysis rearranges to **721** (Scheme 53)[456]. The successive transformation gives indolequinone (**722**). A use of the quinone monoacetal instead of the quinone is the key step in the regiocontrolled cyclization.

Several photochemical cyclizations have been applied for the synthesis of the required carbon framework. Photochemical reaction of the pyrrolidinoquinone (**723**) gives the cyclized product (**727**) in a good yield (Scheme 54)[457,458]. By the photochemical reaction, the cyclized product (**724**) is first obtained via intramolecular hydrogen abstraction and cyclization. Upon silica gel chromatography, an intramolecular attack of a stabilized anion on the iminium salt in **725** is proposed to give **726**, which on acid hydrolysis and decarboxylation gives **727** (Scheme 54)[457,458]. A similar, but a non-photochemical intramolecular nucleophilic attack on an iminium salt has also been investigated (equation 171)[459]. The related intramolecular and electrophilic cyclization of an iminium salt (**729**) is

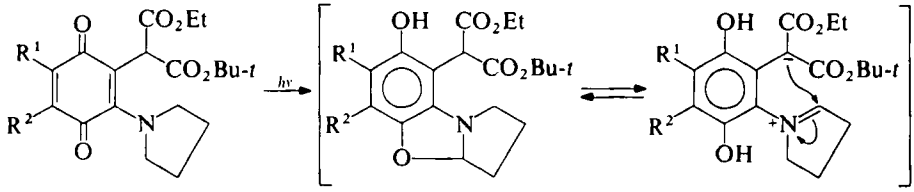


(718) (719) (720)

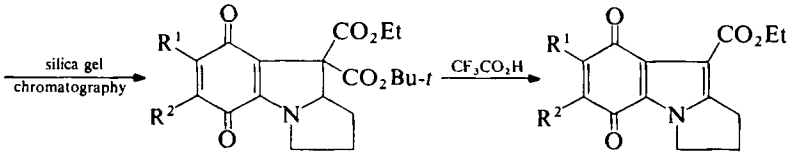


(721) (722)

SCHEME 53

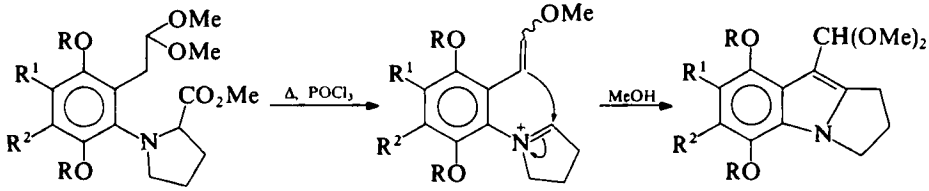


(723) (724) (725)



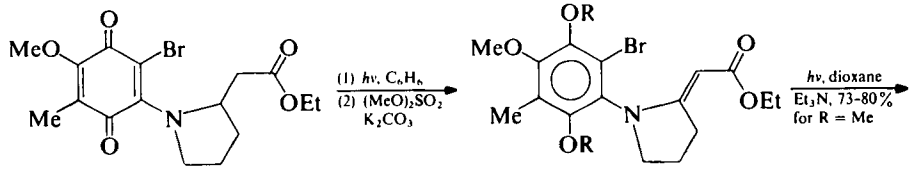
(726) (727)

SCHEME 54



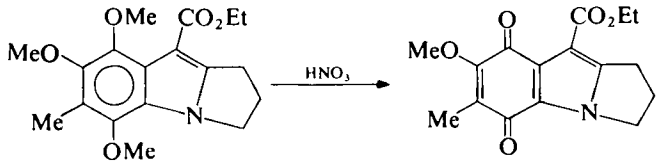
(728) (729) (730) (171)

also reported in the synthesis of the analogous compound (**730**) from **728**[460]. A similar photocyclization to that shown in Scheme 54 is repeatedly used, first for dehydrogenation and then for cyclization (Scheme 55)[461]. The first photochemical reaction of quinone (**731**)



(**731**) (**732**)

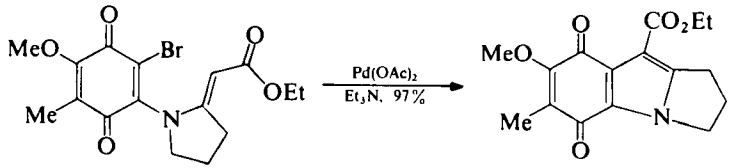
R = H, Me



(**733**) (**734**)

SCHEME 55

gives the enamine (**732**, R = H) after intramolecular hydrogen abstraction. The second photochemical step of the corresponding dimethyl ether (**732**, R = Me) gives indole derivative **733** in a good yield, in a process which is analogous to the photocyclization of *N*-haloaryl substituted enamines. However, direct irradiation of hydroquinone (**732**, R = H) does not give **734**. As an alternative for the photochemical cyclization to the indole, palladium acetate[461] or cupric bromide[112b,462] gives **734** from **735** in an excellent yield (equation 172). This route was also applied to the synthesis of the chiral aziridinomitosene

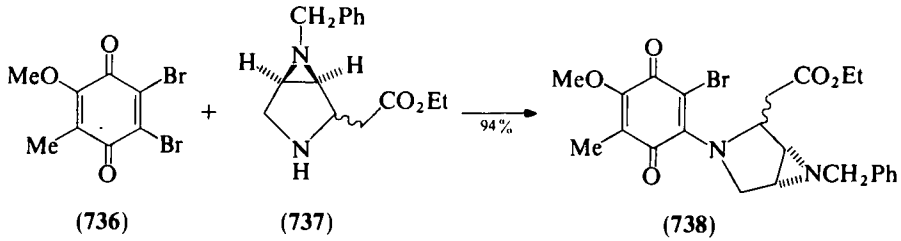


(172)

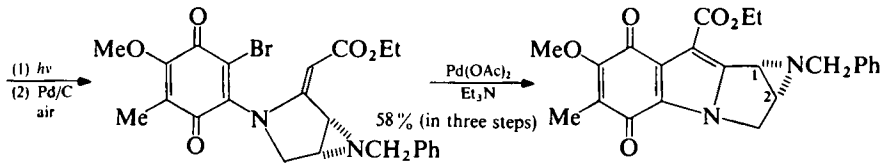
(**735**) (**734**)

(**740**), which has unnatural chirality at C(1) and C(2) (Scheme 56)[463]. The analogous intramolecular cyclization reaction of β-enamino ester (**743**) with its aromatic halide moiety is reported to give **744** in good yield. **744** is then utilized as a precursor to (±)-apomitomycin (**745**) (Scheme 57)[464].

The pyrrolizidine skeleton of mitosene including the quinonoid moiety itself is prepared by a 1,3-dipolar cycloaddition between dimethyl acetylene dicarboxylate and a dipole (**747**) generated from **746**[465]. The quinonoid part is then formed by a Dieckman cyclization of the product **748** to **749**. This tricyclic precursor is ultimately converted to mitosene (**750**) (Scheme 58).

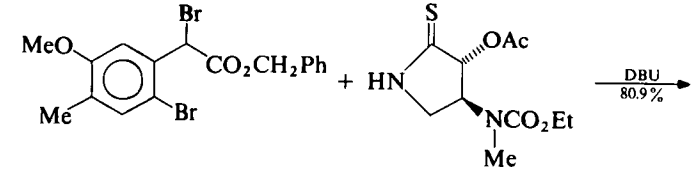


(736) (737) (738)

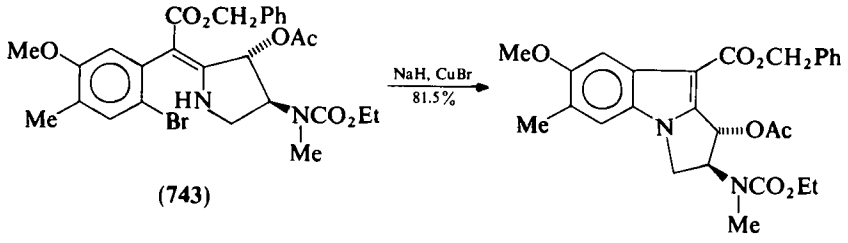


(739) (740)

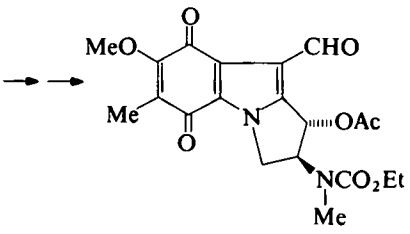
SCHEME 56



(741) (742)

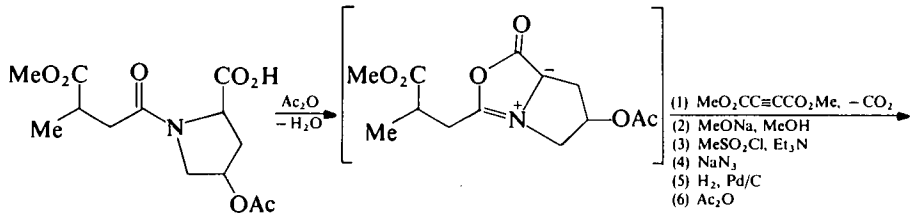


(743) (744)

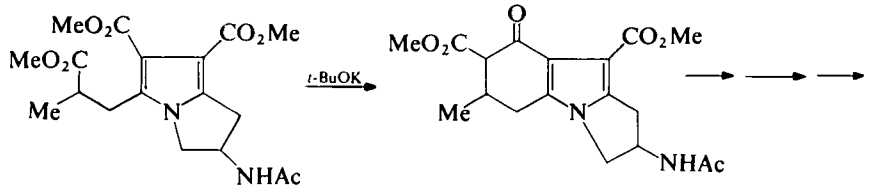


(745)

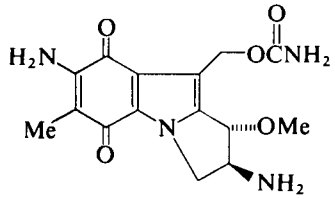
SCHEME 57



(746) (747)



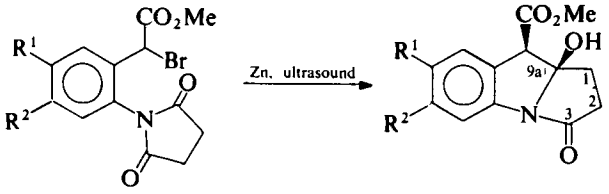
(748) (749)



(750)

SCHEME 58

As another method of pyrroloindole ring synthesis, intramolecular Reformatsky reaction between the bromoester and the succinimido moieties in **751** stereoselectively gives **752** in a high yield under ultrasound irradiation (equation 173)[466]. Interestingly, the amido group of **752** seems to prevent the elimination of hydroxyl group at C(9a) to the corresponding iminium salt.



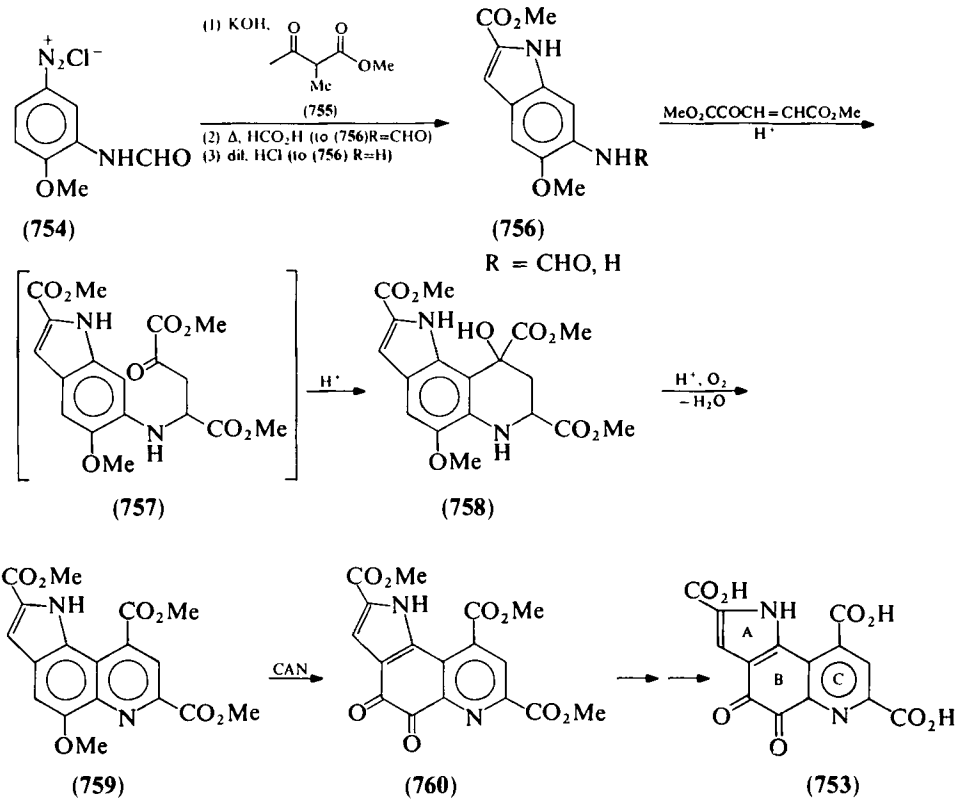
(751) (752) (173)

In addition to the examples mentioned above, various attempts to prepare the required carbon skeleton by means of palladium catalyzed cyclization have been conducted[323,467,468].

E. Miscellaneous Quinones

1. Methoxatin

Methoxatin (**753**) is the cofactor for certain non-flavin or nicotinamide dependent bacterial dehydrogenases found in methylotrophic bacteria, which use one-carbon compounds as their sole source of energy[469-473]. It possesses an interesting *ortho*-quinone structure, which is rather uncommon among naturally occurring quinones. Three types of synthetic approach to the requisite rings were examined: (1) B → AB or BC → ABC, (2) AB or BC → ABC, and (3) A + C → ABC. The first approach is the extension of the A and C rings from ring B as the core compound. The synthesis along this pathway is shown in Scheme 59[474]. Formation of the indole ring is based on the

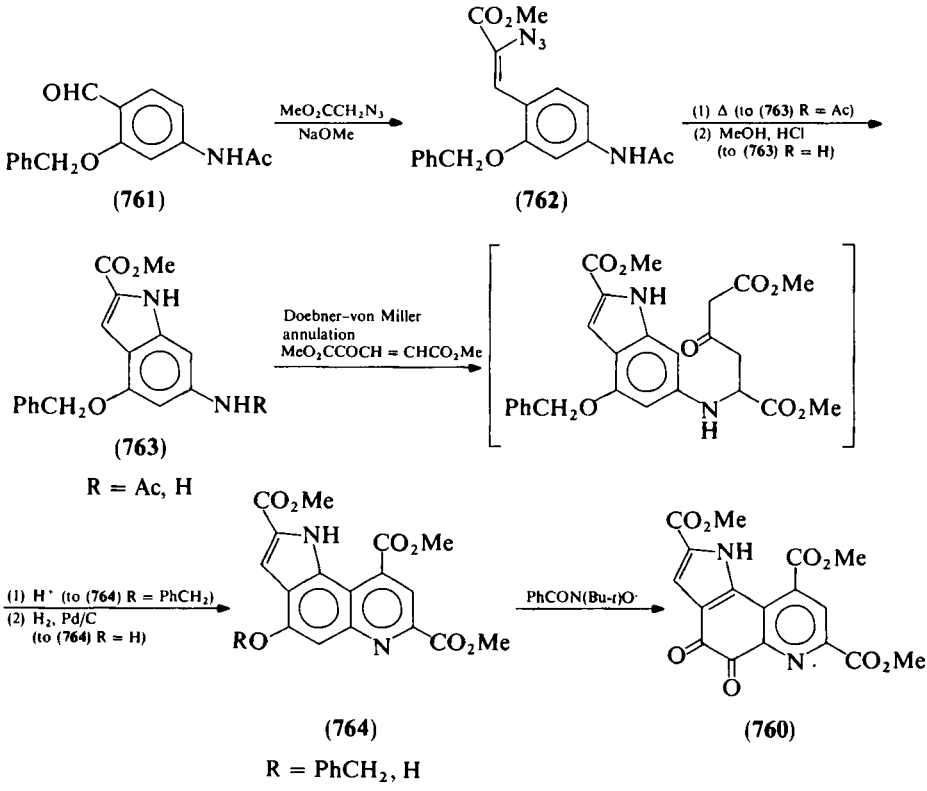


SCHEME 59

Japp–Klingemann reaction and a Fischer indolization. Condensation of the diazonium salt (**754**) with methyl α-methylacetoacetate (**755**) followed by acid treatment gives the corresponding hydrazone, which can be converted to **756** in 79 % yield. After deprotection of the amino group of **756**, a Doebner–von Miller type annulation with dimethyl 2-oxaglutaconate affords **758** via the conjugate adduct (**757**). A following aromatization gives the pyrroloquinoline (**759**) in > 90 % yield. Direct oxidation of **759** by CAN gives the *o*-

quinone (**769**) in 60% yield. Due to the instability of the *o*-quinonoid part in basic media, deprotection of the tricarboxylic acid of **760** could not be performed directly in this synthesis. However, it could be achieved via a monoacetal protection, saponification and deprotection sequence.

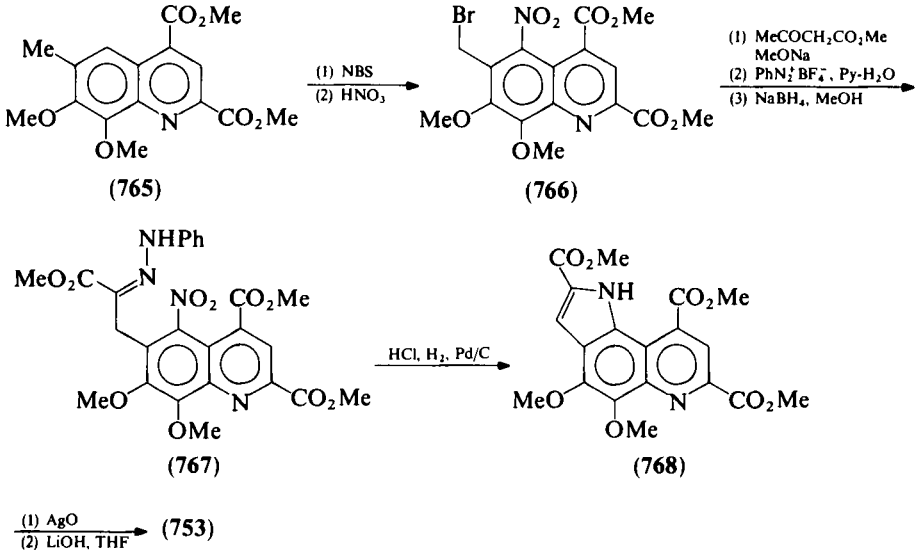
A different method for construction of the indole ring has been developed (Scheme 60)[475]. The methyl α-azidocinnamate (**762**) is obtained by aldol condensation of **761** with methyl azidoacetate and thermal decomposition of **762** gives **763** in a good yield. Additional quinoline ring is then prepared by just the same method shown in Scheme 59. However, oxidation of the phenolic group of **764** (R = H) with Fremy's salt is unsuccessful owing to the insolubility of **764** in aqueous media. An alternative method of oxidation with a lipophylic nitroxide (see Section II.B) gives the target *o*-quinone (**760**) in 93% yield.



SCHEME 60

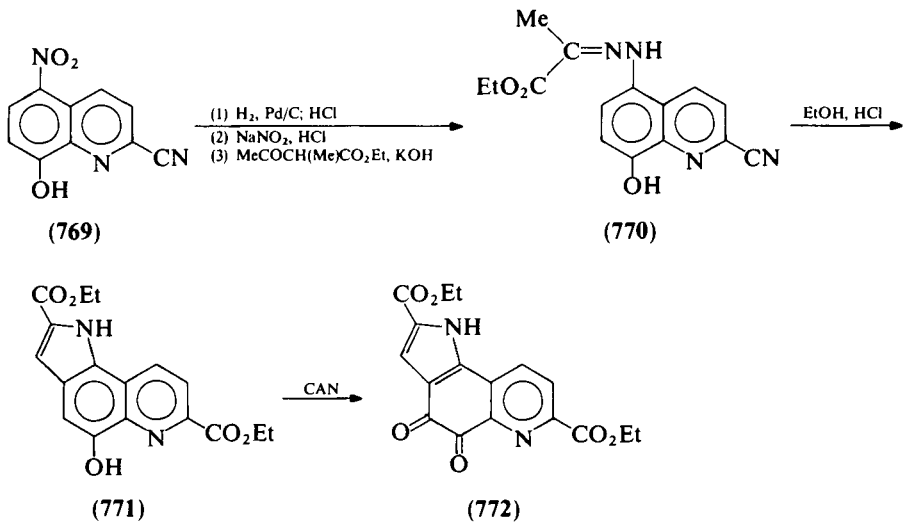
An initial construction of the quinoline ring gives another approach to **753** (Scheme 61)[476]. The quinoline derivative (**765**) is synthesized by means of the Pfitzinger method from the corresponding aniline. Bromination at the benzylic position and nuclear nitration converts **765** to **766**, which is subjected to addition of methyl acetoacetate and then converted to the corresponding catechol (**767**) by Kozikowski's modification of the

Japp–Klingemann reaction in 64% yield in two steps. Hydrogenative reduction of the nitro group in **767** under acidic conditions spontaneously gives the indole (**768**) in 60% yield. Demethylative oxidation is successfully conducted by AgO, and finally the saponification of **768** is achieved by LiOH in aqueous THF. As mentioned above this hydrolysis was unsuccessful in the previous report (Scheme 61)[474].



(765) (766) (767) (768)

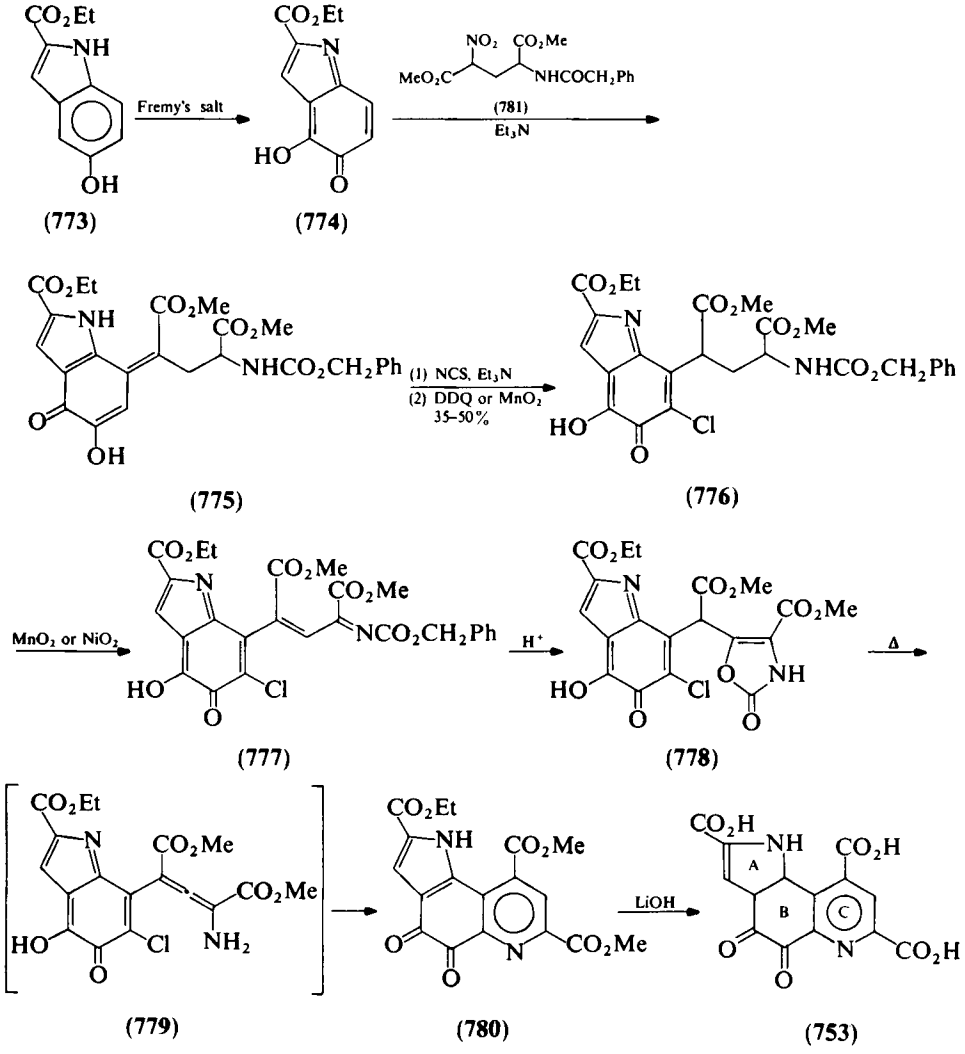
SCHEME 61



(769) (770) (771) (772)

SCHEME 62

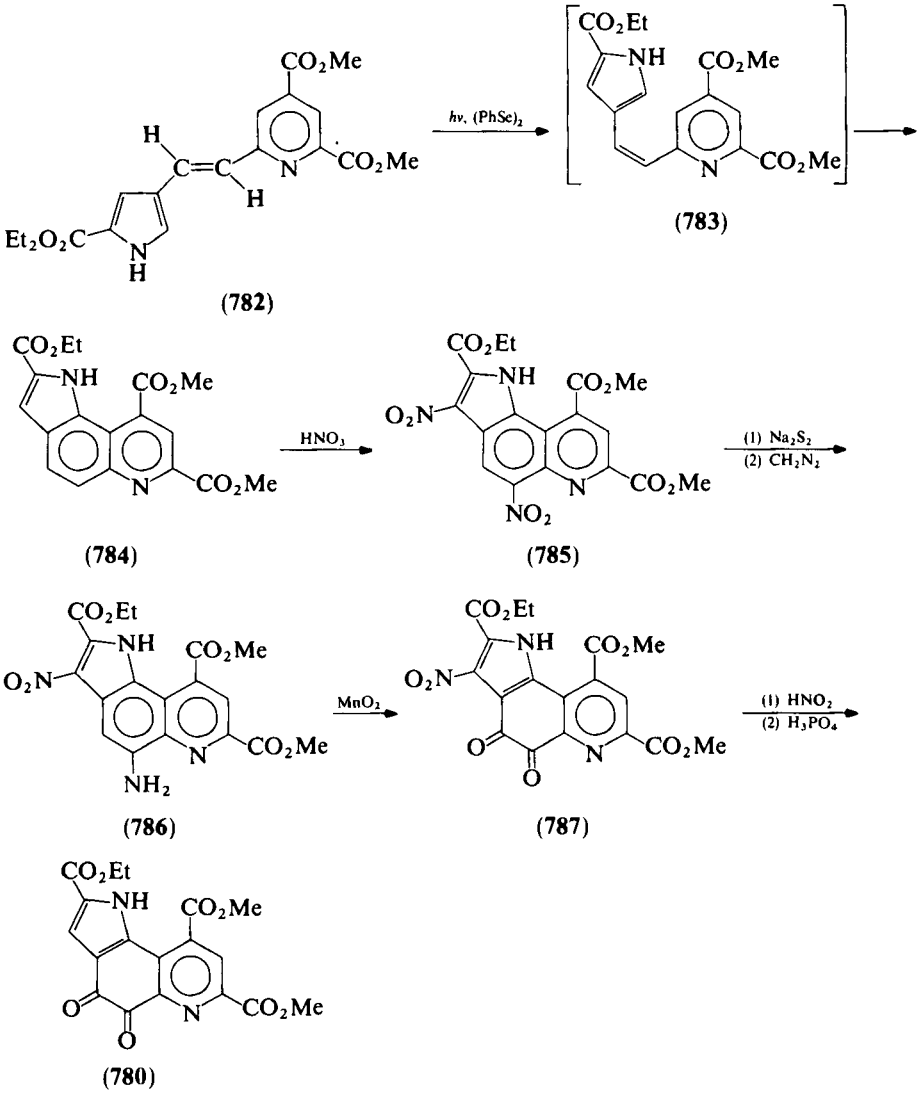
9-Decarboxymethoxatin (**772**) is prepared by a more conventional route starting from 8-hydroxyquinoline, which is converted to **769** in several steps. **769** was converted to the corresponding diazonium salt via the aminoquinoline derivative and then was transferred to the corresponding hydrazone derivative (**770**) by using methyl α-methylacetoacetate in a basic alcohol in a low yield. Cyclization and the following transformation of the nitrile function to ester were conducted in an acidic alcohol to give **771**. The final oxidation of the phenol (**771**) to **772** can be achieved by using CAN (Scheme 62)[477]. A quinone imine → quinone methide → quinone interconversion sequence is utilized in the functionalization of the indole derivative (Scheme 63)[478]. In spite of its low overall yield, this is one



SCHEME 63

of the most interesting synthetic pathways, which fully utilizes the specific interconversion between the quinone imine and the indoloquinone. Fremy's salt oxidation of hydroxyindole (**773**) gives the corresponding *p*-quinone imine (**774**) in 94% yield. A subsequent Michael addition of **781** gives quinone methide **775** in 47% yield, and then stepwise chlorination and oxidation of the formed **775** affords **777** in a low yield (10–15%) from **774**. The final ring-closure to the quinolinoquinone (**780**) includes the intermediary formation of the allene (**779**), of which electrocyclic reaction furnishes **780** in a good yield.

The final example utilizes a photoinitiated oxidative cyclization reaction for construction of the B ring from the AC unit (Scheme 64)[479]. The photochemical cyclization of **782**



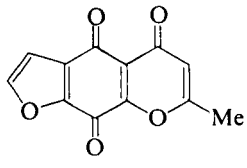
(782) (783) (784) (785) (786) (787) (780)

SCHEME 64

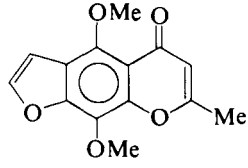
to **784** presumably proceeds via an initial photochemical isomerization to **783** and then an oxidative electrocyclic reaction. It is worthwhile mentioning the other steps of the synthesis. The dinitro compound (**785**) obtained by nitration of **784** is reduced by means of a Zinin reduction to the amine (**786**). The latter is then oxidized by MnO_2 to the corresponding *o*-quinone in 94% yield, while Fremy's salt, as the first choice in such a transformation, is ineffective toward this conversion. Presumably, this can be attributed to the insufficient solubility of the substrate in the aqueous media.

2. *Khellin*

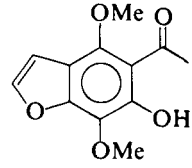
Khellin (**789**) is a member of the family of furochromanones and it possesses a lipid-altering and antiatherosclerotic activity[480,481]. Compounds related to **789** are known as khellinquinone (**788**) and khellinone (**790**), both of which can be derived from khellin. Due



(**788**)



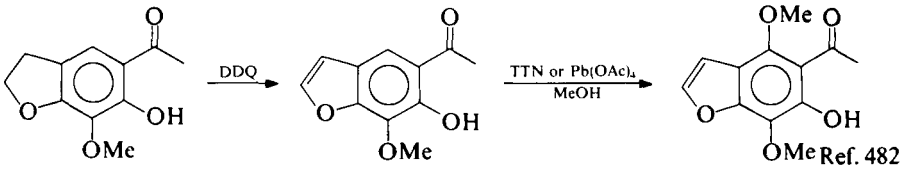
(**789**)



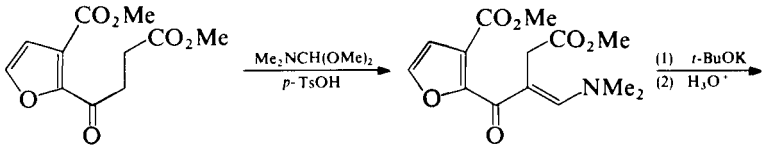
(**790**)

to its structural simplicity, many synthetic efforts to prepare it have appeared for the last 30 years. Several of the recent ones are interesting processes and will be discussed briefly here.

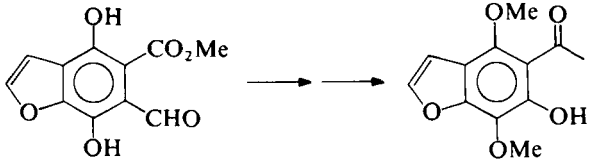
Khellinone is synthesized from the dihydrobenzofuran **791**[482]. For oxidation of the intermediate (**792**), TTN or $Pb(OAc)_4$ are used (equation 174). The Dieckman conden-



(**791**) (**792**) (**790**) Ref. 482 (174)

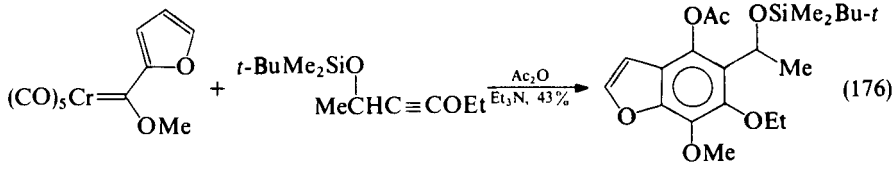


(**793**) (**794**)

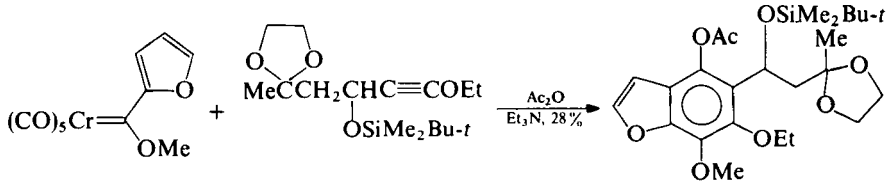


(**795**) (**790**) Ref. 483 (175)

sation of **794** can also be used for the synthesis of the hydroquinone (**795**) with the formyl group, which can be converted to **790** (equation 175)[483]. Annulation of the chromium carbene complex (**796**) is another possibility to obtain the highly functionalized benzofuran[481]. The reaction of **796** with an unsymmetrical alkyne such as **797** or **798** proceeds in a completely regioselective manner (equations 176 and 177). The yields of **799** and **800**, however, are not satisfactory ones. Such a high selectivity is attributed to the steric effect in the annulation stage (see Section III.C). The annulation products **799** and **800** are converted to khellin in several steps.



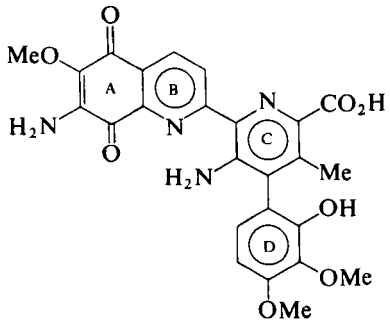
(796) (797) (799) (176)



(796) (798) (800) (177)

3. *Streptonigrin*

Streptonigrin (**801**) is isolated from *Streptomyces flocculus* and is recognized as an antitumor antibiotic. The whole range of its chemistry is covered by reference 484, which

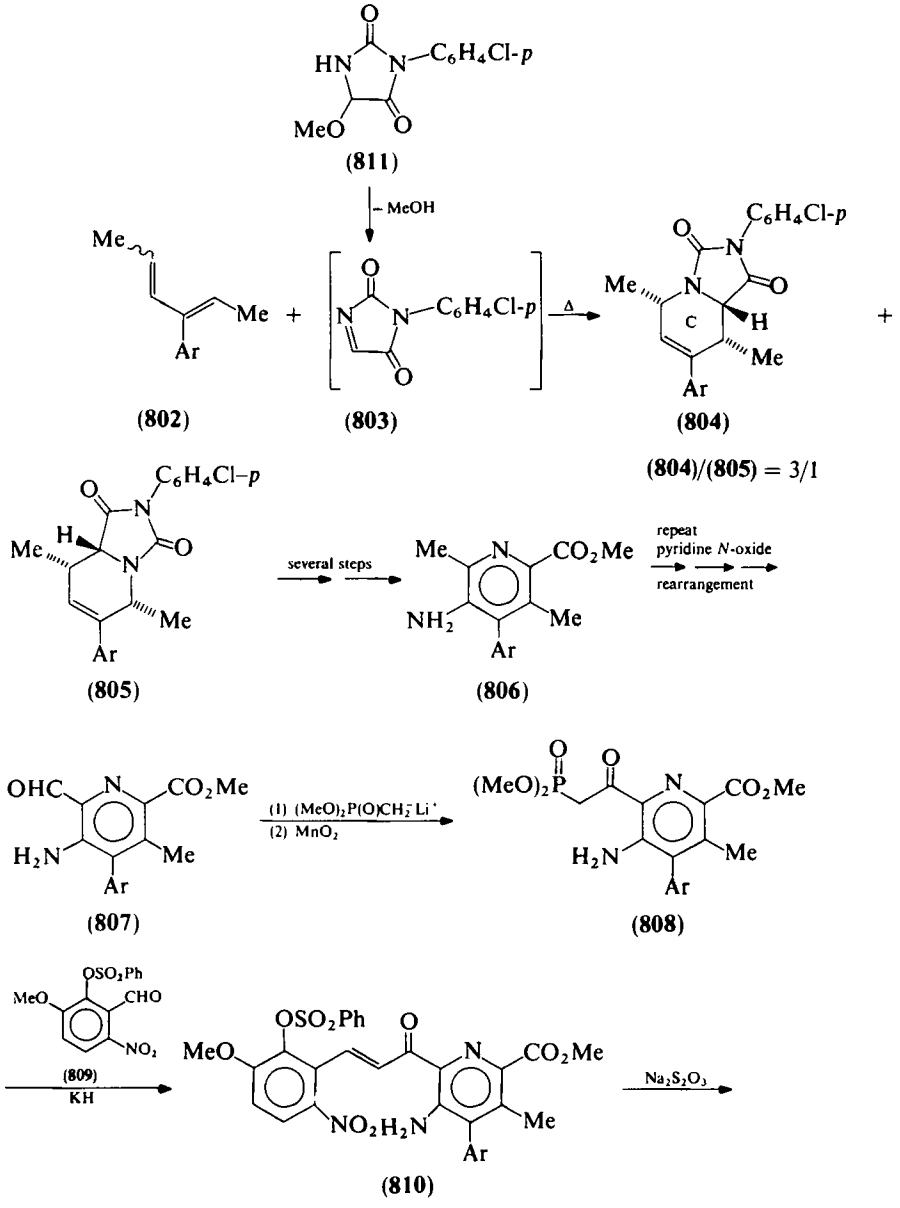


(**801**)

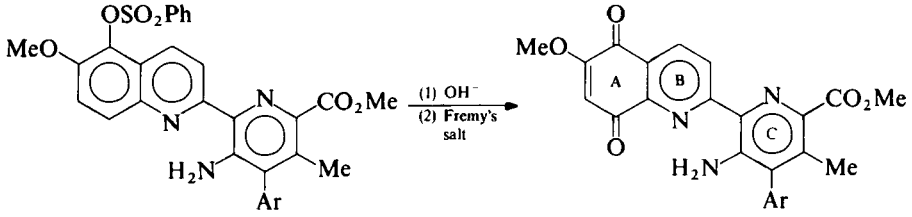
also includes most of the fragment or partial synthesis. Three approaches of the total synthesis are given here.

The major problem in the total synthesis is the binding of the fully functionalized four rings A–D. The first synthesis is due to Weinreb and coworkers[485]. Most of the reactions

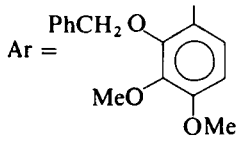
are concerned with the modification of the substituents on ring C. The order of construction of the four aromatic rings is D → CD → ACD → ABCD (Scheme 65). Ring C is synthesized by a Diels–Alder annulation of the diene (**802**) with a dienophile (**803**), which is generated *in situ* from **811**, as a major isomer and it is subsequently converted to the



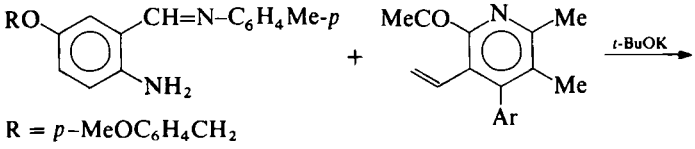
SCHEME 65 (continued)



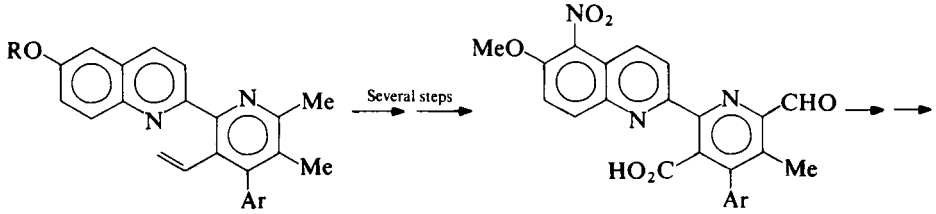
(812) (813)



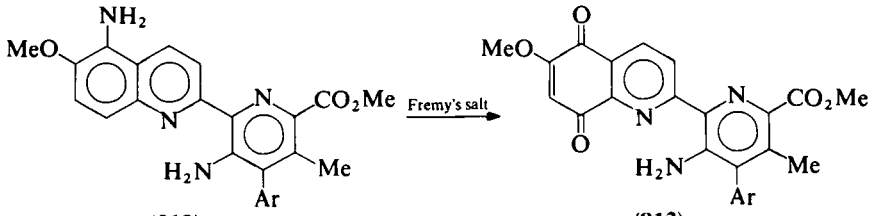
SCHEME 65



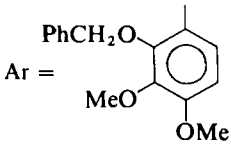
(814) (815)



(816) (817)



(818) (813)

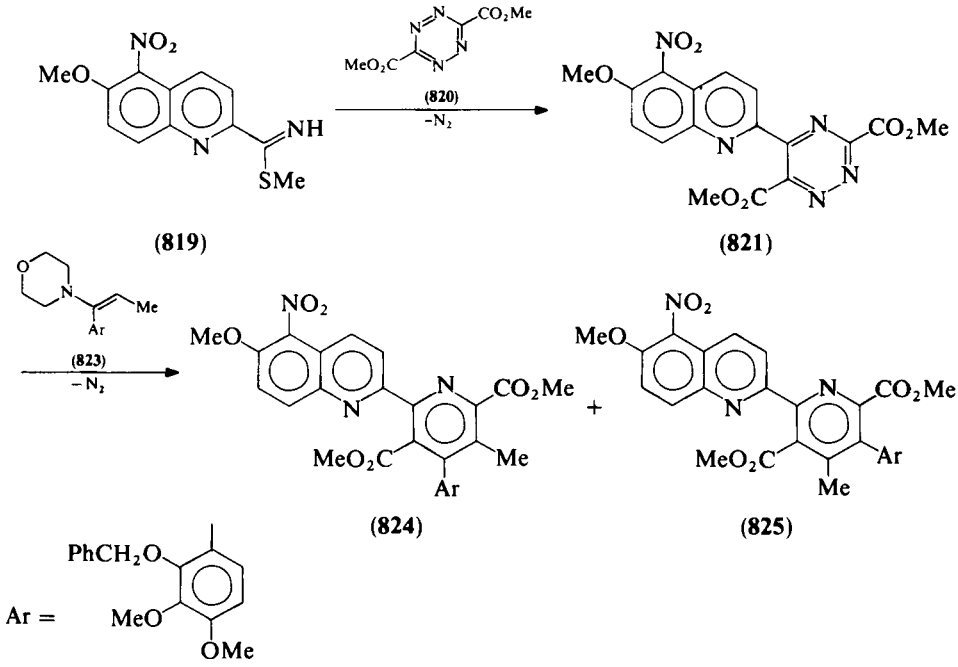


SCHEME 66

pyridine derivative (**806**). After the introduction of the remaining functionalities by means of a repeated use of pyridine *N*-oxide rearrangement, the nitrochalcone (**810**), derived via a Horner–Emmons reaction of **808**, is reductively cyclized to a quinoline (**812**) by a modification of Friedlander quinoline synthesis. The corresponding free phenol obtained from **812** is oxidized by Fremy's salt to give quinolinoquinone (**813**), which is converted to streptonigrine (Scheme 65)[485].

A modified Friedlander quinoline synthesis is also applied in the total synthesis given in Scheme 66[486,487]. Condensation of iminoaniline (**814**) with the acyl pyridine (**815**) in the presence of *t*-BuOK gives the expected quinoline (**816**) in excellent yield. The remaining operation is the conversion of the functionalities on the A and B rings of **817** to the appropriate ones in **818**. Finally, oxidation of the aminoquinoline (**818**) with Fremy's salt gives the same product (**813**) discussed above.

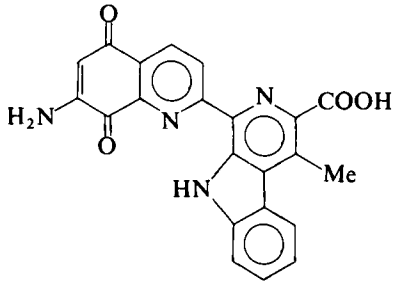
The third approach is based on the inverse electronic demands of azadienes in a Diels–Alder reaction for the construction of the C ring (Scheme 67)[488]. Diels–Alder



SCHEME 67

reaction of the 1,2,4,5-tetrazene (**820**) as the electron-deficient component with the electron-rich thioimide (**819**) gives the corresponding 1,2,4-triazene (**821**). A following annulation reaction with the enamine (**823**) affords the two regioisomeric pyridines, **824** and **825**. The [4 + 2] annulation reaction gives under high pressure a higher proportion of the desired compound (**824**). This procedure is very elegant due to the simplicity of its strategy. A following reaction of **824** affords an important precursor to streptonigrin.

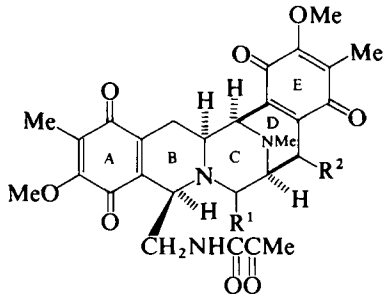
The synthesis of lavendamycin (**826**)[489,490], which is the hypothetical precursor in streptonigrin biosynthesis, has also been reported.



(826)

4. Saframycin

Saframycins are antitumor antibiotics isolated from *Streptomyces lavendulae*[491]. They have a characteristic isoquinoline unit and the structurally similar two components are bound at the central ring. The symmetrical structure is utilized in the total synthesis of



(827)

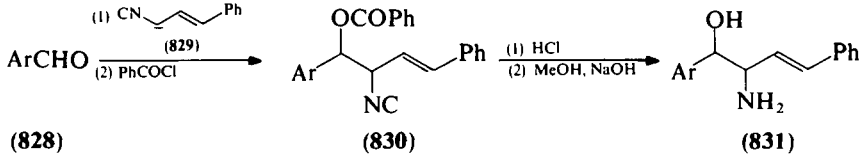
a: $R^1 = CN$, $R^2 = H$
b: $R^1 = R^2 = H$
c: $R^1 = H$, $R^2 = OMe$

827b (Scheme 68)[492]. The key fragments, **831** and **832**, both of which are prepared from the same aromatic aldehyde (**828**), are coupled to give amide **833a**. Aminoaldehyde **834**, which is obtained from **833a** in several steps, undergoes an intramolecular 'phenolic cyclization' between aromatic ring, then the condensation between the amino and the formyl groups gives **835** in a stereoselective manner. For the final construction of B ring from **836**, the same reaction with a protected glycyl aldehyde is efficiently utilized.

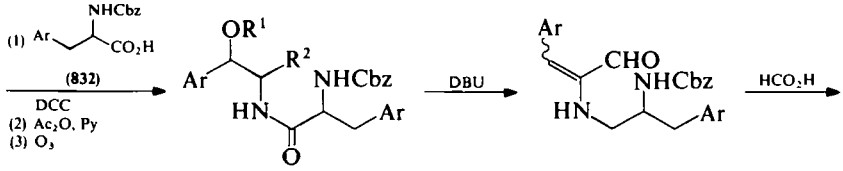
Partial synthesis of the right-hand half of the structure is obtained by means of a double cyclization method[112c]. The reaction proceeds by an electrophilic attack of the intermediate immonium salt on the aromatic nucleus (equation 178).

5. Naphtholidinomycin

Naphtholidinomycin (**842a**) is isolated from *Streptomyces lusitanus*, and its hexacyclic structure as well as those of other three homologues derivatives (**842b**)–(**842d**) is one of the

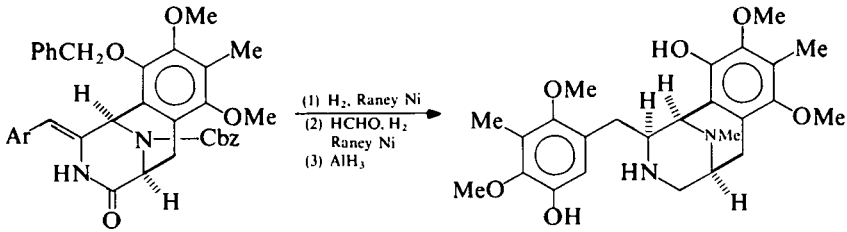


(828) (830) (831)

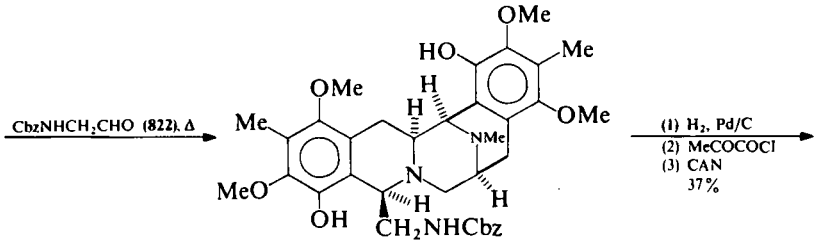


(833) (834)

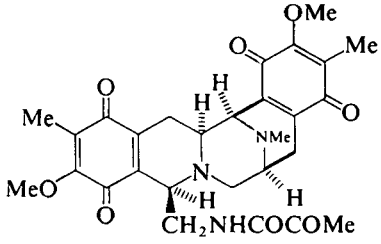
a: $R^1 = H$, $R^2 = CH = CHPh$
b: $R^1 = Ac$, $R^2 = CH = CHPh$
c: $R^1 = Ac$, $R^2 = CHO$



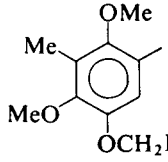
(835) (836)



(837)

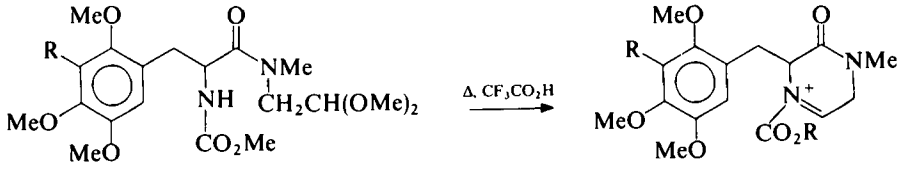


(827b)

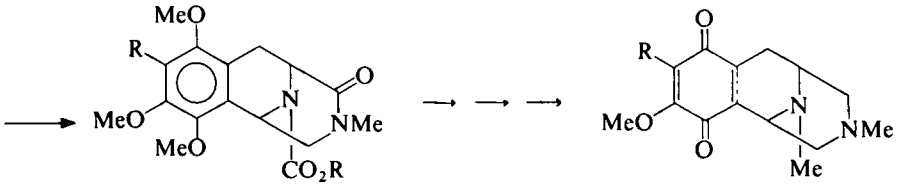
Ar = 

; Cbz = $PhCH_2OCO$

SCHEME 68



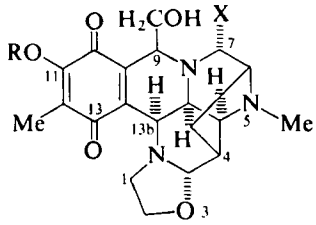
(838) (839)



(840) (841)

(178)

most complex quinonoid metabolite structures isolated from bacteria[493-495]. Recently, they are of interest due to their marked antitumor and antibiotic activity. Three synthetic approaches to naphtholidinomycin are reported so far. The first attempt is based on a

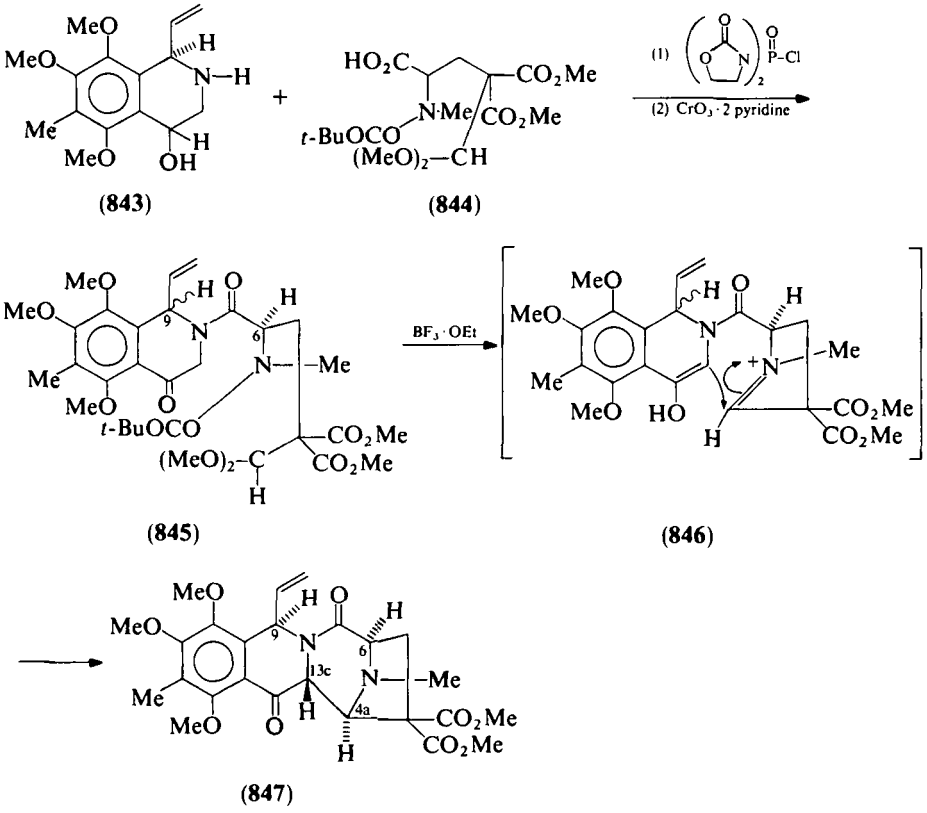


(842)

a: X = OH, R = Me
b: X = CN, R = Me
c: X = OH, R = H
d: X = CN, R = H

naphthyridinomycin
cyanocycline

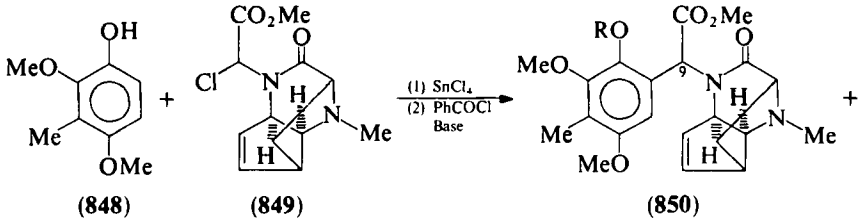
double cyclization reaction of the tetrahydroisoquinoline derivative (**843**), which involves an amide formation between two corresponding fragments **843** and **844** (Scheme 69)[496]. This reaction was originally shown in the partial synthesis of saframycin[112c]. Oxidation of a benzylic hydroxyl group of **843** gives a mixture of diastereoisomers at C(6) and C(9) of the coupling product **845**. $BF_3 \cdot OEt_2$ treatment of **845** at elevated temperature gives **847**, whose stereochemistry at C(13c) is assigned to be an unnatural form, in 30% yield. This double cyclization reaction presumably involves deprotective immonium ion (**846**) formation and a subsequent nucleophilic cyclization between the enol and the immonium ion moieties. This cyclization occurs from the less hindered site of **846** due to the steric interaction between the vinyl group at C(9) and the *N*-methyl group.



SCHEME 69

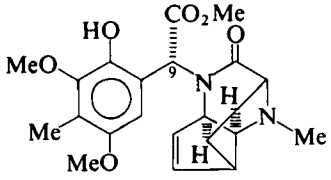
The second approach involves the formation of the isoquinoline ring from two components by means of an intramolecular amidoalkylation, which in the reaction of **848** affords stereoselectively **850a** in 56% yield (Scheme 70)[497]. This stereoselectivity is attributed to a diastereoface selective reaction of a Lewis acid complexed intermediary immonium salt. The benzyl ether of **850** is subjected to sequential ozonolysis and reductive workup to afford an isomeric mixture of the corresponding hemiacetals (**852**). A successive chlorination and Friedel–Crafts type cyclization gives **854**, which possesses most of the required functionalities and carbon skeleton, and is therefore considered as a promising synthetic precursor of (±)-naphtholidinomycin.

A total synthesis of the rather stable congener cyanocyclinone (**842b**) was accomplished by means of 'phenolic cyclization' of the immonium salt (**859**) (Scheme 71)[498]. **850** was converted to the dialdehyde (**857**), which was cyclized with the *O*-protected aminoethanol to give **858**. Acid treatment of **858** gave stereoselectively the cyclized product (**860**) in a fair yield, presumably via iminium salt **859**. Due to the difficulty of the direct and selective reduction of the amido group of **860**, the silatropic product (**861**) derived from (**860**) was stereoselectively reduced to **862** and then converted to the corresponding nitrile derivative (**863**), whose deprotection and an aereal oxidation gave racemic cyanocyclinone, (±)-**842b**.



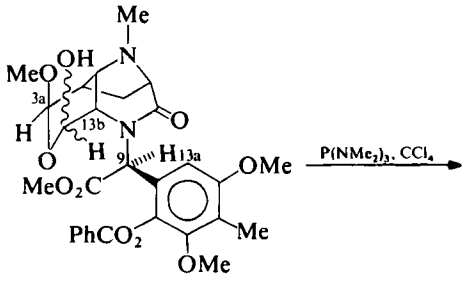
(848) (849) (850)

a: R = H
b: R = COPh

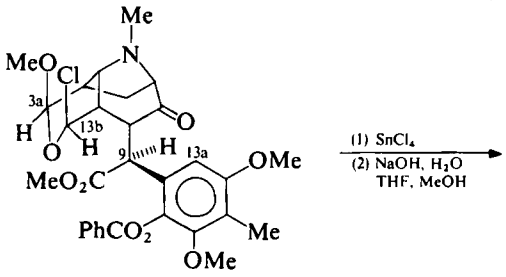


(851)

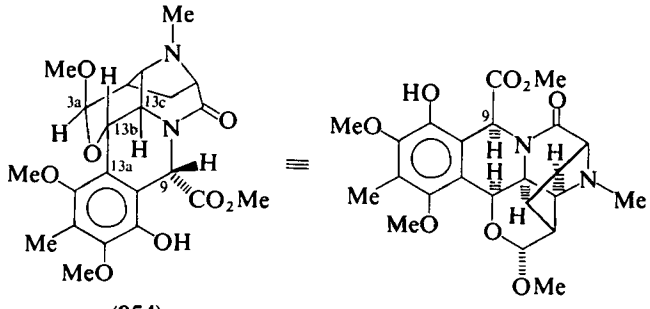
(850a)/(851) = 5.6/1



(852)

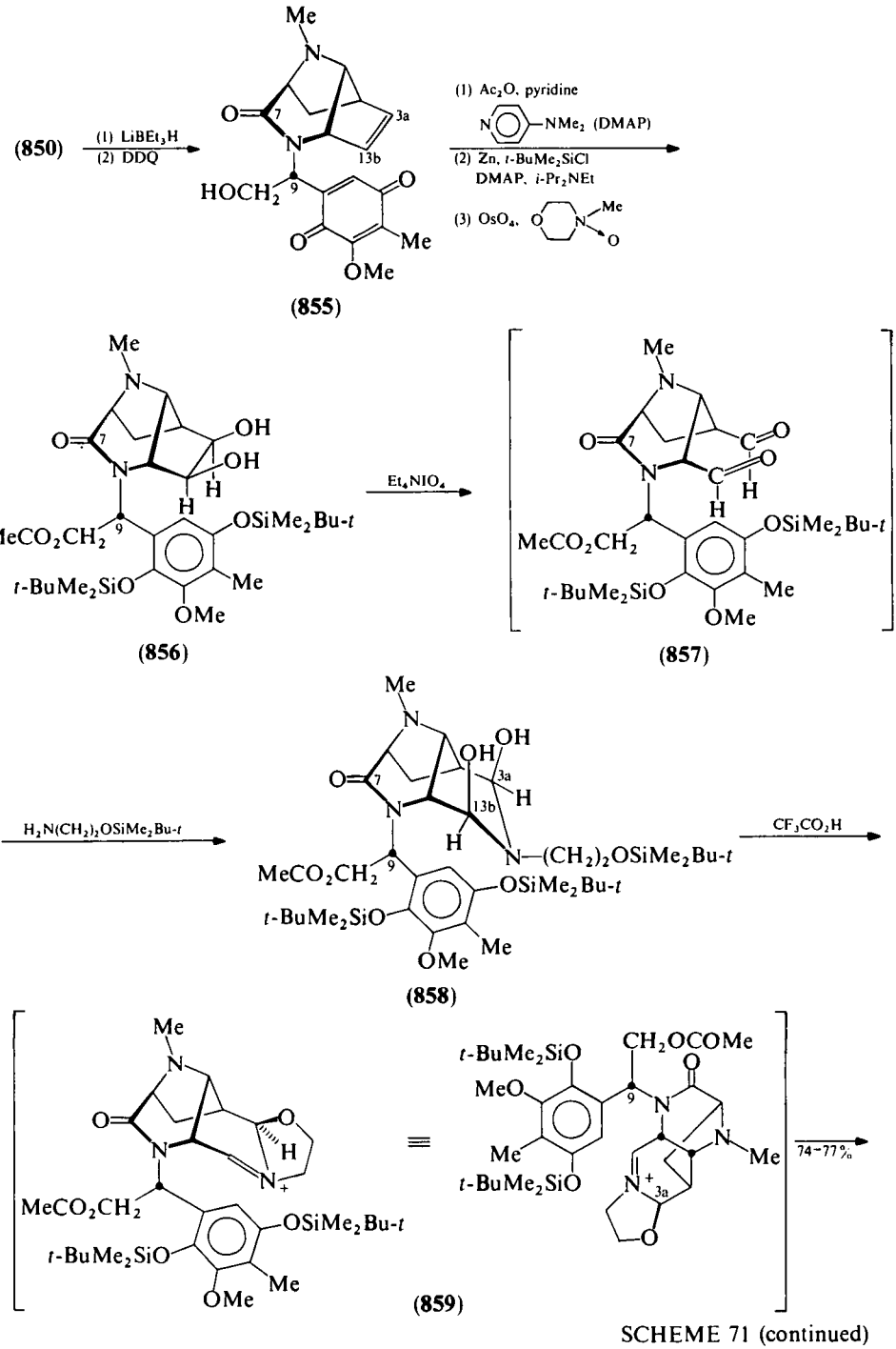


(853)

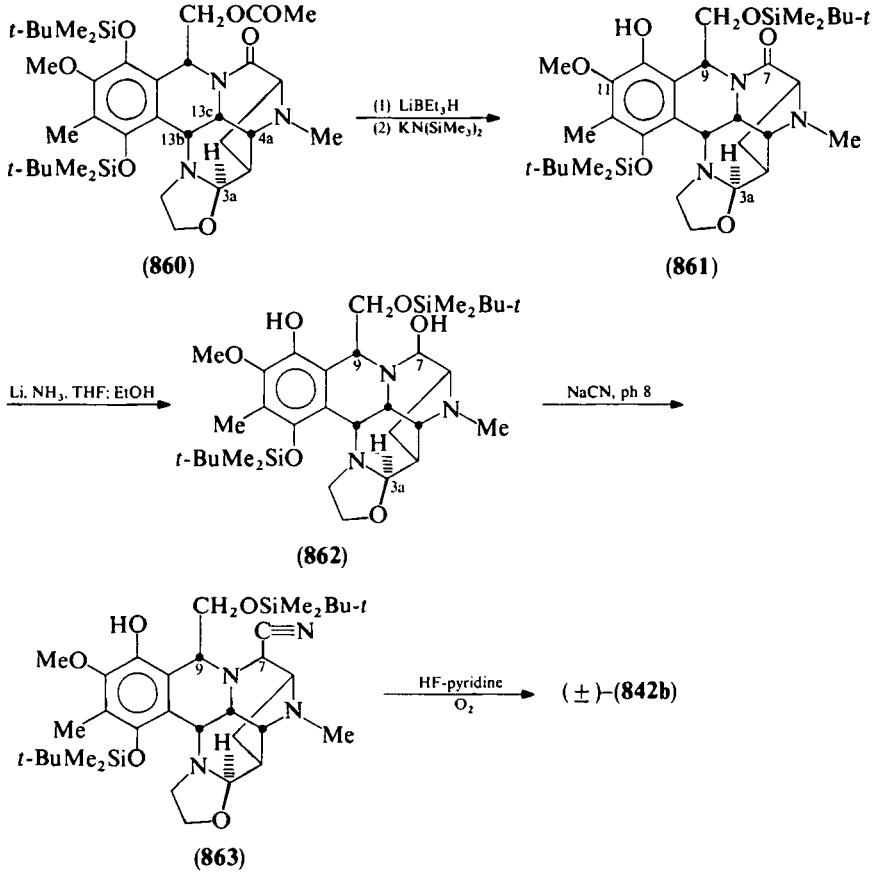


(854)

SCHEME 70



SCHEME 71 (continued)



SCHEME 71

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CHAPTER 9

ortho-Quinonoid compounds

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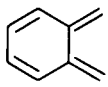
→ 1985

I. INTRODUCTION

A. Reactivity Trends

o-Quinodimethane (*o*-xylylene) (**1**) is a reactive intermediate that dimerizes at −150°C to give the Diels–Alder (spiro-) dimer (**2**). This reactivity as a Diels–Alder diene is manifested to some extent by the variety of other molecules which contain a structural unit related to **1** and even extends to the polynuclear aromatic compound anthracene. Successive replacement of the exocyclic methylene groups of **1** by oxygen atoms leads to increasingly stable compounds. *o*-Quinone methide (**3**) appears to be stable[1] at −50°C but



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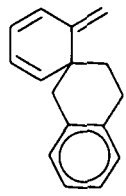

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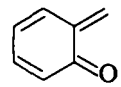

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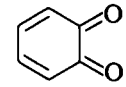
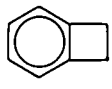
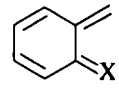


(4)

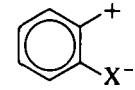
trimerizes at $-20\,^{\circ}C$, and *o*-benzoquinone (**4**) is an isolable crystalline solid which, however, dimerizes readily and can act as both a homo- and a heterodiene in cycloaddition reactions[2]. *o*-Quinodimethane (**1**) is less stable[3] than its bicyclic valence tautomer, benzocyclobutene (**5**), by 10.5 kcal mol^{-1}. The importance of the *o*-quinonoid tautomer in the equilibrium **6** $\rightleftharpoons$ **7** is expected to increase as the electronegativity of X increases and the contribution of the dipolar canonical form (**8**) to the structure of **6** becomes more likely[4].



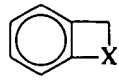
(5)



(6)



(8)



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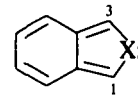
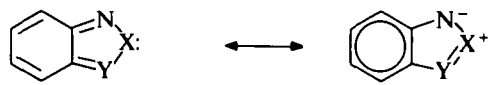


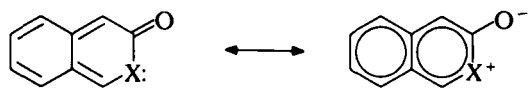
(9)

Indeed benzoxetes (**7**; X = O) are unknown whereas *o*-quinone methides (**6**; X = O) are well known both as reactive intermediates and in certain cases as stable isolable compounds[1]. Although there are no reports of the isolation of a benzoxete, benzothietes (**7**; X = S) and benzazetidines (**7**; X = NR) are stable compounds that can arise by ring-closure of *o*-thioquinone methides (**6**; X = S) and *o*-quinomethide imines (**6**; X = NR) respectively.

The 10π-electron aromatic compounds (**9**; X = O, NH, S) dimerize less readily than *o*-quinodimethane and can be obtained in crystalline form at low temperature. However, they are sensitive to oxygen and polymerize readily and none survives long at $20\,^{\circ}C$. In contrast several stable compounds result by replacement of C(1) and C(3) in **9** by heteroatoms. Of the stable compounds **10** (Y = CH, X = O); **10** (Y = CH, X = S),



(10) (11)

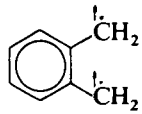


(12) (13)

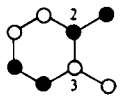
10 (Y = CH, X = NH) and **10** (Y = N, X = S) only the first is reported[5] to react as a Diels–Alder diene. No doubt the lack of pronounced *o*-quinonoid reactivity in these compounds is associated with important contributions from dipolar canonical forms like **11**. Likewise the stability of **12** (X = NH), an isolable crystalline solid[6] which prefers the quinolone tautomeric form (at least in polar solvents[6]) can be attributed to important contribution from the dipolar aromatic structure (**13**, X = NH). In contrast the *o*-quinonoid pyrone (**12**, X = O), for which the dipolar canonical form (**13**, X = O) would be expected to be less important, is stable only at low temperature[7].

B. Biradical Character

On many occasions triplet biradical structures like **14** have been considered for **1** and its derivatives or alternatively biradical character has been attributed to *o*-quinonoid compounds. The highest occupied molecular orbital (HOMO) of *o*-quinodimethane (**15**) would be expected to be of higher energy than the HOMO (**16**) of octatetraene as the result

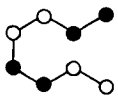


(**14**)



$E = +0.295\beta$

(**15**)



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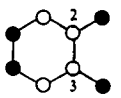
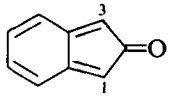


$E = -0.295\beta$

(**17**)

of antibonding interaction between C(2) and C(3) in **15**. Similarly bonding C(2)–C(3) interaction in the lowest unoccupied MO (LUMO) of *o*-quinodimethane (**17**) would be expected to lead to a lower energy LUMO for **1** than for linear octatetraene. *o*-Quinodimethane would therefore be expected to have a lower HOMO–LUMO energy gap than its linearly conjugated counterpart. The energy gap calculated by simple Hückel calculations[8] (0.59 β) is 0.1 β smaller than that calculated for linear octatetraene. The high energy HOMO and low energy LUMO of **1** can account for its easy dimerization and its reactivity towards both electron-rich and electron-deficient olefins. However, the energy gap appears too large to allow serious consideration of a biradical structure for **1**. Even cyclobutadiene, for which the predicted energy gap is zero, escapes a biradical structure by Jahn–Teller distortion involving a rectangular structure with bond alternation. No experimental evidence for the biradical structure **14** has been obtained. Nor is such evidence forthcoming for 2,3-naphthoquinodimethane for which the predicted HOMO–LUMO energy gap is smaller (0.34 β).

Inden-2-one (**18**) is an even more extreme case. For **18** simple Hückel MO calculations make the alarming prediction that the orbital **19** is the HOMO ($E = +0.443\beta$) and **20** the LUMO ($E = +0.295\beta$). The orbital **19** can be seen to be the LUMO **17** of *o*-quinodimethane perturbed to lower energy by bonding combination with a carbonyl π^* orbital whilst the orbital **20** is essentially the unperturbed HOMO **15** of *o*-quinodimethane. The stabilization of the LUMO **17** of *o*-quinodimethane is unlikely to be so great that it becomes the HOMO of **18**; in related calculations localization of the double



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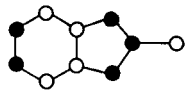

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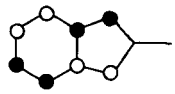
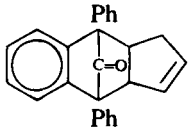


(20)

bonds prevents this situation actually arising[9]. Indeed derivatives of **18** add to one double bond of cyclopentadiene to give **21** rather than 1,4- to the diene system[10]. The observed mode is the mode of addition expected of a molecule with a HOMO of the symmetry **20** and a LUMO with the symmetry **19** rather than vice versa. Thus **20** is the HOMO and **19** the LUMO of inden-2-one (**18**). The LUMO of **18** will be of lower energy than that of *o*-quinodimethane but **1** and **18** will have HOMOs of similar energy. Accordingly **18**, with a



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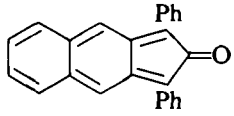
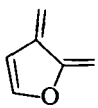


(22)

reduced HOMO–LUMO energy gap, would be expected to show more biradical character than **1**. Since both the 1,3-diphenyl derivative of **18** and the benz[*f*]inden-2-one (**22**) add stereospecifically to olefins[10] no evidence for biradical behaviour is forthcoming even in these auspicious cases.

C. Scope of the Review

In this review *o*-quinonoid compounds are discussed as a group of compounds which have many similar properties and methods of preparation. The observed differences in stability and properties form a fascinating study of reactivity. A disadvantage of this



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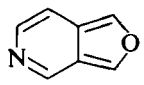

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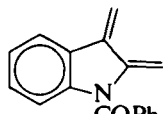

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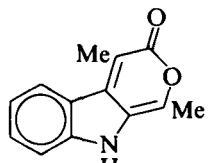

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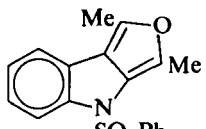

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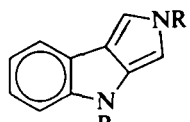
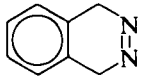


(29)

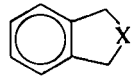
treatment is that not all routes to, or all reactions of a particular kind of *o*-quinonoid compound are described. For isobenzofurans (**9**, X = O)[11], isothianaphthenes (**9**, X = S)[12], isoindoles (**9**, X = NR)[13] and *o*-quinone methides (**3**)[1] this is not serious as the indicated reviews are available. Routes to benzocyclobutenes, which are important precursors to *o*-quinodimethanes (Section III.C), have also been reviewed[14]. Herein and in accord with the philosophy of this series attention is directed to *o*-quinodimethane, *o*-thioquinone methide and *o*-quinone methide imine derivatives which have not been the subject of review. Current interest in *o*-quinonoid compounds centers on their use in synthesis. Aspects of this subject which have not been extensively reviewed elsewhere are described in Section IV.B. Finally attention is drawn to the growing family of heterocyclic *o*-quinonoid compounds **23**[15], **24**[16], **25**[17], **26**[18], **27**[19,20], **28**[21], and **29**[22,23] whose chemistry is emerging rapidly. Space does not permit a detailed treatment of compounds of this type although they have considerable synthetic potential[18,20].

II. *o*-QUINODIMETHANE, 2,3-NAPHTHOQUINODIMETHANE AND THEIR SIMPLE STABILIZED DERIVATIVES

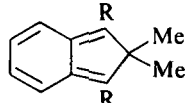
o-Quinodimethane (**1**) has been characterized by the matrix-isolation technique[24]. The 1,4-dihydrophthalazine (**30**) rapidly loses nitrogen above −40°C to give the spiro-dimer (**2**) of *o*-quinodimethane. Upon irradiation ($\lambda < 345$ nm) of a rigid glassy solution of **30** in a matrix of ether–isopentane–ethanol (EPA) at −196°C the characteristic structured UV–visible band of **1** (λ_{max} 373 nm) appears. Upon melting the glassy solution (−150°C) this absorption is rapidly replaced by that due to **2**. Irradiation in the long wavelength band



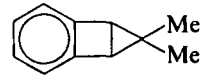
(**30**)



(**31**)

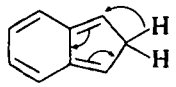


(**32**)



(**33**)

of **1** ($\lambda > 345$ nm) gave benzocyclobutene (**5**). Importantly, matrix-isolated **1** shows no half-field ESR signal and is therefore a ground state singlet; a triplet biradical structure (**14**) is ruled out for the ground state of the molecule. Irradiation of glassy solutions of several other compounds—benzocyclobutene (**5**), the sulphone (**31**, X = SO_2), indan-2-one (**31**, X = CO), the tosylhydrazone salt (**31**, X = $NNNaSO_2Tol$) and even *o*-xylene—all give **1**. However, **30** provides **1** most rapidly and cleanly. Incorporation of the reactive exocyclic diene moiety of **1** into a ring begins the design of sterically stabilized *o*-quinonoid compounds. This technique was probably first used by Alder and Fremery[25] who prepared the isoindene (2*H*-indene) (**32**, R = Ph). The stability of this compound is associated with its inability to undergo thermally allowed conrotatory electrocyclic ring-closure to a benzocyclobutene, the slow 1,5-sigmatropic shift of alkyl groups compared to hydrogen, as well as conjugative stabilization due to the phenyl groups and steric effects associated with both the phenyl and the methyl substituents. The derivative (**32**, R = H) lacking phenyl substituents was subsequently prepared[26–28]. In the absence of oxygen this compound is indefinitely stable at 20°C. Photolysis of **32** (R = H) at or below 0°C gives the pseudoindene **33**[26]. Generation of isoindene (**34**) gives dimeric species at −60°C[29] and indene by 1,5-hydrogen shift (**34**, arrows) at 0°C[28]. Steric shielding of the usually



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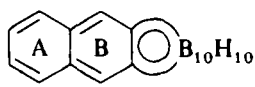

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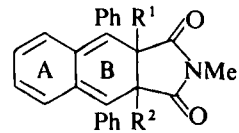
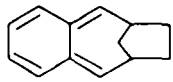


(36)

reactive ring-B diene system is held responsible for the remarkable stability of the isolable crystalline compounds **35**[30], **36** ($R^1 = R^2 = Me$)[31] and **36** (R^1, $R^2 = (CH_2)_4$)[31]. Dienophiles react with all these compounds at the normally less reactive diene system in ring A. The similar long wavelength bands in the electronic spectra of **1**, **35**, and **36** ($R^1 = R^2 = Me$) shows that they are all *o*-quinodimethanes and that in **36** ($R^1 = R^2 = Me$) the phenyl groups conjugate very little with the quinonoid system. Rather these groups are forced by steric factors to lie orthogonal to the quinonoid system in which position they provide substantial steric stabilization[31]. Steric shielding is probably also responsible for the greater stability of the *o*-quinodimethane **37** compared to **1**[32]. Irradiation of the *exo*-benzyne–norbornene adduct (**38**) in a degassed rigid matrix at 77 K gave **37** which persisted on warming the matrix to 20°C. Since irradiation of **38** in solution failed to result in ring-opening, two photons of UV light may be involved in the conversion of **38** into **37**[32].



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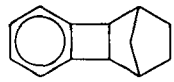

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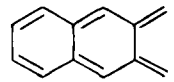
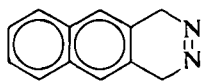


(39)

2,3-Naphthoquinodimethane (**39**) has also been observed in a matrix isolation study[33]. Irradiation of **40** in an EPA matrix at 77 K gave rise to a ruby colour (λ_{max} 541 nm) attributed to **39**. In the presence of oxygen the peroxide **41** was obtained. The latter had



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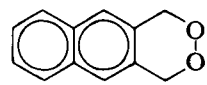
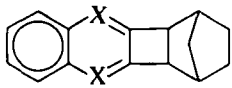
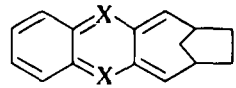


(41)

earlier been observed as a trapping product of **39**[34]. Photolysis of **42** (X = CH) in a rigid glass at −196°C gave **43** (X = CH) which was stable in fluid solution to ≈ 200 K, and in a plastic medium (polyvinyl acetate matrix) briefly to 20°C. Destruction of **43** (X = CH) was purely intermolecular with no detectable reversion to **42** (X = CH). In contrast the diaza-analogue (**43**, X = N) underwent thermally forbidden disrotatory ring-closure to **42** (X = N) at 120 K[35]. The sterically stabilized 2,3-naphthoquinodimethanes analogous to **36** ($R^1 = R^2 = Me$) and **36** (R^1, $R^2 = (CH_2)_4$) are long-lived in fluid solution at 20°C[10b].

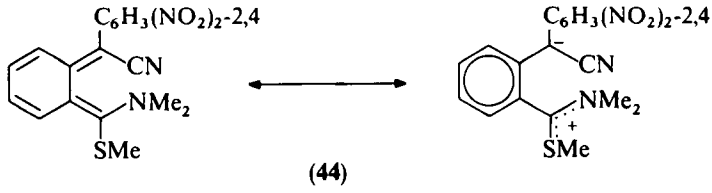


(42)



(43)

o-Quinodimethanes stabilized by push–pull resonance include **44**[36], the isobenzofulvene (**45**)[37], the highly coloured *o*-quinone methides **46**[38] and **47**[39], and the quinone methide imine **48**[40].



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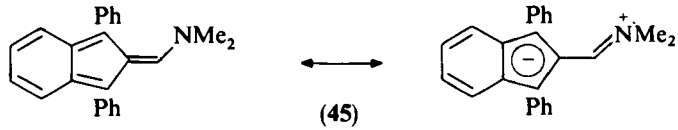

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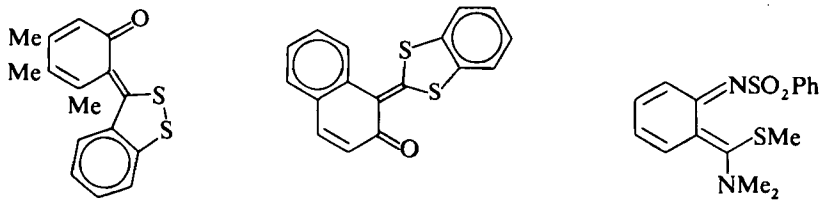
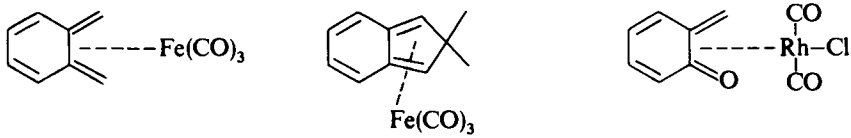


(46) (47) (48)

In common with other reactive intermediates *o*-quinonoid compounds have been isolated in the form of stable metal complexes. The first complexes of this type were **49** and **50**[41a].



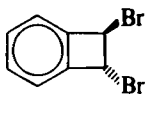
(49) (50) (51)

Subsequently several other complexes of *o*-quinodimethane have been made[41b] and the *o*-quinone methide–rhodium complex (**51**)[42] isolated.

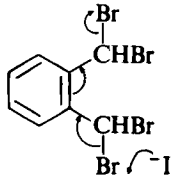
III. GENERATION OF *o*-QUINONOID COMPOUNDS

A. 1,4-Elimination Reactions

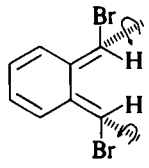
The preparation of 1,2-dibromobenzocyclobutene (**52**) by reaction of *o*-xylylene tetrabromide (**53**) with sodium iodide is an early example of the 1,4-elimination route[43]. Elimination (**53**, arrows) leads to the *o*-quinodimethane (**54**) which gives **52** by conrotatory ring-closure; **54** can be trapped with *N*-phenylmaleimide. In contrast reaction of dimethyl α,α′-dibromo-*o*-phenylene diacetate with sodium iodide gives no monomeric benzocyclobutene analogous to **52**. Rather the spiro-dimer (**55**) of α,α′-bis(methoxycarbonyl)-*o*-quinodimethane is obtained in good yield. Trapping experiments with *N*-phenylmaleimide and dimethyl fumarate strongly indicate intermediacy of the *E,E*-*o*-



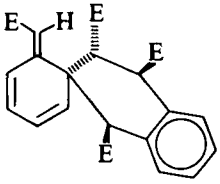
(52)



(53)

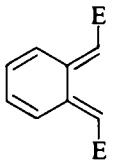


(54)



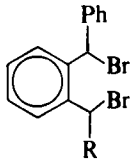
E = CO_2Me

(55)

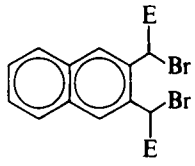


E = CO_2Me

(56)



(57)

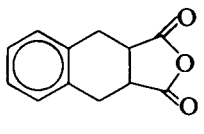


E = CO_2Me

(58)

quinodimethane (**56**) in these eliminations[44]. Upon similar debromination **57** (R = H) and **58** give mixtures of products derived by ring-closure and dimerization of intermediate *o*-quinodimethanes, whereas **57** (R = Ph) gives mainly the benzocyclobutene[45]. A similar dehalogenation route has been used to generate indole-2,3-quinodimethanes, e.g. **25**[17] (Section I.C).

1,4-Dehalogenation using zinc was used to generate *o*-quinodimethane from *o*-xylylene dibromide; in the presence of maleic anhydride the adduct **59** was formed in good yield[25a]. The use of ultrasound has been recommended to improve the efficiency of these reactions; adduct **59** is then obtained in 89% yield[46].



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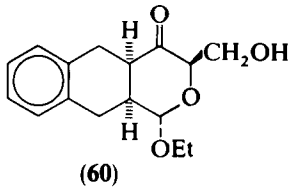
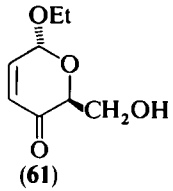


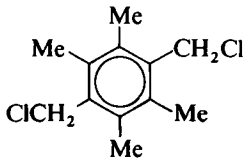
(60)



(61)

Similarly, the adduct (**60**) of *o*-quinodimethane with the moderately reactive dienophile (**61**) was obtained in 70% yield upon ultrasound-promoted zinc debromination of *o*-xylylene dibromide in the presence of **61**[47].

1,4-Dehydrohalogenation of *o*-methylbenzyl chlorides is conveniently accomplished by flash vacuum thermolysis; good yields of benzocyclobutenes are obtained under these



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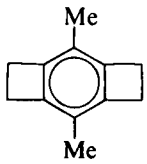
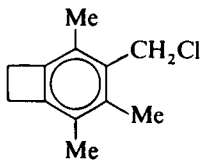
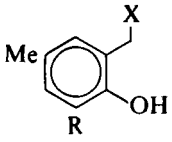


(63)

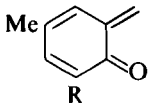


(64)

conditions and dimerization of the intermediate *o*-quinodimethane is minimized[48]. A particularly interesting example of this method[49] involves bis-dehydrohalogenation of **62** to **63** via **64**. Elimination of HCl from **65** (R = Me, X = Cl) and of HBr from **65** (R = Et, X = Br)[50] yields *o*-quinone methides **66** (R = Me) and **66** (R = Et) respectively; in the

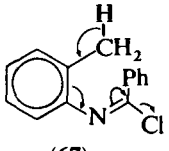


(65)

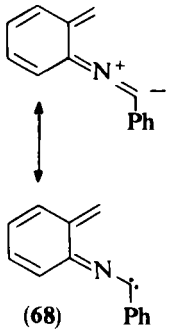


(66)

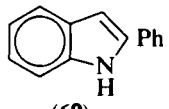
absence of traps these *o*-quinone methides form dimers. The novel *o*-quinone methide imine (**68**) has been proposed as an intermediate in the flash vacuum pyrolysis of imidoyl chloride (**67**) which affords 2-phenylindole (**69**) (76 %). This appears to be a general route to 2-phenylindoles as similar pyrolysis of **70** yields indole **72**, possibly via ring-closure of the *o*-quinone methide imine (**71**)[51].



(67)



(68)



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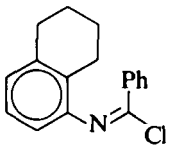

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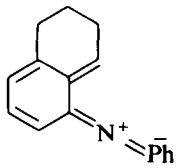

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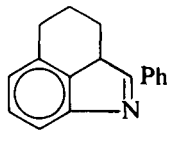
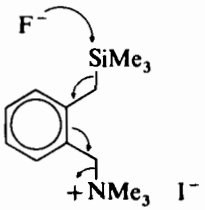
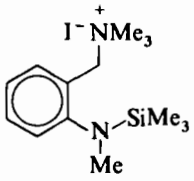


(72)

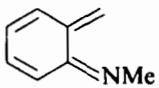
The synthetic use of *o*-quinodimethanes as reactive diene components in Diels–Alder additions has prompted the development of particularly mild 1,4-elimination methods. The fluoride ion induced elimination of the type (**73**, arrows) has been used in a neat estrone synthesis[52]. This elimination proceeds so rapidly at or below 20°C that the UV–visible band of *o*-quinodimethane can be observed (λ_{max} 367 nm) and its second order decay followed kinetically[53]. The same approach has been used to generate pyridine[52] and indole-2,3-quinodimethane[17b] systems. Similarly, *o*-quinone methide imine (**75**) can be produced at 20°C by this type of elimination of the salt (**74**). However, despite attempts to trap **75** only the dimer **76** could be isolated[54]. A related elimination has been utilized to generate *o*-quinone methides. Treatment of bis-trimethylsilyl ether (**77**) with fluoride ion produces cycloadduct (**79**) by intramolecular trapping of *o*-quinone methide (**78**)[55].



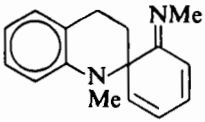
(73)



(74)



(75)



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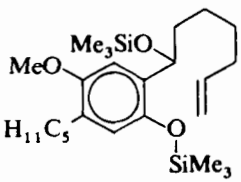

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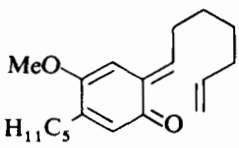

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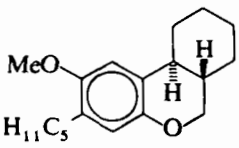
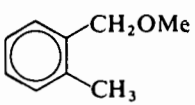
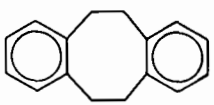


(79)

Rickborn and his collaborators have used 1,4-methanol elimination induced by a strong base to generate *o*-quinodimethanes[56]. Thus treatment of (**80**) with lithium tetramethylpiperidide (LTMP) gives both the spiro-dimer (**2**) and the linear dimer (**81**) of *o*-quinodimethane as well as a polymer. Trapping of the intermediate (**1**) can be carried out



(80)



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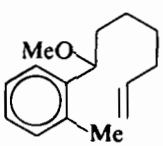
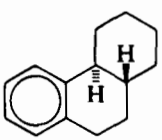
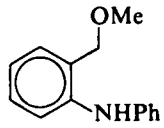


(82)



(83)

efficiently with norbornene (70%) and norbornadiene (56%). The process is also an efficient route to polycycles when trapping is intramolecular, e.g. **82** gives **83** in 71% yield on treatment with LTMP[56a].



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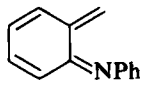

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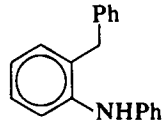
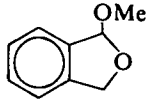


(86)

Elimination of methanol from amine ether (**84**) to yield *o*-quinone methide imine (**85**) was postulated to occur in the reaction of **84** with phenylmagnesium bromide. The ultimate formation of amine (**86**) was explained by nucleophilic attack of a second molecule of Grignard reagent on the intermediate (**85**)[57]. Methanol elimination from *o*-tolualdehyde dimethyl acetal generates 1-methoxy-*o*-quinodimethane[56b], and reaction of the cyclic acetal (**87**) with lithium di-isopropylamide (LDA) generates benzo[*c*]furan



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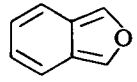

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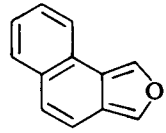
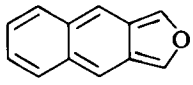


(89)

(**88**)[56c]. Acetic acid catalysed loss of two molecules of methanol from the dimethyl acetal of *o*-hydroxymethylbenzaldehyde also gives **88** which can be trapped with a variety of dienophiles[56d]. Both benz[*e*]isobenzofuran (**89**) and benz[*f*]isobenzofuran (**90**) can be



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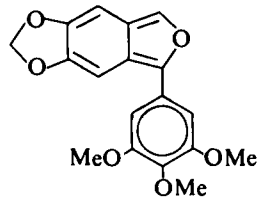
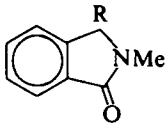


(91)

generated using the strong base elimination of acetals[58a,c] or the related acetic acid catalysed dehydration of cyclic hemiacetals[58b]; **89** is isolable[58a] whereas **90** is a reactive intermediate[58b,c]. Rodrigo and his collaborators used the acid catalysed route to generate the isobenzofuran (**91**) as part of their synthesis of podophyllotoxin[59]. A popular route to *N*-methyl-substituted isoindoles starts with addition of an alkyl-lithium to an *N*-methylphthalimidine (**92**); the adducts (**93**) undergo 1,4-elimination of water to give the isoindoles (**94**)[60]. Other *N*-alkylisoindoles have been prepared from dihydroisoindoles



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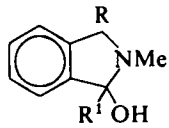

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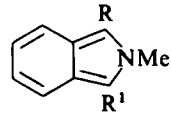
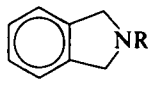
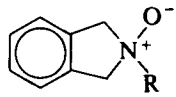


(94)

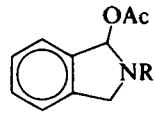
(**95**)[61] by reaction with hydrogen peroxide and dehydration of the *N*-oxides (**96**) either by heat or upon treatment with acetic anhydride. If this reaction involves Polonovski rearrangement, e.g. to the acetate (**97**) then it too is a 1,4-elimination. Related elimination



(**95**)

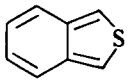


(**96**)

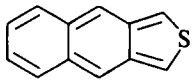


(**97**)

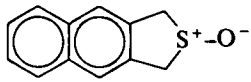
of water from sulphoxides is an excellent route to isothianaphthene (**98**)[62] and benz[*f*]isothianaphthene (**99**)[63]. The latter was deposited as a bright yellow solid at liquid nitrogen temperature following flash vacuum pyrolysis of the sulphoxide (**100**).



(**98**)

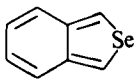


(**99**)

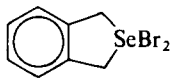


(**100**)

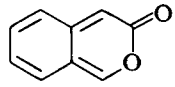
Benzo[*c*]selenophene (**101**) can be generated by treatment of the dibromide (**102**) with sodium hydroxide solution[64]. The benzopyrone (**103**) is generated by heating *o*-formylphenylacetic acid (**104**) in acetic anhydride[65]. If **104** is stirred with cold acetic



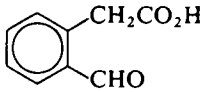
(**101**)



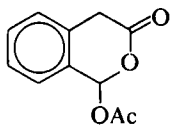
(**102**)



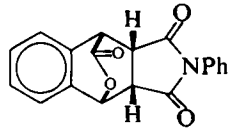
(**103**)



(**104**)

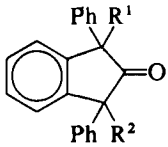


(**105**)

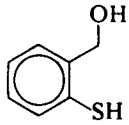


(**106**)

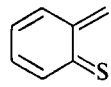
anhydride and the latter is removed under a high vacuum the residue has a PMR spectrum consistent with the presence of the pseudo-acid anhydride (**105**)[65b]. With *N*-phenylmaleimide in boiling xylene **105** undergoes 1,4-elimination of acetic acid to give the *o*-quinonoid pyrone **103** isolated as the adduct **106**[65b]. Likewise the 1,3-diphenyl derivative of inden-2-one (**18**) can be generated by acetic anhydride dehydration of **107** (R^1 = OH, R^2 = H). However, iodide reduction of **107** (R^1 = R^2 = Br) is a more efficient



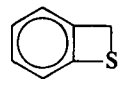
(**107**)



(**108**)

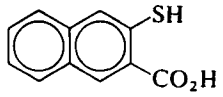


(**109**)

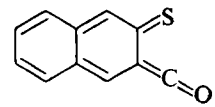


(**110**)

route to 1,3-diphenylinden-2-one[10]. 1,4-Dehydration has also been applied widely to the generation of other *o*-quinonoid species, although this usually involves the use of flash vacuum pyrolysis. For example such dehydration of thiol (**108**) produces a good yield of benzothiete (**110**) from ring-closure of *o*-thioquinone methide (**109**)[66]. Similarly, pyrolysis of carboxylic acid (**111**) at 840 °C produces naphthothioquinone methide (**112**) which



(111)



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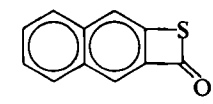
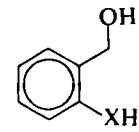


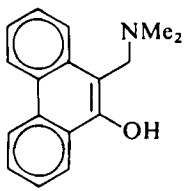
(113)

closes to the stable naphthothietone (**113**)[67]. *o*-Quinone methide imines, e.g. **85**[68,69] and *o*-quinone methide (**3**) itself[70], are produced by flash vacuum pyrolysis of amines, e.g. **114** (X = NPh) at 750 °C and the alcohol (**114**, X = O) at 600 °C respectively.



(114)

Gardener[1b] has reported that elimination of dimethylamine from amine (**115**) yields the highly unstable *o*-quinone methide (**116**) which promptly dimerizes to **117**. It should be



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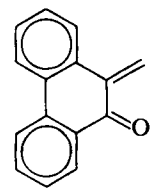

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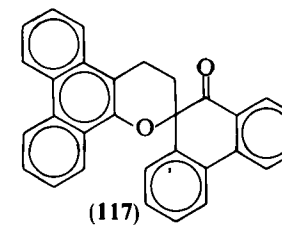
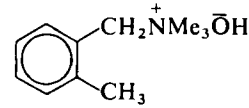


(117)

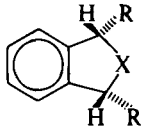
noted that Errede used vinylogous Hofmann elimination of the quaternary ammonium hydroxide (**118**) in the first detailed study of the generation of *o*-quinodimethane[71].



(118)

B. Extrusion Reactions and Reverse Diels–Alder Processes

Thermal or photochemical extrusion of a small molecule X from structures of the general type **119** is a popular route to *o*-quinodimethanes. Thus vapour phase pyrolysis of 1,3-dihydrobenzo[*c*]thiophene 2,2-dioxide (**119**, X = SO_2, R = H) gives benzocyclobutene (**120**, R = H), the linear dimer (**81**) of *o*-quinodimethane, and *o*-xylene in proportions that vary with concentration and temperature; in boiling diethyl phthalate



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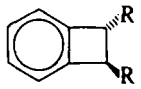
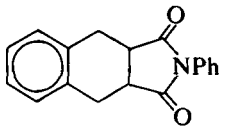
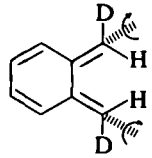


(120)

(300 °C) **119** (X = SO_2, R = H) gives **81** in 48% yield but low pressure vapour phase pyrolysis (460–670 °C) gives mainly (59–63%) benzocyclobutene[72]. Pyrolysis of **119** (X = SO_2, R = H) at 280 °C in the presence of *N*-phenylmaleimide gives the expected *o*-quinodimethane adduct **121**[72]. Thermolysis of the *cis*-dideuteriated sulphone (**119**, X = SO_2, R = D) gives **120** (R = D). This agrees with a suprafacial (*cis*) elimination of sulphur dioxide to give the *E,E*-(**122**) and *Z,Z*-dideuterio-*o*-quinodimethanes both of

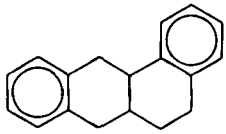


(121)

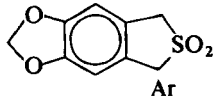


(122)

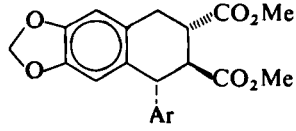
which undergo conrotatory ring-closure, e.g. **122** (arrows) to give **120**[73]. Although sulphur dioxide extrusion is a high temperature reaction it finds extensive use and can be very effective. Thus thermolysis of **119** (X = SO_2, R = H) in refluxing 1,3,5-trichlorobenzene in the presence of 1,2-dihydronaphthalene gave the adduct **123** in 92% yield[74] and thermolysis of **124** (Ar = 3,4,5-trimethoxyphenyl) at 170–210 °C in the presence of dimethyl fumarate gave the adduct **125** (> 90% yield)[75a]. The synthesis of aromatic steroids has also employed extrusion of sulphur dioxide from sulphones[76].



(123)

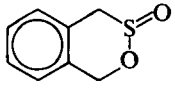


(124)

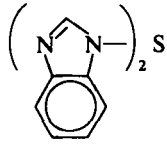


(125)

The benzo-3,6-dihydro-1,2-oxathi-in-2-oxide (**126**) extrudes sulphur dioxide at temperatures some 200 °C lower than those required for the related sulphone[77]. Heating **126** and maleic anhydride in benzene gave **59** (> 95% yield). The availability of a convenient new route to sultines like **126** involving, e.g. reaction of the reagent **127** with phthalyl



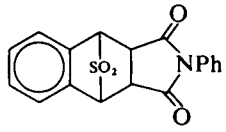
(126)



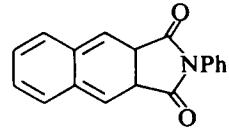
(127)

alcohol should make this route to *o*-quinodimethanes more popular[78]. It is noteworthy that in the addition of sulphur dioxide to *o*-quinodimethane the sultine **126** is kinetically favoured over sulphone (**119**, X = SO_2, R = H)[79] by a factor of 9:1.

In view of the high temperatures required for SO_2 extrusion from sulphones like **119** (X = SO_2) it is interesting that triethylamine catalyses SO_2 loss from strained cyclic sulphones like **128**. Although purely thermal extrusion of SO_2 from **128** requires heating



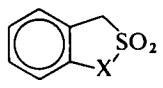
(128)



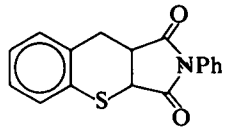
(129)

at 150–170 °C, addition of triethylamine produces **129** at 20 °C. The mechanism of this catalysis is not understood but does seem to require a strained sulphone; decomposition of **119** (X = SO_2, R = H) was not catalysed by triethylamine[80].

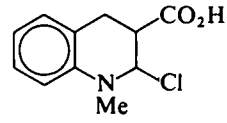
The extrusion of sulphur dioxide has also proven useful for the generation of other *o*-quinonoid intermediates. Photochemical elimination of SO_2 from **130** (X = S) yields *o*-thioquinone methide (**109**) which in the presence of *N*-phenylmaleimide gives the adduct **131** in 43 % yield. In the absence of a trap only polymeric material is obtained[81]. Photolysis



(130)

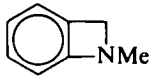


(131)

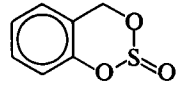


(132)

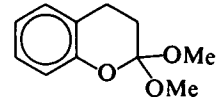
of the sultam (**130**, X = NMe) in the presence of *E*-chloroacrylic acid gives the Diels–Alder adduct (**132**) of *o*-quinone methide imine (**75**); in the absence of dienophiles, the benzazetidine (**133**) is formed in 62 % yield as a white crystalline solid. This is a rare example of the ring-closure of an *o*-quinone methide imine to the corresponding benzazetidine[82]. Photolysis of **134**, the oxygen analogue of **126**, yields *o*-quinone methide (**3**) which adds to 1,1-dimethoxyethylene to give adduct **135**[70]. However, thermal conversion of **134** to *o*-quinone methide was not reported.



(133)

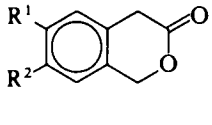


(134)

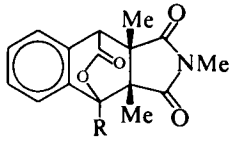


(135)

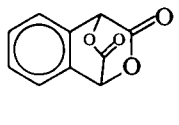
Thermal decarboxylation of isochromanones, e.g. **136** (R^1 = OMe, R^2 = H), by flash vacuum thermolysis at ca. 500 °C is a convenient route to certain benzocyclobutenes[83]. Photodecarboxylation of **137** (R = Ph) and **137** (R = Me) allowed observation of the UV–visible bands of the corresponding *o*-quinodimethanes[84]. 2-Benzopyran-3-one (**103**) can be generated either by thermal (ca. 150 °C) or photochemical decarboxylation of the bis-lactone (**138**). The photochemical method is useful in the low temperature characterization of **103**[7].



(136)

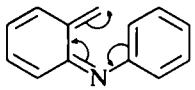


(137)

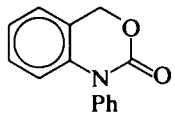


(138)

Generation of the *o*-quinone methide imine **139** by flash vacuum pyrolytic decarboxylation of the 1,4-dihydro-3,1-benzoxazin-2-one (**140**) gives acridine (**141**) by electrocyclization (**139**, arrows) and dehydrogenation. Similarly, the intramolecular Diels–Alder



(139)



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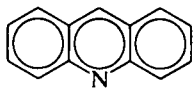
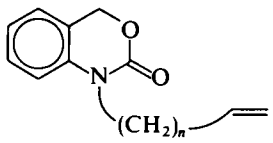
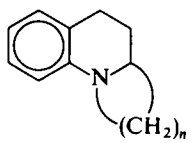


(141)

cycloadducts **143** ($n = 3$) and **143** ($n = 4$) may be obtained from pyrolysis of benzoxazinones **142** ($n = 3$) and **142** ($n = 4$) respectively, although in only moderate yield.



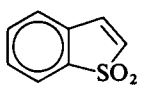
(142)



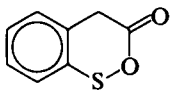
(143)

Interestingly, it was later reported that substantially higher yields of these cycloadducts can be obtained by conducting these pyrolyses in the presence of alumina or silica when the temperature required for decarboxylation is lowered by 400 °C[85].

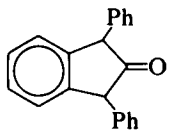
Van Tilborg and Plomp[86] have reported that pyrolysis of thianaphthene 1,1-dioxide (**144**) at 1000 °C induces an unusual rearrangement to yield benzothiete (**110**) (42 % yield). They propose a mechanism involving rearrangement of **144** to **145**, followed by decarboxylation to **109** which ring closes to **110**.



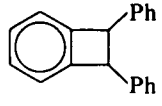
(144)



(145)



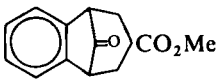
(146)



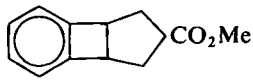
(147)

Photodecarbonylation of indan-2-ones (**146**) is the method of choice for the preparation of 1,2-diphenylbenzocyclobutenes (**147**)[87]. Irradiation of *cis*-**146** ($\lambda > 300$ mm) in ether solution gives *trans*-**147** (89 %) and only 11 % of the *cis*-isomer. Since photochemical *cis–trans* isomerization of *cis*-**146** and photodecarbonylation of *cis*-**146** involve the same singlet excited state a stepwise loss of carbon monoxide via a biradical intermediate is indicated[88a]. In agreement with loss of stereochemistry via such an intermediate, photodecarbonylation of *cis*-**146** in the crystalline state[88b] results in much greater retention of stereochemistry giving *cis*-**147** (95 %) and only 5 % of *trans*-**147**. The sterically

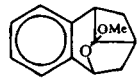
stabilized *o*-quinodimethanes (**36**) were also prepared in high yield by photodecarbonylation[31]. Similarly, photolysis of **148** gives a mixture of products **149**, **150** and **151** clearly derived from the *o*-quinodimethane intermediate (**152**). The 1,5-hydrogen shift (**152**, arrows) leading to **151** is a thermal process that is suppressed below $-40\,^{\circ}C$[89].



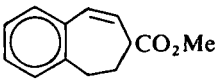
(**148**)



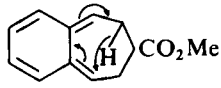
(**149**)



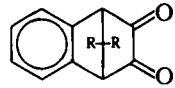
(**150**)



(**151**)

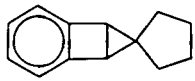


(**152**)

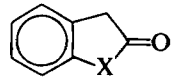


(**153**)

Photo-bisdecarbonylation of α-diketones is an effective route to isoindenes[28, 90] which, however, ring-close to pseudoindenes under the reaction conditions. Thus irradiation of **153** (R, R = $(CH_2)_4$) gives the pseudoindene **154**. Photodecarbonylation of **155** (X = O[70],



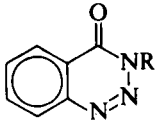
(**154**)



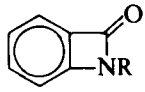
(**155**)

S[91], NPh[92]) provides *o*-quinone methide (**3**), *o*-thioquinone methide (**109**) and *o*-quinone methide imine (**85**) respectively, and flash vacuum thermolysis of **155** (X = O) gives the trimer of **3** (68%) in addition to fulvene (5.5%) and benzene (22%)[93].

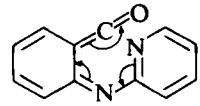
Extrusion of nitrogen from dihydrophthalazines can be carried out photochemically, a process useful in matrix isolation studies (Section II), or under very mild thermal conditions (ca. $-40\,^{\circ}C$). The easy tautomerism and thermal decomposition of dihydrophthalazines limits their preparative use. The more stable benzotriazinones **156** (R = 2-pyridyl and 2-thiazolyl) also undergo thermal loss of nitrogen[94]. However, the expected



(**156**)

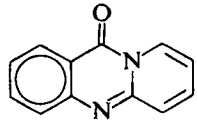


(**157**)



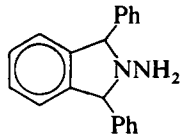
(**158**)

benzazetidinones (**157**) ring-open to *o*-quinone methide imines, e.g. **158**, which ring-close, e.g. **158**, arrows to the observed fused products, e.g. **159**.

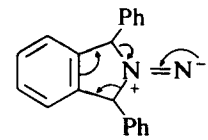


(**159**)

Oxidative loss of nitrogen from *N*-aminoisoindolenines (**160**) can be brought about by mercuric oxide or through reaction with *p*-toluenesulphonyl chloride in pyridine to give diphenylbenzocyclobutene (**147**)[95]. In either case it is believed that fragmentation of the



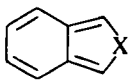
(**160**)



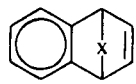
(**161**)

amino-nitrene (**161**) is involved. Although the preformed tosylate of *trans*-**160** gives *trans*-**147** (80% yield) the equally high yield conversion of the tosylate of *cis*-**160** gives *cis*-**147** and *trans*-**147** in a ratio of 3:1. Although the instability of *cis*-**147** under the reaction conditions (KOH/EtOH, 20 °C) is suggested to explain this lack of stereospecificity a non-cheletropic nitrogen loss from **161** is not ruled out.

Fragmentation involving a reverse Diels–Alder reaction has been extensively used to generate *o*-quinodimethanes of the type **162** from the adducts (**163**) readily available by addition of benzyne to the dienes **164** (X = O, X = CH_2, X = NR and X = C=CMe_2).



(**162**)

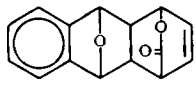


(**163**)

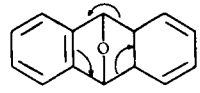
(**164**)

(**165**)

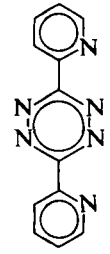
Formal removal of an acetylene unit from the benzyne adducts (**163**) to give the *o*-quinonoid compounds (**162**) can be accomplished in several ways. Most simply the reduced adducts (**165**) are subjected to flash vacuum pyrolysis which induces reverse Diels–Alder reaction (**165**, arrows). This method has allowed the preparation of both isobenzofuran (**162**; X = O)[96] and isoindole (**162**; X = NH)[97]. Fieser and Haddadin[98] reacted **163** (X = O) with α-pyrone to give the adduct **166**. In boiling toluene **166** loses carbon dioxide to



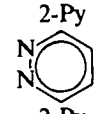
(**166**)



(**167**)

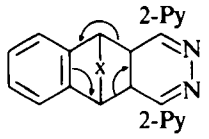


(**168**)

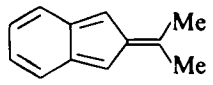


(**169**)

give **167** which then loses benzene (**167**, arrows) to give **162** (X = O). Vacuum thermolysis of **166** allowed isolation of both **162** (X = O) and the intermediate **167**[99]. Warrener[100] used the tetrazine (**168**), which behaves as an electron-deficient Diels–Alder diene, to convert **163** (X = NH) to isoindole. Reaction of **163** (X = NH) with **168** occurs at −25 °C to give **162** (X = NH) and the pyridazine (**169**). The intermediate (**170**, X = NH) which should be formed from **163** (X = NH) and **168** by Diels–Alder addition and nitrogen loss could not be detected, presumably because of its very rapid reverse Diels–Alder



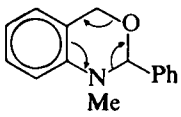
(170)



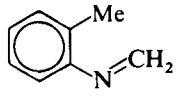
(171)

fragmentation (**170**, arrows). The oxygen analogue (**170**, X = O) although isolable dissociates to benzo[*c*]furan and **169** at 20 °C. This and related methods have been used to generate isoindene[101] and isobenzofulvene (**171**)[102].

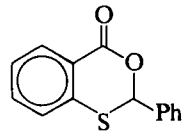
A formal reverse Diels–Alder process is involved in the flash vacuum pyrolysis of benzoxazine (**172**) which gives benzaldehyde and a trimer of imine (**173**); the latter is



(172)

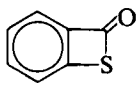


(173)

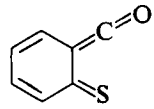


(174)

thought to arise by 1,5-hydrogen shift in the quinone methide imine (**75**) formed by the fragmentation (**172**, arrows)[69]. Similar photochemical fragmentation of **174** at 77 K gave rise to infrared absorptions consistent with formation of the thiolactone (**175**). Upon warming the product to −40 °C a dimer of **176** was isolated[103].



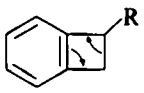
(175)



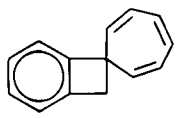
(176)

C. Electrocyclic Ring-opening Reactions of Benzocyclobutenes and Related Compounds

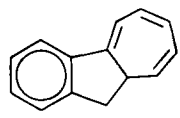
The ease of the electrocyclic ring-opening of benzocyclobutenes (**177**, arrows) is markedly dependent upon the substituents present on the four-membered ring[104]. The parent system (**177**, R = H) ring-opens on heating above 200 °C. When the substituent R



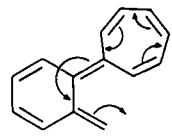
(177)



(178)



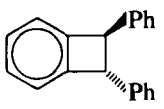
(179)



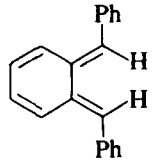
(180)

on the cyclobutene ring is capable of donating an electron pair the ease of ring-opening parallels the availability of the electron pair: **177** (R = NH_2) ring-opens at 25 °C, **177** (R = OH) at 80 °C, **177** (R = NHCOR′) at 110 °C and **177** (R = Alk) at 180 °C. The alkoxides related to **177** (R = O^-) produced by benzyne addition to enolate anions ring-

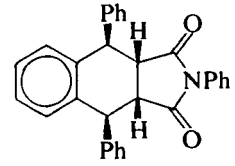
open under very mild conditions[105]. Conjugating electron-withdrawing substituents also accelerate ring-opening; the ketones (**177**; R = COR') ring-open at ca. 150°C. Substituents which are only conjugating also accelerate ring-opening, e.g. **178** is converted to **179** at 40–60 °C. Ring-opening of **178** to **180** is followed by 10π-electron ring-closure (**180**, arrows) to **179**[106]. The *trans*-diphenylbenzocyclobutene (**181**) reacts with dienophiles at 20 °C to give adducts derived from the *E*, *E*-*o*-quinodimethane (**182**)[87b]. Huisgen's



(**181**)

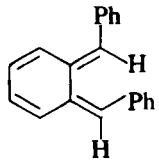


(**182**)

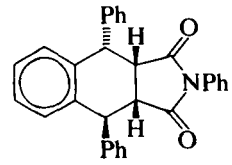


(**183**)

mechanistic investigation has shown[107] that an equilibrium between **181** and **182** precedes adduct formation. In solution at 20 °C the concentration of **182** is small but at 120 °C a yellow colour, probably due to **182** is observed. In agreement with orbital symmetry control the *trans* isomer (**181**) gives the *E*,*E*-diene (**182**), the product of least hindered conrotatory ring-opening. With *N*-phenylmaleimide this gives the *cis-endo*-adduct (**183**). The *cis* isomer of **181** undergoes slower (ca. 70 times at 80 °C) conrotatory ring-opening via a necessarily more hindered transition state (TS) involving inward rotation of one phenyl group towards the centre of the breaking cyclobutene ring. The resulting *Z*,*E*-*o*-quinodimethane (**184**) gives the adduct (**185**) with *N*-phenylmaleimide. The preference for

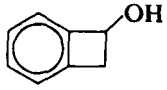


(**184**)

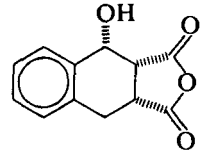


(**185**)

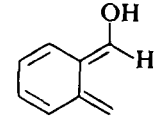
outward rotation of a substituent on the benzocyclobutene ring extends to monosubstituted benzocyclobutenes and is particularly marked when the substituent is an electron donor. Thus benzocyclobutenol (**186**), available by photolysis of *o*-tolualdehyde[108a], gives only the adduct (**187**) derived by *endo*-addition of the *E*-dienol (**188**) with maleic



(**186**)

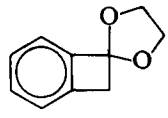


(**187**)

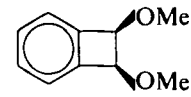


(**188**)

anhydride[108b]. The acetal (**189**) and the *cis*-1,2-bismethoxybenzocyclobutene (**190**) for which conrotatory ring-opening would necessarily involve inward rotation of one oxygen substituent fail to undergo ring-opening[108c]. The effect of substituents on the rate and stereochemistry of benzocyclobutene ring-opening noted above are paralleled in the ring-opening of simple cyclobutenes, and have been discussed and rationalized[109]. Steric effects

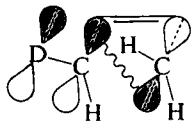


(189)

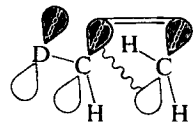


(190)

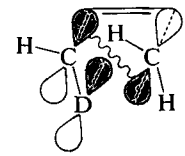
are only partly responsible for the preferred outward rotation of alkoxyl groups in the ring-opening of simple cyclobutenes. Good quality calculations trace the electronic contribution to reduced destabilizing donor $\leftrightarrow\sigma$ interaction (**191a**) and improved stabilizing donor $\leftrightarrow\sigma^*$ interaction (**191b**) in the transition structure (**191**) for outward rotation in comparison with better destabilizing donor $\leftrightarrow\sigma$ overlap (**192a**) and poorer stabilizing



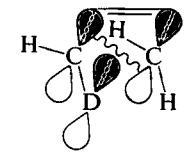
(191a)



(191b)



(192a)

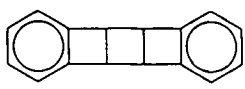


(192b)

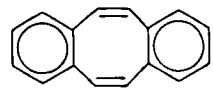
D = donor atom; ∿∿ = breaking σ-system

donor $\leftrightarrow\sigma^*$ overlap (**192b**) in the transition structure (**192**) for inward rotation[109]. The HOMO and LUMO of the transition structures **191** and **192** are to a good approximation σ and σ^* of the breaking cyclobutene σ-bond.

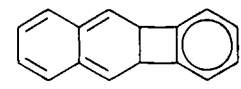
Even when allowed conrotatory ring-opening of benzocyclobutenes is prevented by ring-fusion, *o*-quinodimethanes may be obtained under mild conditions when ring-strain is relieved, e.g. pseudo-indene (**33**) gives isoindene (**32**, R = H) above 0 °C[26]. Similarly **193** gives **194** at 180 °C. This conversion is dramatically accelerated by Ag(I) salts, occurring almost instantly at 20 °C. The presumed *o*-quinodimethane intermediate (**195**) is then



(193)

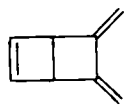


(194)

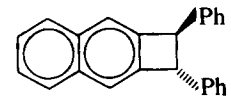


(195)

efficiently trapped by *N*-phenylmaleimide[110]. The novel *o*-quinodimethane precursor, Dewar *o*-quinodimethane (**196**), ring-opens[111] at 60 °C. The greater aromaticity loss accompanying ring-opening to give 2,3-naphthoquinonoid systems is reflected in the great



(196)

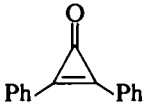


(197)

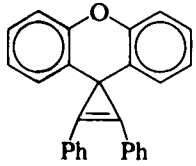
difficulty of such reactions. Whereas *trans*-1,2-diphenylbenzocyclobutene reacts with *N*-phenylmaleimide at 20 °C, **197** requires fusion with the dienophile at 150 °C for adduct formation[112].

There are few simple examples of the electrocyclic ring-opening of benzothietes, benzazetidines and benzoxetes. In agreement with theoretical prediction[4] (Section I.A)

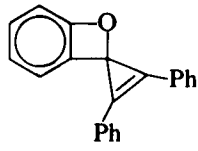
benzoxetes appear to be much less stable than their ring-opened *o*-quinone methide tautomers and in several reactions where benzoxetes could have been produced the isolated products can be seen to be derived from the corresponding *o*-quinone methides. For instance, generation of benzyne in the presence of diphenylcyclopropenone (**198**) gives **199**



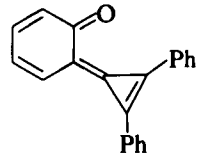
(**198**)



(**199**)

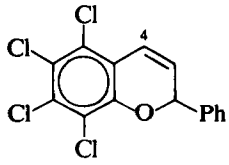


(**200**)

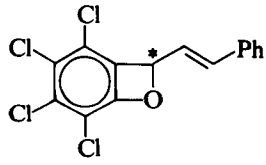


(**201**)

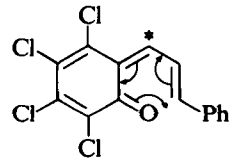
which is probably derived by addition of benzyne to the carbonyl group of **198** to give benzoxete (**200**) which undergoes rapid ring-opening to the *o*-quinone methide (**201**); addition of benzyne to **201** then affords **199**[113]. Similarly addition of tetrachlorobenzyne to cinnamaldehyde gives the chromene (**202**)[114]. In this case when the carbonyl carbon of



(**202**)



(**203**)

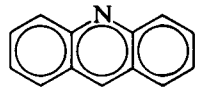


(**204**)

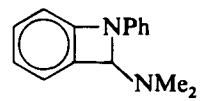
cinnamaldehyde is labelled the label appears at C(4) of the product (**202**). This agrees with intermediacy of the benzoxetene (**203**) and its rapid ring-opening to the quinone methide (**204**) which undergoes the indicated 6π-electron electrocyclic ring-closure to **202**.

In a similar attempt to prepare benzazetidines, benzyne was generated in the presence of amidine (**205**)[115]. This produced acridine (**206**) in place of the expected **207**. Initial

(**205**)

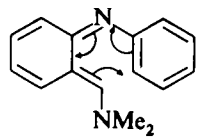


(**206**)



(**207**)

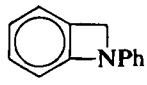
formation of **207** followed by ring-opening would give **208**, which upon 6π-electrocyclization (**208**, arrows) and loss of dimethylamine would give **206**. Rapid



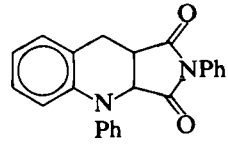
(**208**)

electrocyclic ring-opening of **207** may be associated with the presence of the strongly electron-donating NMe_2 group. Certainly other benzazetidines appear to be more stable;

thus **209** was heated with *N*-phenylmaleimide at 200 °C to form the adduct (**210**)[116]. Benzothiete **110** is also a stable isolable compound which undergoes ring-opening only if

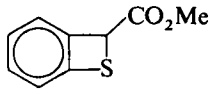


(**209**)

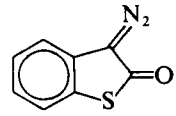


(**210**)

heated to 140 °C; the *o*-thioquinone methide produced can be trapped, and in the absence of traps forms a dimer. Although the benzothiete **211** is available via Wolff rearrangement of the diazo compound **212** by photolysis in methanol its ring-opening does not appear to

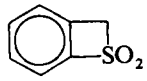


(**211**)

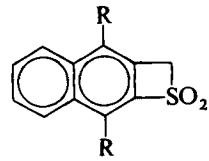


(**212**)

have been studied[117]. The thiete-1,1-dioxides **213**[118] and **214** (R = H and Ph)[119, 120] are also known but their ring-opening does not appear to have been achieved.



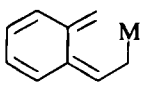
(**213**)



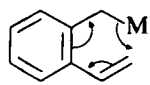
(**214**)

D. Sigmatropic Shifts

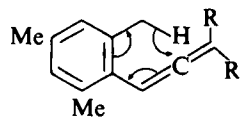
In principle *o*-quinodimethanes with *Z*-geometry (**215**) are available by 1,5-shift of a group M in the styrenes (**216**). This route has not been much exploited although at 170 °C



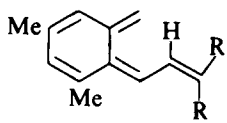
(**215**)



(**216**)

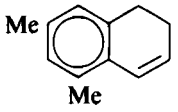


(**217**)

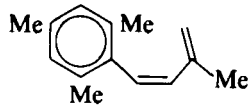


(**218**)

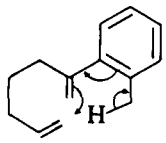
the allenes (**217**, R = H or Me) undergo a 1,5-hydrogen shift which involves as migration terminus the particularly reactive central carbon of the allene unit (**217**, arrows) to give the *o*-quinodimethanes (**218**, R = H or Me); **218** (R = H) cyclizes to dihydronaphthalene (**219**) and **218** (R = Me) undergoes antarafacial 1,7-hydrogen shift to the diene (**220**)[121]. An example of a photochemically driven process that is formally a 1,5-shift (**221**, arrows) converts **221** into **222** and **223**[122]. Here the expected *E*-*o*-quinodimethane (**224**) can account for the *trans* isomer (**222**) formed, by assuming an *exo*-selective internal



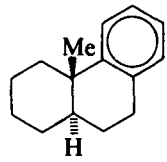
(219)



(220)

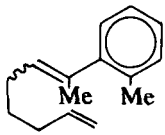


(221)

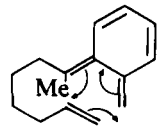


(222)

Diels–Alder reaction (**224**, arrows). However the 1,5-hydrogen shift product (**223**) indicates participation of the *Z*-isomer of **224**.

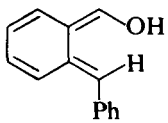


(223)

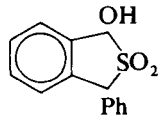


(224)

The well established[123] photoenolization of *o*-tolualdehyde[108a] and related compounds is only a formal 1,5-sigmatropic process as it is believed to involve biradical intermediates which may have zwitterionic character[124]. A recent application[75b] involved trapping the photoenol (**225**) from *o*-benzylbenzaldehyde with sulphur dioxide to give the sulphone



(225)



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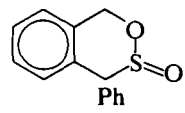
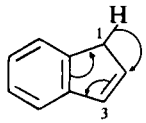


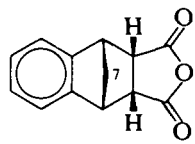
(227)

(**226**). Reduction of **226** ($NaBH_4$) and acid treatment led to the sultine (**227**) which was useful for the generation of 1-phenyl *o*-quinodimethane under mild thermal conditions.

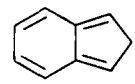
1,5-Hydrogen shift in indene (**228**, arrows) was first[125] postulated to explain formation of the adduct (**229**) from indene and maleic anhydride at 180°C. Elegant D-labelling experiments support the intermediacy of isoindene (**230**) in this reaction. Thus after



(228)

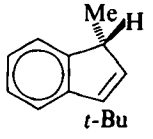


(229)

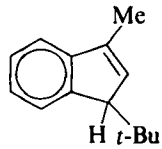


(230)

heating at 200°C 1-deuterioindene has the label statistically distributed over C(1), C(2) and C(3)[126] and 2-deuterioindene provides the adduct (**229**) in which 90% of the label is located in the bridge methylene[127]. On heating the optically active indene (**231**) the isomer (**232**) is formed in optically inactive form, showing that the isoindene (**233**) is involved[128]. A 1,3-hydrogen shift in **231** would have given optically active **232**.



(231)



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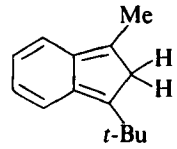
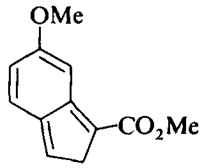
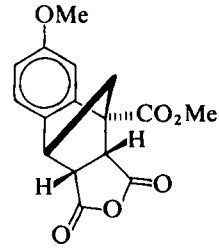


(233)

Despite their easy generation isoindene intermediates have not been extensively employed in synthesis. In one example the isoindene (**234**) generated by heating 5-methoxy-3-methoxycarbonylindene at 170°C was trapped efficiently with maleic anhydride to give **235**, a useful intermediate in the synthesis of diterpene alkaloids[129].

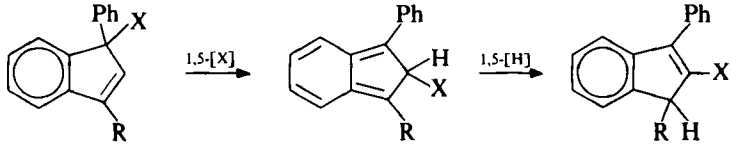


(234)



(235)

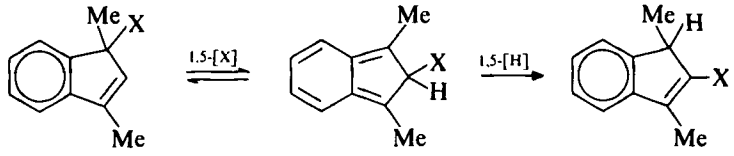
A kinetic study[130] of the thermal rearrangement of the indenes (**236**) to their 2-substituted isomers (**237**) via the intermediate isoindenes (**238**) has shown the order of migratory aptitude is H > Ph > Me. It is interesting that isoindene intermediates are also



(236) (238) (237)

obtained by apparent photochemical 1,5-aryl migration. Using the flash photolysis technique the transients can be observed and their decay by 1,5-hydrogen shift to give simple indenes monitored[131]; they have half-lives of less than a minute at 20°C.

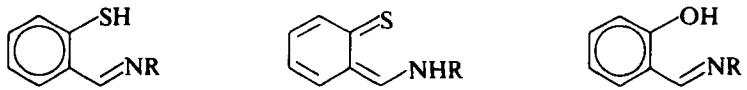
Migratory aptitudes of a variety of groups have been measured using the optically active 1,3-dimethylindenes (**239**, X = migrating group). Upon 1,5-shift of X the symmetric isoindenes are formed with consequent loss of optical activity. This method allowed the determination of accurate migratory tendencies for groups like the formyl group which migrate more rapidly than hydrogen. In such cases isoindene formation is reversible and the rate of formation of the 2-substituted indenes (**240**) underestimates the migratory



(239) (240)

aptitude of X. Migratory ability decreases in the order: HCO > PhCO and MeCO > H > vinyl > CONHMe and CO_2Ph > CO_2Me > CN and C ≡ CH > alkyl. The formyl group migrates ca. 10^5 times more rapidly than hydrogen whilst the CO_2Me group migrates ca. 10^2 times more slowly than hydrogen. The fast migration of formyl, benzoyl and acetyl groups has been attributed to secondary MO ↔ MO interaction involving the carbonyl π^* orbital of the migrating acyl group[132]. The migratory aptitude of the formyl group is comparable with that of trimethylsilyl and related groups. 1-Trimethylsilylindenes are in equilibrium with isoindenes produced by 1,5-silyl migration under mild thermal conditions[133]. Trimethylstannyl and trimethylgermyl groups are likewise very mobile in the indene system[133b, 134]. As yet the synthetic potential in the isoindene intermediates involved here has not been exploited.

1,5-Shifts of the type **216** (arrows) correspond to tautomerism in the mercaptobenzaldimines (**241**). In several cases the *o*-thioquinone methide tautomers (**242**) have been detected

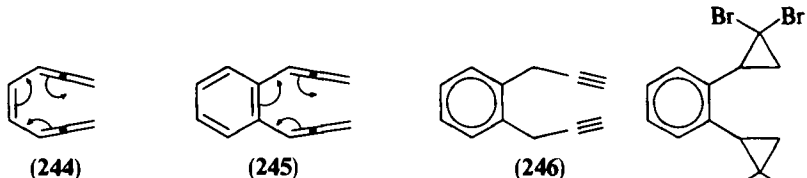


(241) (242) (243)

spectroscopically[135]. In contrast it appears that the oxygen analogues prefer to exist as the imine tautomers (**243**)[135].

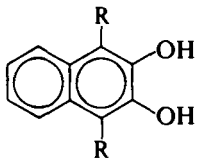
E. Other Routes to *o*-Quinonoid Compounds

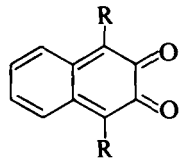
The allenes **244** and **245** undergo 6π-electron cyclization generating *o*-quinodimethane[136] and 2,3-naphthoquinodimethane[34] respectively. The allene **245** could be isolated following base treatment of the diacetylene (**246**)[34] or reaction of the

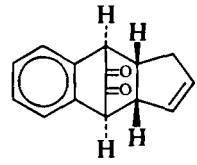


(244) (245) (246) (247)

tetrabromide (**247**) with methyl-lithium[137]. Reaction of **245** with dimethyl maleate and dimethyl fumarate is stereospecific in agreement with a singlet ground state for the intermediate 2,3-naphthoquinodimethane[34]. Oxidative generation is applicable to 2,3-naphthoquinones and *o*-quinone methides. Potassium iodate oxidation of naphthalene-2,3-diol (**248**, R = H) is believed to give transient 2,3-naphthoquinone (**249**, R = H) which

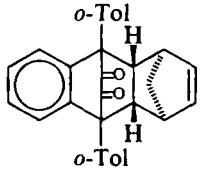

(248)

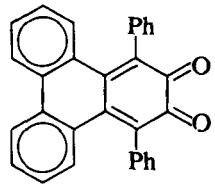

(249)

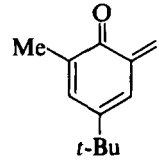

(250)

is trapped by a large excess of cyclopentadiene as the adduct (**250**)[138]. Low temperature oxidation of **248** (R = Ph) with lead tetra-acetate gives a green colour attributed to 1,4-diphenyl-2,3-naphthoquinone (**249**, R = Ph) which can be trapped with a variety of olefins; the green colour faded rapidly and disappeared after 45 min at $-20°C$[139].

In contrast the similarly generated green colour due to the sterically stabilized derivative (**249**, R = *o*-tolyl) remained unchanged after 2 h at $-20°C$; this compound was characterized by UV and IR spectroscopy, as the adduct (**251**) formed with norbornadiene,


(251)

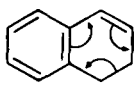

(252)

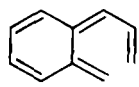

(253)

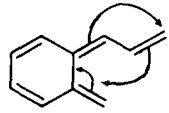
and by a comparison of its properties with those of the stable quinone (**252**); **249** (R = *o*-tolyl) could be isolated albeit in somewhat impure form[140].

Oxidation of a 2,6-dimethylphenol blocked in the *para* position with a group lacking α-hydrogen results in the formation of an *o*-quinone methide[141]. Thus oxidation of 4-*t*-butyl-2,6-dimethylphenol with silver oxide gives the *o*-quinone methide (**253**).

In principle the photochemical 6π-electron electrocyclic ring-opening of dihydronaphthalene (**254**) should provide the *o*-quinodimethane (**255**). However the observed product is **257** derived via ring-closure (**256**, arrows) of the transoid isomer (**256**) of **255**[142];


(254)


(255)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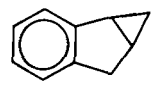
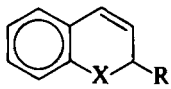
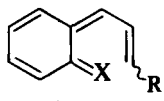
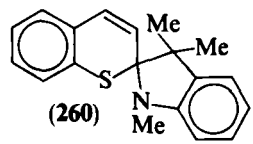

(257)

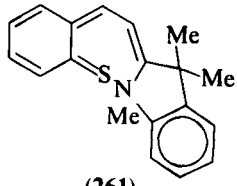
255 polymerized so readily even at low temperature that it could not be observed. In contrast irradiation of heterocyclic analogues of **254** produce observable *o*-quinonoid species. Thus **258** (X = S, R = H)[143] and **258** (X = O, R = H)[144] give the coloured *o*-quinonoid species **259** (X = S, R = H) and **259** (X = O, R = H) respectively. Similarly,


(258)


(259)

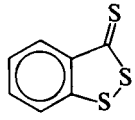

(260)

irradiation of **260** at 77 K gives the green *o*-thioquinone methide **261**[143] and **258** (X = NCO_2Et, R = CN) gives **259** (X = NCO_2Et, R = CN) upon irradiation at low temperature[145].



(261)

In an intriguing reaction, irradiation of **262** in the presence of olefins yields relatively stable, deep blue *o*-thioquinone methides, e.g. **263**[146]. Treatment of **263** with an ethylene



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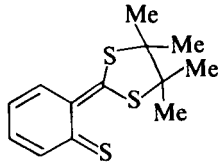

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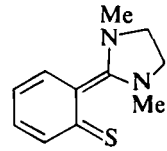
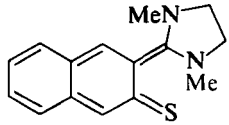


(264)

diamine gives the stable *o*-thioquinone methide (**264**). Stabilization of **264** by push–pull resonance is supported by its NMR spectrum[146]. The 2,3-naphthoquinone methide (**265**)



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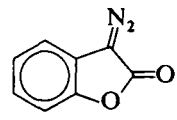
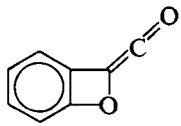
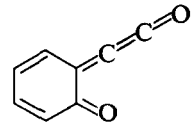


(266)

can also be prepared by this route[147]. Irradiation of **266** in an argon matrix at 8 K gave rise to two primary products, **267** and **268**, which could be interconverted photochemically. Prolonged irradiation of **267** led to decarbonylation to benzyne[148].



(267)



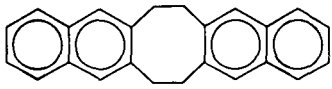
(268)

IV. REACTIONS OF *o*-QUINONOID COMPOUNDS

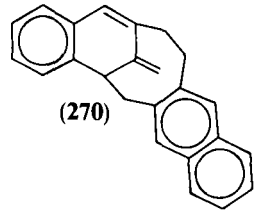
A. Dimerization and Related Processes

When *o*-quinodimethane is generated under mild conditions in solution the spiro-dimer (**2**) (Section I.A) is the main product[24]. However, in solution at higher temperatures the linear dimer (**81**) (Section III.A, B) is increasingly dominant[56a, 72]. In contrast 2,3-

naphthoquinodimethane appears to give no spiro-dimer analogous to **2**; instead in addition to the linear dimer (**269**) the (6 + 4)π-dimer (**270**) is formed[34b]. An analogous

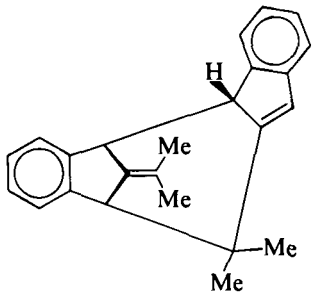


(**269**)

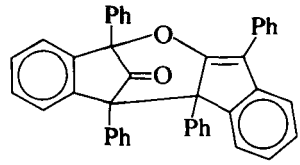


(**270**)

formal (6 + 4)π-dimer (**271**)[102] from 8,8-dimethylisobenzofulvene is known and the labile (6 + 4)π-dimer (**272**) of 1,3-diphenylinden-2-one (**273**, X = CO) is isolable together with

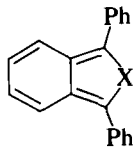


(**271**)

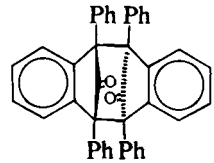


(**272**)

the major dimer (**274**) of linear type[10a] when **273**, X = CO is generated at low temperature; **272** rearranges to **274** on heating in benzene[65b]. The benz[*f*]derivative of **273** (X = CO) forms a linear dimer analogous to **274**[10b].

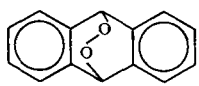


(**273**)

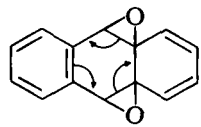


(**274**)

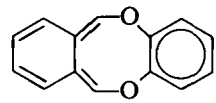
Anthracene *endo*-peroxide (**275**) rearranges upon irradiation to **276** which on heating undergoes ring-opening (**276**, arrows) to the novel *o*-quinodimethane (**277**). The latter decays by formal (6 + 4)π-dimerization[149]. Steric effects have a marked influence on the



(**275**)

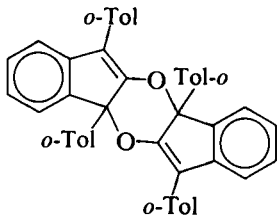


(**276**)

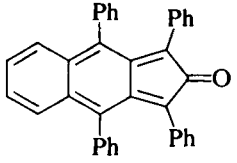


(**277**)

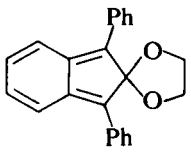
mode of dimerization of inden-2-ones for in contrast to the 1,3-diphenyl derivative (**273**, X = CO) the 1,3-di-*o*-tolyl derivative gives the formal (6 + 6)π-dimer (**278**)[140]. The tetraphenyl derivative of benz[*f*]inden-2-one, **279**, behaves analogously[10b].



(278)

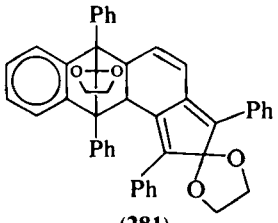


(279)

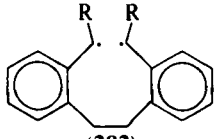


(280)

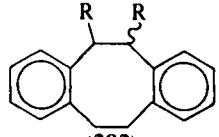
As the result of spiroconjugative interaction* between the oxygen lone pairs and the termini of the *o*-quinonoid system the ethylene acetal (**280**) dimerizes readily[150]. This is in contrast to the stability of the isolable isoindene (**273**, X = CMe_2)[25]. Spiroconjugative interaction is predicted to raise the HOMO of **280** whilst leaving the LUMO unperturbed. In agreement **280** shows λ_{max} 537 nm whilst **273** (X = CMe_2) has λ_{max} 444 nm. The higher energy HOMO of **280** will interact more strongly with the LUMO of a second molecule of **280** in a dimerization TS resulting in a more ready dimerization of **280** than of **273** (X = CMe_2). The dimer of **280** has structure **281**; steric effects associated with the acetal



(281)



(282)

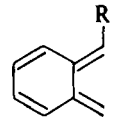


(283)

groups presumably prevent linkage of two molecules of **280** using the usually reactive diene systems of both. Related phosphole oxides, e.g. **273** (X = P(O)Ph) and **273** (X = P(O)Me)[150] and the sulphone (**273**, X = SO_2)[80], also absorb at much longer wavelength than **273** (X = CMe_2) and the phosphole oxides form dimers of the type **281**. These compounds are very likely also destabilized by spiroconjugative effects.

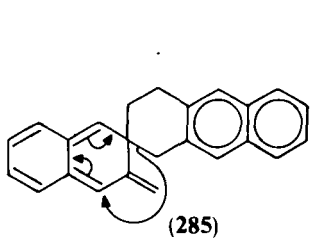
Of the several dimerization modes observed for *o*-quinonoid species the most intriguing are those which correspond to orbital symmetry forbidden processes. However, it is not clear even for *o*-quinodimethane itself whether the spiro-(**2**) and linear-(**81**) dimer are formed via a common biradical intermediate (**282**, R = H) or whether instead **2** is the product of an allowed Diels–Alder addition and **81** alone is formed via the biradical (**282**, R = H). Formation of the more stable biradical intermediate (**282**, R = substituent) will explain the head-to-head linear dimers (**283**) obtained from the *o*-quinodimethanes **284** (R = $PO(OR)_2$[151], R = SMe[152], R = CN[153] and R = CONHR′[154]). A biradical is also an

* When the termini of two conjugated systems are united to the same spiro-centre, the through-space interaction between the termini of the two systems is termed spiroconjugation. In acetals of cyclopentadienone a through-space interaction of two oxygen lone pairs constitutes one conjugated system and the diene system the other[9].



(284)

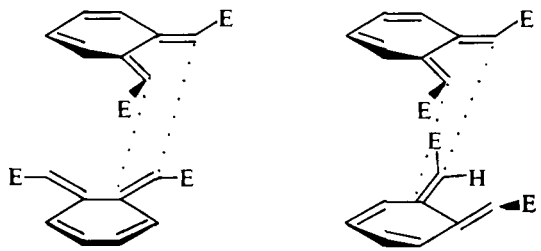
attractive intermediate to explain the reversible dimerization of **273** (X = CO), the easy conversion of **272** into **274** and formation of formal (6 + 6)π-dimers like **278**. Whether or not the formal (6 + 4)π-dimers **270**, **271** and **272** are formed directly by orbital symmetry allowed concerted cycloaddition is also unknown; **270** could form from the unobserved spiro-dimer **285** of 2,3-naphthoquinodimethane by a 1,5-benzyl shift (**285**, arrows) which



(285) (286)

might be expected to occur readily. Similarly the formal (6 + 4)π-dimer (**271**) of 8,8-dimethylisobenzofulvene (**171**) could arise from the *exo*-(4 + 2)π-dimer **286** by Cope rearrangement (**286**, arrows). This would explain the unusual *endo* stereochemistry of the major apparent (6 + 4)π-dimer (*endo*:*exo* ratio, 3). There is good analogy for preferred *exo* adduction in the Diels–Alder additions of **171**. With dimethyl maleate **171** gives *exo* and *endo* adducts in a ratio of 2[102].

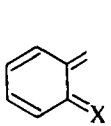
Formation of the spiro-dimer **55** of *E*,*E*-α,α′-bis(methoxycarbonyl)-*o*-quinodimethane is remarkably stereoselective[44]. If **55** is formed by concerted (4 + 2)π-addition the TS arrangement (**287**) must be preferred to the alternative (**288**). Since **287** allows a greater



(287) (288)

'accumulation of unsaturation' than **288** it is reasonable that **287** should be preferred[155] if dimerization is indeed a concerted (4 + 2)π-addition. This stereoselectivity is more difficult to explain if spiro-dimer formation proceeds via a biradical intermediate.

o-Quinone methide imines (**289**, X = NMe or NPh) resemble *o*-quinodimethane itself in providing spiro-dimers **290** (R = Me[54] or Ph[92, 116]). Even the ketene (**291**) gives a simple (4 + 2)π-dimer (**292**) or one of its tautomers[156]. Similarly, *o*-quinone methides give no evidence for formation of linear dimers. The parent (**289**, X = O) forms the trimer (**293**)[1]



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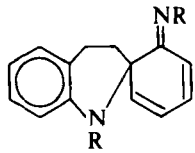

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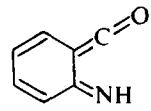

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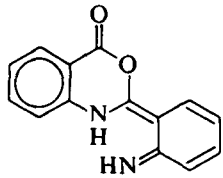

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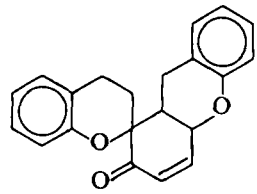
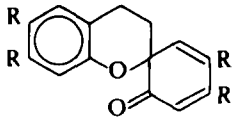


(293)

clearly derived by addition of a third molecule of **289** (X = O) to the spiro-dimer **294** (R = H). For more sterically hindered quinone methides, dimers rather than trimers, are



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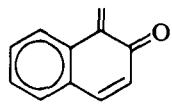

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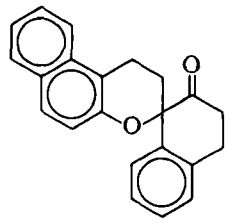
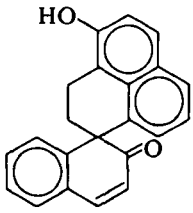


(296)

obtained, e.g. **294** (R = *t*-Bu)[1]. Naphthoquinone methide (**295**) also forms only the spiro-dimer (**296**), in this case reversibly[157]. However, generation of **295** by dissociation of **296** is complicated by formation of the isomeric dimer (**297**)[158]. *o*-Thioquinone methide (**289**, X = S) gives the head-to-tail linea dimer (**298**)[66,86]. Indeed most other *o*-thioquinone



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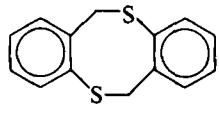

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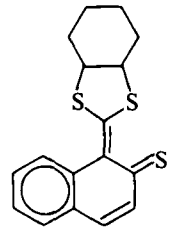
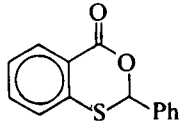


(299)

methides form linear dimers; steric factors may be responsible for the exceptional case of **299** which forms a spiro-dimer of uncertain structure[159]. Photolysis of **300** at 77 K provides a route to the ketene (**301**) which ring-closes to **302**. On warming to −40°C the head-to-tail dimer (**303**) is obtained[103]. However, in an apparently contradictory report it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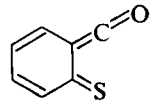
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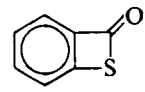
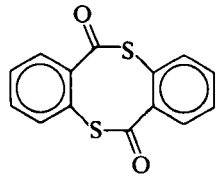

(302)

is noted that photolysis of **300** at 77 K yields the head-to-head dimer (**304**)[160]. It seems possible that **303** is the result of a thermal, and **304** the result of a photochemical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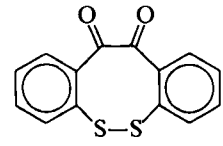
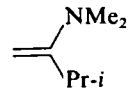
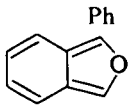

(304)

dimerization. Whether **263** gives a head-to-tail or a head-to-head linear dimer depends on the presence or absence of the hindered enamine (**305**)[161]!


(305)

B. Diels–Alder Reactions

Apart from the numerous Diels–Alder additions carried out to intercept or characterize unstable *o*-quinonoid compounds, and the use of *o*-quinonoid compounds to intercept other transient species, the reactive *o*-quinonoid diene and heterodiene systems have found use in testing fundamental aspects of the Diels–Alder reaction. More recently the coupling of *o*-quinonoid reactivity with the advantages of the intramolecular Diels–Alder reaction has led to numerous elegant syntheses of complex structures of natural origin. In some cases the intermolecular Diels–Alder reactions of *o*-quinonoid compounds are also synthetically useful. The Diels–Alder reactivity of the isolable isobenzofuran (**306**) has long been exploited by organic chemists. Thus in addition to being a well-known aryne trap, **306** was used by Wittig and Wilson[162] who obtained evidence for cyclohexyne by isolation of the adduct **307** (43 %) from the reaction of 1,2-dibromocyclohexene (**308**) with magnesium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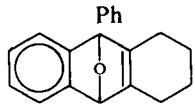
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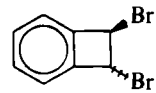
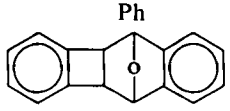

(309)

in the presence of **306**. Cava and his collaborators found **306** to be an efficient trap for transient benzocyclobutadienes. Thus reaction of *trans*-1,2-dibromobenzocyclobutene (**309**) with Li/Hg gave the adduct **310** (57 %) in the presence of **306**. Halogen derivatives of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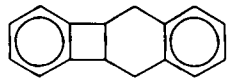
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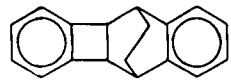
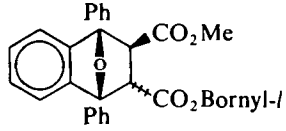

(312)

benzocyclobutadiene were even more efficiently trapped[163]. Interestingly cogeneration of benzocyclobutadiene and either *o*-quinodimethane or 2,3-dihydronaphthalene results in remarkably high yield mutual trapping giving **311** (44%) and **312** (65%) respectively[164].

More recently **306** has been used to probe the timing of formation of the two bonds in the Diels–Alder reaction[165]. When methyl *l*-bornyl fumarate adds to **306** the enantiomeric ratio is 1.53 in the *endo*-bornyl adduct (**313**) and 1.41 in the *exo*-bornyl adduct (**314**). If both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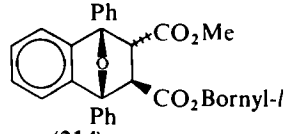
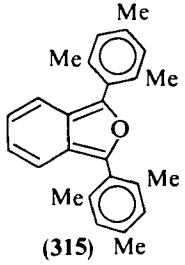

(314)

new bonds are formed to the same extent in the TS for addition of di-*l*-bornyl fumarate to **306** the enantiomeric ratio should be $1.41 \times 1.53 = 2.16$; the observed enantiomeric ratio was 2.08. The cooperativity of asymmetric induction observed here provides evidence for synchronous formation of the new σ bonds in this Diels–Alder reaction.

In contrast to **306**, 1,3-dimesitylisobenzofuran (**315**) is inert to several dienophiles even under forcing conditions. Newman[166] therefore proposed that the observed additions to 1-mesityl-3-phenylisobenzofuran (**316**) were two-step processes involving diradical or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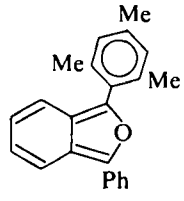
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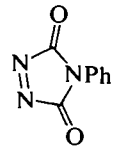
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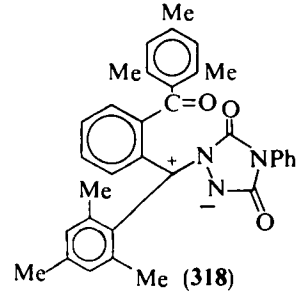
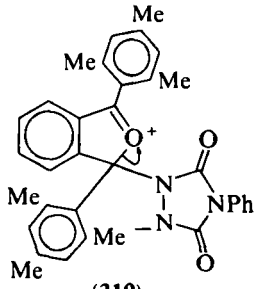

(318)

zwitterionic intermediates. Reaction of **315** with 4-phenyltriazoline-3,5-dione (**317**) gives the stable zwitterion (**318**)[167a] which is clearly derived (**319**, arrows) from the kind of dipolar intermediate (**319**) envisaged by Newman. Interestingly **306** is reported to react normally with **317**[167b].

The high reactivity of *o*-quinonoid dienes has been employed in a test of the FMO theory of regioselectivity in cycloadditions[168]. Whilst the theory concurs with the rule of '*ortho–para*' addition for most Diels–Alder additions, the addition of an electron-rich diene with an electron-rich dienophile provides an excellent test of the theory.

Matching the larger coefficients in both HOMO–LUMO pairs as in **320** and **321** predicts predominant formation of the '*meta*' isomer. Were a diradical an intermediate in such an addition the '*para*' isomer would be expected to predominate. Since Diels–Alder reactions between electron-rich partners were virtually unknown and would be expected to



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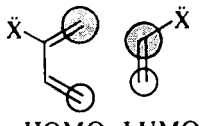

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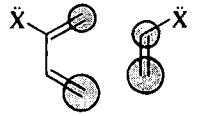
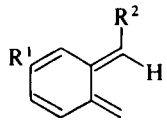


(321)

require harsh conditions the reactive *o*-quinodimethanes **322** (R^1 = H, R^2 = Me) and **322** (R^1 = OMe, R^2 = H), generated by electrocyclic opening of benzocyclobutenes, were employed. Trapping with prop-1-yne and ethoxyacetylene gave in each case more of the unusual '*meta*' adduct, e.g. **323** and **324** were formed in a ratio of 1.56.



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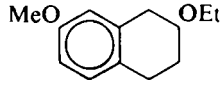

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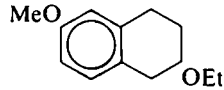
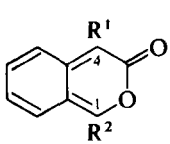


(324)

Diels–Alder addition of simple olefins like cyclopentene and *cis*-but-2-ene to the pyrones **325** (R^1 = R^2 = H) and **325** (R^1 = H, R^2 = Me) and the *o*-quinodimethanes **326** (R = CN) and **326** (R = CO_2Me) showed a preference for *endo* addition[153] varying from 6.5:1 to 2:1. This was taken as evidence for diene–alkyl group attraction in the TSs of the additions. Earlier it had been observed[169] that diene **327** gave almost equal quantities of



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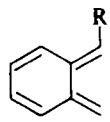

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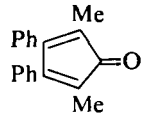

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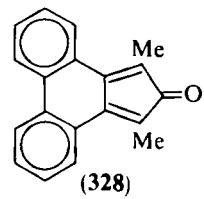
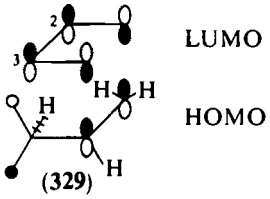


(328)

endo and *exo* adducts with cyclopentene, whereas with cyclopentadiene as dienophile, **327** gave mainly the *endo* adduct. This result had been taken to show the presence of secondary attractive forces in the cyclopentadiene addition and their absence in the *endo*-cyclopentene addition. The result was extrapolated to suggest the absence of attractive diene–alkyl group interactions in the Diels–Alder additions of simple olefins. Indeed a critical survey of mechanistic aspects of the Diels–Alder reaction[170] cites this work as demonstrating the importance of secondary interactions. Since it seemed likely that non-coplanarity of the phenyl groups and the diene system in **327** would impose a greater steric barrier to the *endo* addition of cyclopentene than cyclopentadiene the 9,10-phenanthroquinodimethane **328** in which the aryl groups are forced to lie in the same plane as the diene system was generated and added to several simple olefins[171]. In contrast to the addition of cyclopentene to **327**, corresponding addition to **328** in which the steric barrier is removed gives only the *endo* adduct. Thus diene **327** is probably a poor diene for use in

testing for secondary interactions. The course of its additions to cyclopentene and cyclopentadiene probably reflect the greater number of out-of-plane hydrogens in cyclopentene as well as the somewhat greater importance of secondary interactions involving unsaturated than saturated groups. The existence of diene–alkyl group attraction is supported by other evidence[172]. Although the nature of the attractive interaction is unknown it could be of the orbital interaction type arising as a consequence of hyperconjugation between the allylic hydrogen atoms and the π system of the olefin. The allylic hydrogen atoms in the HOMOs of cyclopropene, cyclopentene and cyclobutene[173] carry small coefficients of appropriate phase for bonding interaction with C(2) and C(3) of a diene LUMO as shown in **329** for propene. This effect has been termed steric attraction,



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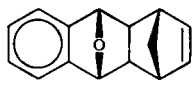
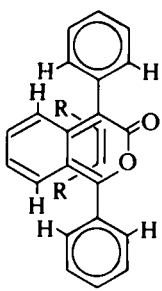


(330)

and used to explain certain aspects of carbene addition to olefins[174a]. Houk now seems to accept the existence of secondary interactions involving alkyl groups[174b]. Cyclopentene and cycloheptene also add to benzo[*c*]furan to give mostly *endo* adducts[153], but addition to norbornadiene gives mostly the *exo* adduct (**330**) (*exo*:*endo* ratio, 1.8:1). In contrast 1,3-diphenylbenzo[*c*]furan gives *only* the *exo* adduct with norbornadiene[175]. This difference reflects an effect due to phenyl substitution more strikingly observed in additions to the stable diphenyl-substituted pyrone (**325**, $R^1 = R^2 = Ph$). In complete contrast to the parent pyrone (**325**, $R^1 = R^2 = H$), the diphenyl derivative adds a range of dienophiles (butadiene, isoprene, cyclopentadiene, dimethyl maleate, norbornadiene and cyclopentene) with marked *exo* selectivity[176]. Although the origin of this effect is unclear it appears to be associated with the more congested environment of the olefinic substituents (R) in the



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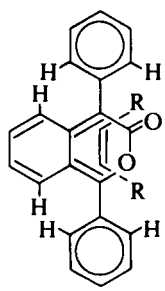

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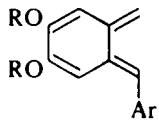

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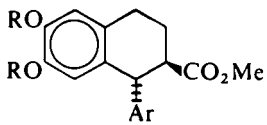
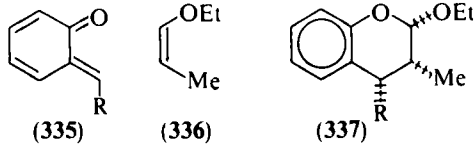


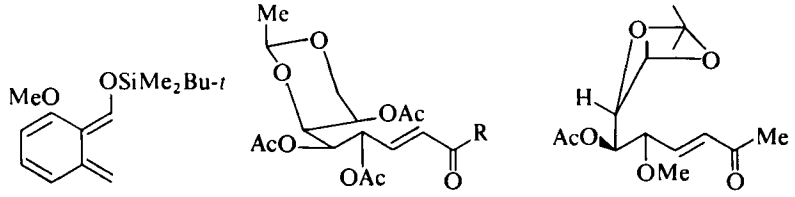
(334)

endo array (**331**) than in the *exo* array (**332**). Related effects are observed in additions to 1,4-diphenyl-2,3-naphthoquinone (**249**, R = Ph)[139] and *o*-quinodimethanes of type **333** which give mostly the *exo* adducts (**334**) with methyl acrylate[75]. The same trend is discernible in additions to *o*-quinone methides[177]. Thus **335** (R = Me) and *Z*-methyl propenyl ether (**336**) give the *endo* adduct **337** and its *exo* isomer in a ratio of 9:1 whereas the corresponding ratio for addition to **335** (R = Ph) is 2.33:1.



(335) (336) (337)

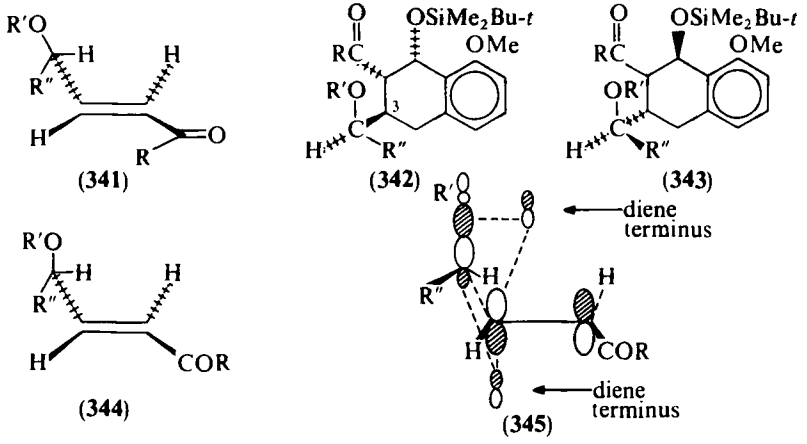
The benzo[*c*]heterocycles (**162**, X = O, N, S) all react with *N*-phenylmaleimide to give mixtures of *endo* and *exo* adducts[62, 96, 178]. Since this dienophile normally strongly prefers *endo* addition and reversibility of addition is unlikely to be a problem in at least two cases (**162**, X = O and NH)[96, 178] another explanation is required; secondary interaction involving the hetero atoms of diene and dienophile is one possibility. The *o*-quinodimethane **338** generated by benzocyclobutene ring-opening has been used to test diastereoface selection in additions to the olefins **339** (R = OEt), **339** (R = Me) and



(338) (339) (340)

340[179]. Assuming a ground state conformation (**341**) for the olefins (R″ = sugar residue), with the small allylic C–H bond in the plane of the carbon–carbon double bond, and an *endo*-COR TS, steric factors associated with R″ might be expected to direct attack of the diene **338** to the *upper* face of the olefin leading to adducts (**342**) of *R*-configuration at C(3). In fact addition of **339** (R = OEt) gives mostly **343** derived by addition to the *lower* face of **341** (four parts) and only one part of **342**. Preferred attack of the diene on the face of **341** opposite the allylic oxygen substituent is also observed for the ketones **339** (R = Me) and **340**.

The ideas of Houk and his collaborators[180] which have in part appeared subsequent to these experimental observations are readily extended to accommodate them. The idea of staggering forming bonds with allylic bonds[180a, b] suggests that **344** rather than **341** is the

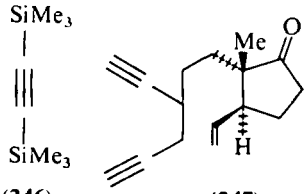


(341) (342) (343)

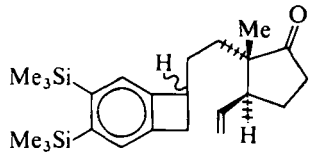
(344) (345)

more likely olefin conformation in the TS of the addition. In **344** better overlap of the C–O σ^* orbital with π and π^* of the double bond results in electron withdrawal from the double bond making it a more electron-deficient dienophile. Secondary interactions with the modified LUMO (**345**) ($= \sigma^* + \pi^*$) then determine which face of the olefin is preferentially attacked. As shown in **345** approach of a diene terminus from above gives rise to antibonding interaction involving the σ^* component whilst approach from below gives rise to bonding secondary interaction. These ideas help explain why (with one exception[181]) the most reactive conformation of an allylic ether changes[180a] when the reagent is electron-deficient. These effects are clearly of importance in planning chiral syntheses using Diels–Alder and other reactions.

The use of *o*-quinonoid compounds in intramolecular Diels–Alder reactions is detailed both in the extensive review literature of the intramolecular Diels–Alder reaction[104b, 182] and in reviews of the use of this process in steroid synthesis[183]. Nevertheless we must mention the stunning work of Vollhardt and his collaborators[184] who showed that co-oligomerization of **346** and **347** with $CpCo(CO)_2$ as catalyst led via the stereoisomeric

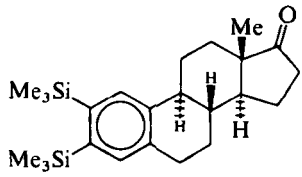


(**346**) (**347**)

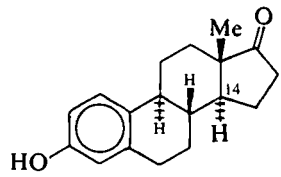


(**348**)

benzocyclobutenes (**348**) to the steroid (**349**); selective protodesilylation of **349** at C(2) (CF_3CO_2H) and oxidative [$Pb(OCOCF_3)_4$] removal of the remaining $SiMe_3$ group gave

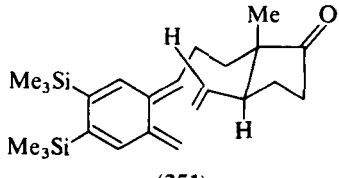


(**349**)

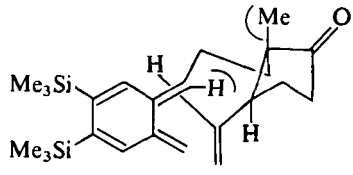


(**350**)

oestrone (**350**). The intramolecular cycloaddition leading to **349** involves the chair-like *exo*-TS arrangement **351**. The alternative *exo* array (**352**) which would have given a *cis* disposition of hydrogens at C(8) and C(14) is presumably destabilized by repulsion between bowsprit and flag-pole in the developing boat conformation of ring C. The synthesis of resistomycin by Rodrigo and Keay is also remarkable for the efficiency with

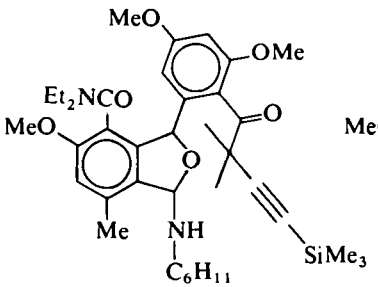


(**351**)



(**352**)

which a polycyclic molecule is assembled[185]. Reaction of **353** with iodoacetic acid in refluxing benzene gave the isobenzofuran (**354**) which underwent spontaneous intramolecular Diels–Alder reaction to **355**. Reaction of **355** with pyridine hydrochloride



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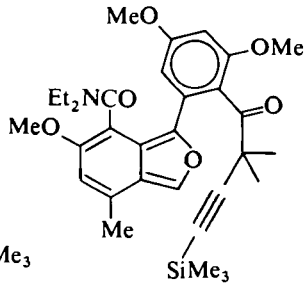

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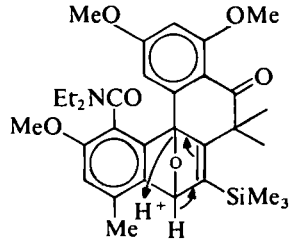
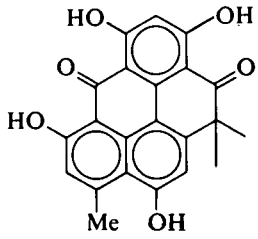


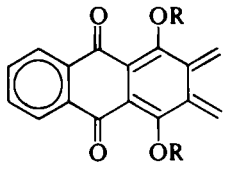
(355)

resulted in acid-catalysed aromatization (**355**, arrows), protodesilylation, demethylation and an intramolecular Friedel–Crafts acylation to give resistomycin (**356**) in high yield.



(356)

Intermolecular Diels–Alder reactions of *o*-quinodimethanes are also synthetically valuable. The *o*-quinodimethanes **357** (R = Me)[186] and **357** (R = H)[187] were generated by 1,4-elimination of bromine (NaI), and benzocyclobutene ring-opening respectively. In both cases trapping with the moderately reactive dienophile (**358**) gave the adducts (**359**) in



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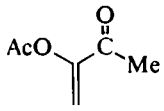

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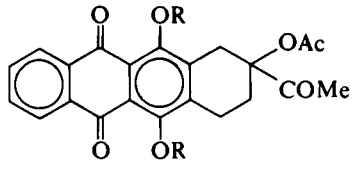
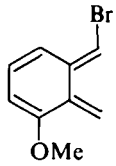


(359)

fair yield. These compounds are closely related to 4-deoxydaunomycinone, a compound with useful anti-cancer properties. The problem of regioselectivity which is generally greater in inter- than intramolecular additions is not acute for *o*-quinodimethanes that are differently substituted at the termini of the quinonoid system. Thus the *o*-quinodimethane **360** adds regio- and site-selectively to the quinone (**361**) to give after *in situ* dehydrobromination the quinone (**362a**) which could be converted to islandicin. On the other hand addition of **360** to **363** led to the regioisomeric quinone **362b** which could be converted to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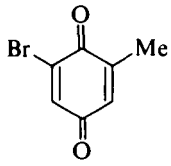
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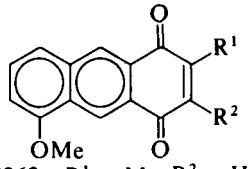
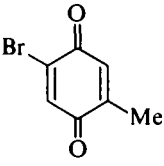
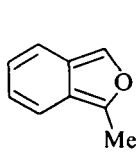

(362a, R^1 = Me, R^2 = H)
(362b, R^1 = H, R^2 = Me)


(363)

digitopurpone[188]. In these reactions the bromine atom in the quinone determined both regio- and site-selectivity and is subsequently removed. Such a substituent has been described as a 'ghost' substituent[189]. Addition of 1-methylisobenzofuran (**364**) as well as other 1-substituted isobenzofurans to quinone dimethyl acetals like **365** is also both site- and regioselective; **365** gives the tetracyclic *endo* adduct **366**, of interest in the synthesis of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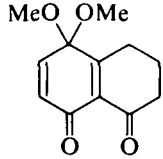
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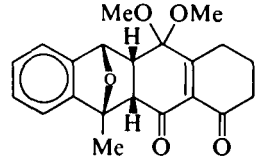
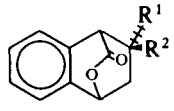
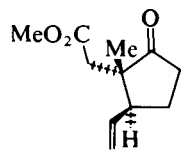
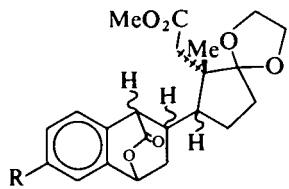

(366)

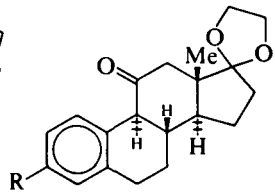
anthracyclines[190]. 2-Benzopyran-3-one (**325**, $R^1 = R^2 = H$) undergoes strongly regioselective additions to a range of electron-rich olefins[191, 192]. In such inverse electron demand Diels–Alder additions the HOMO-dienophile–LUMO-diene frontier orbital interaction should be more important. Simple Hückel calculations show that the LUMO of **325** ($R^1 = R^2 = H$) has a much larger coefficient at C(1) than at C(4) whereas the HOMO of **325** ($R^1 = R^2 = H$) is polarized in the opposite sense. Since the HOMOs of electron-rich olefins have the larger coefficient at the less substituted end, their reaction with **325** ($R^1 = R^2 = H$) should lead to adducts of the type **367**. This is indeed what is observed;


(367)

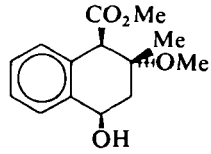

(368)

isobutene gave **367** ($R^1 = R^2 = Me$) as the only isolable product. The olefin (**368**) gave a 70% yield of adducts with those adducts (**369**, R = H) with the correct regiochemistry for steroid synthesis predominating (ratio 5.1:1). The adducts **369** (R = H) and **369** (R


(369)


(370)

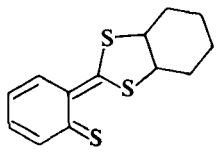
= OMe) were readily transformed into the 11-oxo aromatic steroids (**370**)[191]. The adduct **367** (R^1 = OMe, R^2 = Me) was prepared by Jung and his collaborators and shown to react with sodium methoxide to give **371**, an AB-ring analogue of the anthracyclines[192]. The



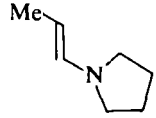
(**371**)

pyrone (**325**, $R^1 = R^2$ = H) appears less prone to dimerization and other self-destructive processes than related *o*-quinonoid compounds, allowing its efficient trapping even with simple olefins. In contrast α-cyano-*o*-quinodimethane (**326**, R = CN) shows a strong tendency to dimerize[193].

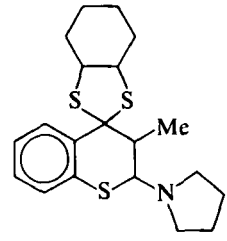
Oxa, aza and sulpha derivatives of *o*-quinodimethane have all been trapped as Diels–Alder adducts. Such reactions include the previously mentioned reactions of *o*-thioquinone methide with *N*-phenylmaleimide (**109** giving **131**), *N*-methyl-*o*-quinone methide imine with chloroacrylic acid (**75** giving **132**), and *o*-quinone methide with 1,1-dimethoxyethylene (**3** giving **135**). Certain stabilized *o*-thioquinone methides also readily undergo cycloaddition; **372** adds to enamines like **373** to give adducts like **374** in good yield, and probably by a stepwise, ionic reaction mechanism. With electron-deficient olefins like maleonitrile and fumaronitrile, the cycloadditions appear to be concerted as indicated by the retention of stereochemistry in the adducts[194, 195]. *o*-Quinone methides are



(**372**)

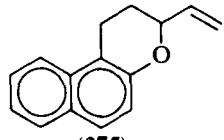


(**373**)



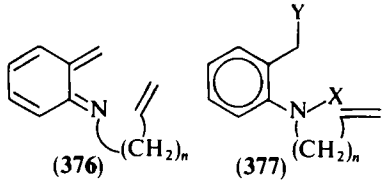
(**374**)

efficiently trapped with electron-rich dienophiles. For example the parent system (**3**) reacts with styrene to yield a chroman[141] and naphthoquinone methide (**295**) adds to butadiene



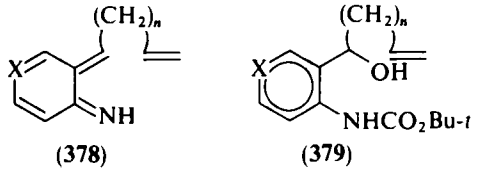
(**375**)

to give a good yield of **375**[196]. Intramolecular Diels–Alder additions to hetero-*o*-quinonoid species are also viable processes. Thus the *o*-quinone methide imines (**376**, *n* = 3 or 4) yield the tricyclic adducts (**143**, *n* = 3 or 4). The same adducts are formed by decarboxylation of the benzoxazinones (**142**) (Section III.B), by flash pyrolytic dehydration of the alcohols (**377**, X = H, Y = OH)[69] and by reaction of fluoride ion with the

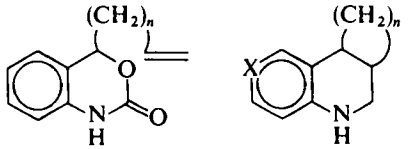


(376) (377)

cations (**377**, X = $SiMe_3$, Y = $\overset{+}{N}Me_3$)[54]. The analogous carbon-substituted *o*-quinone methide imines (**378**, X = CH) generated by flash vacuum pyrolysis of either **379** (X = CH) or **380**, gave the cycloadducts (**381**, X = CH). Tricycle (**381**, X = CH, *n* = 3) was



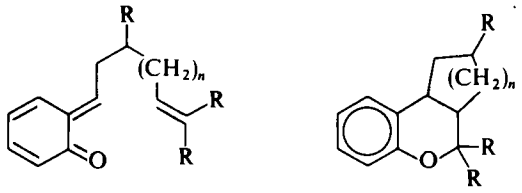
(378) (379)



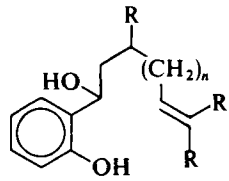
(380) (381)

stereochemically pure and was tentatively assigned the *cis* ring junction stereochemistry, whereas **381** (X = CH, *n* = 4) was a 3:1 mixture of *cis* and *trans* isomers. The pyridine based *o*-quinone methide imine (**378**, X = N, *n* = 3) generated by flash pyrolysis of **379** (X = N, *n* = 3) similarly gave the adduct (**381**, X = N, *n* = 3) in 64% yield[197].

Mao and Boekelheide have reported[66] the intramolecular Diels–Alder trapping of *o*-quinone methide (**382**, R = H, *n* = 1) to give the *cis*-fused product (**383**, R = H, *n* = 1); **382** (R = H, *n* = 1) was generated by flash vacuum pyrolysis of diol (**384**, R = H, *n* = 1).

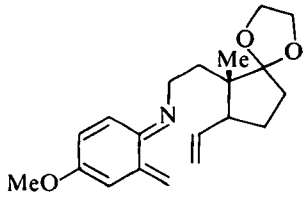


(382) (383)

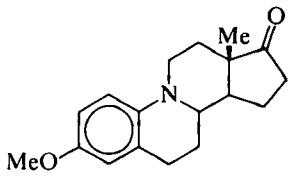


(384)

Thermolysis of diol (**384**, R = Me, n = 2) at 180°C is also reported[198] to yield the adduct (**383**, R = Me, n = 2). There have been a number of reports concerning the use of *o*-quinone methide imines and *o*-quinone methides for the synthesis of natural products. These include the synthesis of 9-azaoestrone (**386**) via cycloaddition of **385** followed by

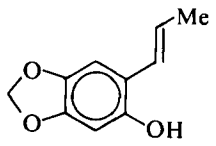


(**385**)

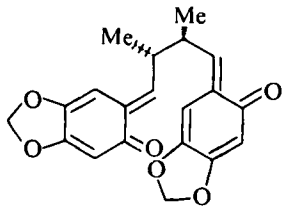


(**386**)

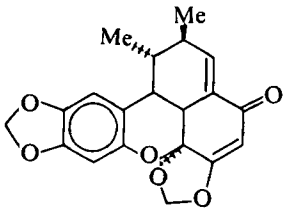
deprotection[54] and the synthesis of the lignan carpanone (**389**) via cycloaddition of *o*-quinone methide (**388**), generated by phenolic coupling of **387**[199].



(**387**)

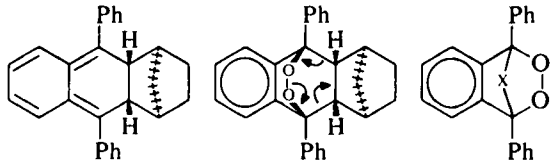


(**388**)



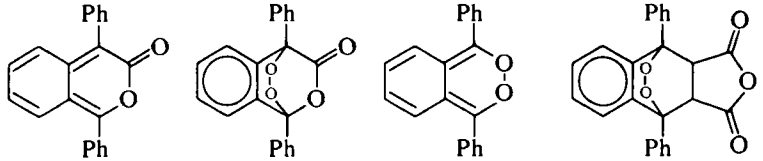
(**389**)

Certain *o*-quinodimethanes also form peroxides when exposed to oxygen, a process which formally involves a Diels–Alder reaction. However, although 2,3-naphthoquinodimethane forms a peroxide with atmospheric oxygen (Section II) a similar peroxide has not been reported for *o*-quinodimethane itself. It seems likely that similar peroxides contribute to the deterioration of many *o*-quinonoid compounds upon exposure to air and that such peroxides could be prepared if more rapid decay modes did not supervene. Thus the *o*-quinodimethane **390**, in which the usual decay modes of conrotatory ring closure, 1,5-hydrogen shifts and dimerization are suppressed, rapidly absorbs atmospheric oxygen to yield the isolable peroxide (**391**) which upon thermolysis eliminates norbornene (**391**, arrows) to give *o*-dibenzoylbenzene[200]. The explosive peroxide (**392**, X = O) obtained by photosensitized oxygenation of 1,3-diphenylisobenzofuran was the first isolated furan endoperoxide[201] and a similar peroxide (**392**, X = NPh) was obtained from 1,2,3-triphenylisoindole[202]. In solution both peroxides decompose to *o*-dibenzoylbenzene.



(390) (391) (392)

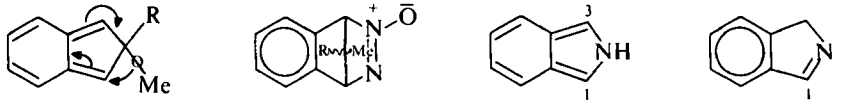
Photosensitized oxygenation[203] of the stable pyrone (**393**)[204] gives the peroxide (**394**). Thermolysis of **394** at ca. 110°C proceeds by two pathways, both of which give *o*-dibenzoylbenzene as the major product observed. Surprisingly, loss of CO_2 with cleavage of the O–O bond is the minor path, and CO_2 loss to give the remarkable *o*-quinodimethane **395** is the major process (ca. 70%). In the presence of maleic anhydride **395** can be efficiently trapped as the adduct (**396**).



(393) (394) (395) (396)

C. Other Reactions

Generation of *o*-quinodimethanes by benzocyclobutene ring-opening (Section III.C) and 1,5-sigmatropy (Section III.D) are equilibria which strongly favour the benzenoid isomers. Accordingly such benzenoid isomers are often encountered as products from reactions proceeding through transient *o*-quinodimethanes. Developing benzenoid aromaticity in the TS may also considerably ease the rearrangement of *o*-quinonoid compounds. Thus alkyl shifts in simple cyclopentadienes commonly require temperatures above 330°C but generation of the isoindene (**397**, R = Me) by thermolysis of **398** (R = Me) at 180°C affords products derived via the 1,5-methyl shift shown in **397**. In **397** (R = Et) the ethyl



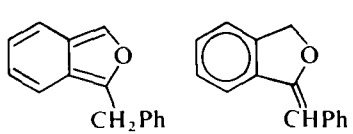
(397) (398) (399) (400)

group migrates six times faster than the methyl group and benzyl migrates 56 times faster than methyl[26a].

When the *o*-quinonoid isomer is itself aromatic the position of equilibrium with a benzenoid isomer can be finely balanced. Thus isoindole (**399**) exists mostly as the 10π-electron aromatic *o*-quinonoid tautomer in both $(CD_3)_2CO$[178] and $CDCl_3$[205] but the isoindolenine form (**400**) can be detected even in the hydrogen-bonding solvent $(CD_3)_2CO$[205] and is quite important in $CDCl_3$[205]. For 1-aryl substituted isoindoles the importance of the isoindolenine tautomer increases as the donor ability of the aryl group increases and the electron deficiency at C(1) in **400** is diminished; for 1-ethoxyisoindolenine the isoindole form is not detectable[206]. The decomposition of isoindole has been associated with reaction between **399** which is electron rich at C(1) and C(3) and its

tautomer (**400**) which is electron deficient at C(1)[178]. This agrees with the stability of both *N*-substituted isoindoles and those that exist exclusively in the isoindole form[207].

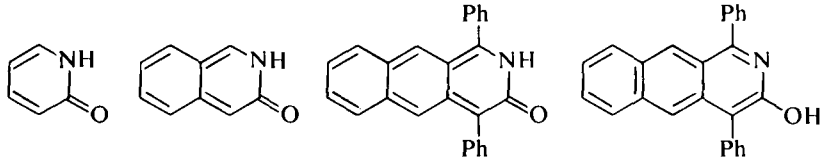
Less highly developed aromaticity in oxygen than nitrogen heterocycles can account for the complete conversion of **401** to **402** on standing in benzene or (rapidly) upon treatment



(**401**) (**402**) (**403**)

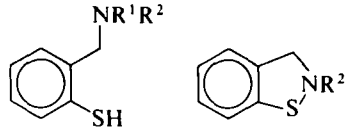
with trifluoroacetic acid[208]. Although the *o*-quinonoid tautomer (**401**) could not be detected by NMR spectroscopy it was trapped as the adduct (**403**) by heating **402** with dimethyl acetylenedicarboxylate and a trace of acid[209].

The effect of increasing *o*-quinonoid character upon tautomeric equilibrium is illustrated by the series **404**, **405** and **406**. For **404** the α-pyridone tautomer shown is overwhelmingly favoured. For **405** equilibrium with 3-hydroxyisoquinoline is more evenly balanced, the pyridone form (**405**) being favoured in ethanol and the pyridinol form in ether[6]. For **406** the pyridinol tautomer (**407**) is favoured (ca. 90%) even in ethanol[210].

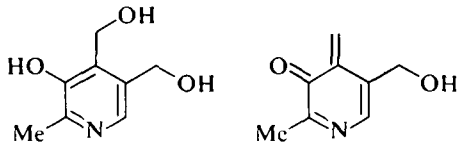


(**404**) (**405**) (**406**) (**407**)

As one might expect, the presence of the heteroatoms in the hetero-*o*-quinonoid species polarize the system and renders it prone to attack by nucleophiles. The numerous examples of this reaction include the formation of thiols (**408**, $R^1 = R^2 = i$-Pr) from attack of secondary amines[66] and **408** (R^1 = H, R^2 = alkyl) from primary amines. In the case of additions of primary amines, benzisothiazoles (**409**) are formed by autoxidation[211].



(**408**) (**409**)



(**410**) (**411**)

This type of process has also been implicated in certain biological systems. For example, nucleophilic addition to the pyridine-quinone methide (**411**), formed from pyridoxine (**410**) has been reported, and it has been suggested that the potent alkylating activity of **411** may be involved in the enzymatic reactions of vitamin B_6 and in certain toxicological reactions induced by pyridoxine[212].

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CHAPTER 10

meta-Quinonoid compounds

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I. HISTORICAL BACKGROUND

The roots of the *meta*-quinone problem go deep into the intellectual history of chemistry. Kekulé proposed the cyclic formula for benzene in 1865, and in the following decades, legions of organic chemists explored the consequences of the theory. Only with effort can the modern scholar's imagination recapture the atmosphere of mingled excitement and conjecture which prevailed in that early morning of organic chemistry a century or more ago. Major elements of the physical basis of chemical theory, which today are commonplace, then were either bewilderingly new or had not been conceived. For example, the concepts of bond length and bond angle were vague, and the nature of the physical forces holding atoms together in molecules was unknown. A certain indulgence therefore is required if the reader of today is to appreciate the challenge of the structure of *m*-quinonoids as it existed then.

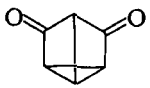
In the context of that time, the relevance of *m*-quinones to the problem of benzene was made clear by Zincke[1], whose own words (translated here from the German and augmented by structures drawn in the modern style) state the matter succinctly:

> By all means, the discovery of a *meta*-benzoquinone would be of significance for the theory of benzene; as the presence of a meta-bond in the former must be assumed, it can only be expressed by [one of] the formulas **1** and **2**.

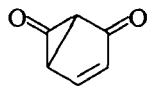
Zincke implicitly assumed that Kekulé's standard valence rules were inviolable. From this it followed that a *m*-quinone could not be constructed wholly with bonds between adjacent (*ortho*) carbons on the six-membered ring.

Zincke continues:

> Since I have been able to convert catechol into derivatives of *ortho*-benzoquinone, I have not neglected attempts to prepare analogous derivatives of the *meta* series, but so far without success; it appears in fact as if derivatives of this kind are incapable of existence.

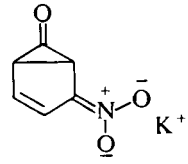


(1)



(2)

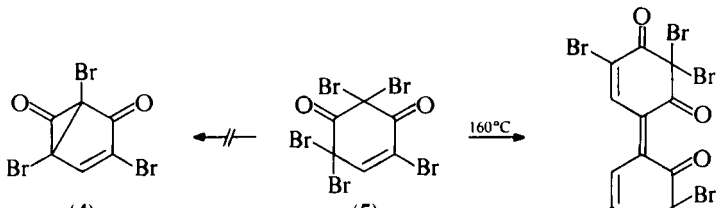
Hantzsch[2,3] also expressed doubt that *uncharged* *m*-quinonoid substances could exist but believed that the *anions* of certain metallic salts obtained by the action of strong alkalis on *m*-nitrophenols might have such a structure (**3**). The methods of physical characterization



(3)

available at the time did not suffice to establish this assignment, and the elucidation by Meisenheimer[4] of the reactions of strong bases with aromatic nitro compounds suggests plausible alternative formulations.

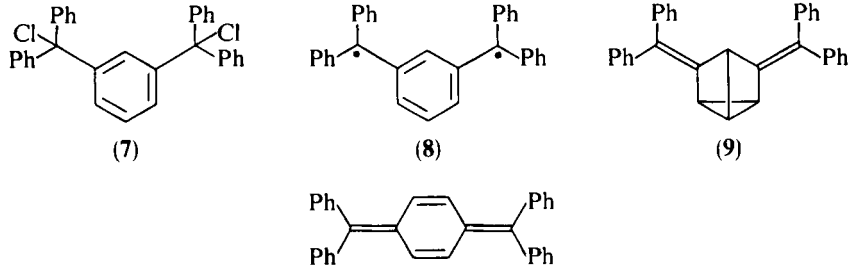
In an extension of work of Liebermann and Dittler[5], Meyer and Desamari[6] assigned a *meta*-quinone structure (**4**) to 'tribromoresoquinone', the product of the pyrolysis of pentabromoresorcinol (**5**). However, Zincke and Schwabe[7] and later, in a second paper,



(4) (5) (6)

Meyer and Desamari[8] themselves showed that 'tribromoresoquinone' is dimeric and has the diphenoquinone structure **6**, not the *m*-quinone structure **4**. Zincke[7] took the occasion to reiterate his earlier opinion[1] by remarking that 'the existence of *meta*-quinones appears to us improbable; years ago, one of us made many attempts to obtain halogen derivatives of these quinones, but without success'.

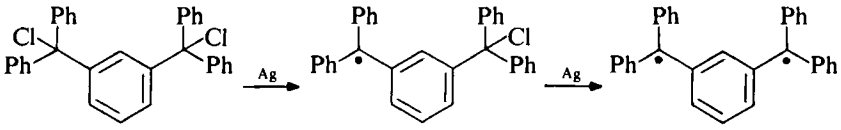
Nevertheless, Stark and his coworkers[9-12] undertook further attempts to prepare a *meta*-quinonoid system. Modeling their experiments on those of Gomberg, whose preparation of triarylmethyl radicals was already widely known, they treated tetraphenyl-*m*-xylylene dichloride (**7**) with metals such as zinc or silver. Implicitly, they used analogical criteria to decide whether the reaction gave a bis-triphenylmethyl (**8**) or a *m*-quinonoid, e.g. **9**. Gomberg's work had established the extreme reactivity of triphenylmethyls to oxygen, whereas a true quinonoid substance, by analogy to Thiele's tetraphenyl-*p*-quinodimethane (**10**), Stark assumed, would be colored but relatively insensitive to oxygen.



(7) (8) (9)

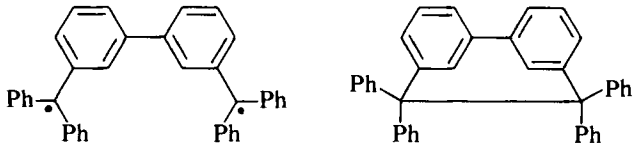
(10)

The materials obtained in Stark's experiments appeared to conform to the quinonoid criteria, but the results were brought under question by later studies of Schlenk and Brauns[13, 14]. The latter authors, by meticulous exclusion of air from their reaction mixtures and by the use of rigorously prepared and purified starting materials, demonstrated the sequential removal of the two chlorines of **7**, forming successively solutions of the yellow chlorotriphenylmethyl derivative **11** and the deep violet bis-triphenylmethyl **8**. Both species **11** and **8** were inordinately sensitive to oxygen, which



(7) **(11)** **(8)**

discharged the color instantaneously[13]. Schlenk and Brauns extended this work soon after to the preparation of the biradical **12** by similar methods[14]. This paper contains one of the first clear recognitions that the 'spatial relationship' (i.e., distance) of the atomic centers involved may preclude the formation of a bond (as in **13**).



(12) **(13)**

With respect to the *m*-quinone problem, Schlenk and Brauns[13] concluded that 'the formation of a bis-triarylmethyl from tetraphenyl-*m*-xylylene dichloride is a new indication that *m*-quinonoid compounds do not exist'.

The dramatic series of refutations encountered to this point seemed to settle the matter in the minds of most chemists, for no further attempts to make *m*-quinonoids were reported for many years. They were considered to be somehow outside the structural theory. For example, in the 1940s, popular undergraduate textbooks[15, 16] discussed a very old structural problem also first formulated by Zincke[17] and much debated thereafter[18–23]: should *ortho*-quinones be formulated as ketones (**14**), in accord with their carbonyl group reactivity, or as peroxides (**15**), in accord with their oxidizing power?

(14) **(15)**

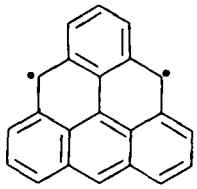
The decision rendered in 1941[15] relied on the following argument:

> It is a fact that only *para* and *ortho* quinones have been obtained. The peroxide theory allows *meta*-quinones to exist. But the keto structure is impossible for a *meta*-quinone, as the student will see if he tries to draw one with four bonds to each carbon.

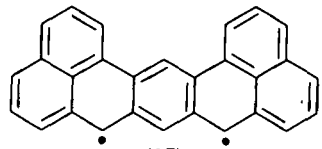
Note that the reasoning again embodies the implicit assumptions that Kekulé's valence numbers are inviolable and that *m*-quinonoids cannot exist.

In the 1950s, Clar and coworkers invoked related arguments to explain the failure to observe the hypothetical hydrocarbon biradicals triangulene (**16**)[24] and dibenzopentacene (**17**)[25] when partially hydrogenated precursors were heated over palladium, conditions that had succeeded in generating fully aromatic polycycles in other cases. Thus,

> . . . the interpretation of this result is that Kekulé structures are of paramount importance when considering the stability of aromatic hydrocarbons. . . . This excludes the existence of *m*-quinonoids and similar systems which cannot be expressed in terms of Kekulé structures.[26]



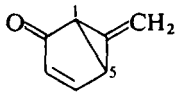
(**16**)



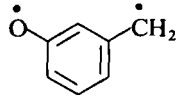
(**17**)

Clar did not take into account the two hydrocarbon biradicals **8** and **12** of Schlenk and Brauns, of which the former is closely related structurally to **16** and **17**. Neither **8** nor **12** can be expressed in terms of Kekulé structures.

It was not until 1979 that the first *m*-quinonoid pair of valency tautomers, the covalent (**18**) and biradical (**19**) forms of *m*-quinomethane, were prepared[27], 88 years after the problem had been presented by Zincke. The structural relationship of the bicyclic, fully covalent *m*-quinonoid **18** to **2**, one of Zincke's hypothetical *m*-quinones, will be immediately apparent. In modern terms, the valency tautomerism **18** → **19** involves cleavage of a carbon–carbon bond (C(1)–C(5)), planarization of the six-membered ring, and other adjustments of the atomic coordinates.



(**18**)



(**19**)

As has been noted here, the supposed non-existence of *meta*-quinones was a key logical element in deciding the diketone vs. peroxide controversy over the structure of *ortho*- and *para*-quinones. Although the choice of the diketone formula ultimately was proven by other means to be correct, the synthesis of **18** and other *m*-quinonoids invalidates the form of argument outlined above. The appeal to isomer number, so often invoked in structural organic chemistry, has only an experiential basis and therefore is vulnerable, should subsequent events establish the existence of an isomer previously thought to be impossible.

The struggles of earlier chemists with the *m*-quinone problem paralleled the growth and improvement of the structural theory of organic chemistry itself. In the realization that future generations probably will hold our theories in the same tolerant regard as we hold those of our predecessors, we do well to shun what E. P. Thompson (in another context) has called 'the enormous condescension of posterity'.

II. THEORETICAL ASPECTS OF HUND'S RULE

A. Quantum Mechanical Justification

In one way, the hydrocarbon biradicals **8** and **12** synthesized by Schlenk and Brauns in 1915[13,14] became available far ahead of their time. One could justifiably argue that their true significance transcended the obvious fact that they were bifunctional examples of Gomberg's triphenylmethyl, which had been a discovery of the immediately preceding era around the turn of the century. Moreover, although the Schlenk–Brauns work must have influenced contemporary thinking in the context which the authors constructed for it, namely as the refutation of a supposed *m*-quinonoid structure, our vantage point in time allows us to see the more important questions to which these compounds were the first answers: is it possible to make molecules for which no full-valence Kekulé structure can be written, i.e. in Dewar's coinage[28], 'non-Kekulé' molecules? What physical and chemical properties should be expected of such species? The Schlenk–Brauns work thus looked forward to quantum mechanics, which was still a decade beyond the horizon.

Actually, more than two decades passed before the first important quantum mechanically inspired experiments on the Schlenk–Brauns systems were carried out. In 1936, Müller and Bunge[29] determined the magnetic susceptibility of these substances and found them both to be paramagnetic. This was a gratifying observation, for the application of Hund's rule[30] would predict exactly this property for biradicals. Since these pioneering observations, it has become clear that an appreciation of the sources of such paramagnetism is crucial to understanding not only the magnetic and spectroscopic behavior of non-Kekulé molecules but also their chemistry. A brief digression here is intended to provide a qualitative background to this subject.

Hund's rule, originally an empirical generalization based upon experimental atomic spectroscopy, states that of the terms of a given electron configuration, the one of lowest energy is the one of highest multiplicity. Although many of the key features of the multiplet structure of atomic spectra in applied magnetic fields (Zeeman effect) had been analyzed by the Russell–Saunders coupling model in the early 1920s, it was not until the concept of electron spin had been introduced by Uhlenbeck and Goudsmit in 1925 that the present interpretation of these phenomena became established[31]. The multiplicity is given by $2S + 1$, where S is the total electron spin. In a simple example, Hund's rule would predict that the triplet state ($S = 1$) of a two-electron atom should be more stable than the singlet state ($S = 0$) of the same configuration.

To understand the origin of the singlet–triplet energy splitting, it is helpful to recall that the Pauli exclusion principle, as interpreted by Heisenberg and Dirac, requires that the total atomic (or molecular) wave function be antisymmetric (change into its own negative) upon an interchange of the space and spin coordinates[32–34]. For example, consider the lowest excited configuration of the helium atom, in which the 1s and 2s orbitals each are assigned one electron. If the electrons are identified as (1) and (2) and their spins are identified by the quantum symbols α or β, the total wave functions are products of a space wave function, which can be expressed as a product of a linear combination of the 'independent electron' wave functions (1s and 2s) and a spin wave function. The space wave functions are either symmetric or antisymmetric, according to whether the sign in the linear combination is positive or negative. The spin wave functions are symmetric if both electrons have the same spin or if the spin is represented as a positive linear combination of opposite spins; they are antisymmetric if the spin is represented as a negative linear combination of opposite spins. The only total wave functions for the He 1s2s electron configuration that satisfy the exclusion principle, therefore, are those shown in equations 1–4, where the subscripts s and a designate symmetric and antisymmetric, respectively, and the designations refer, in order, to the space and spin parts of the wave function.

$$\psi_{s,a}(1,2) = (1/\sqrt{2})[1s(1)2s(2)+2s(1)1s(2)]1/\sqrt{2}[\alpha(1)\beta(2)-\beta(1)\alpha(2)] \quad (1)$$

(space part) (spin part)

$$\psi_{a,s}(1,2) = (1/\sqrt{2})[1s(1)2s(2)-2s(1)1s(2)] \begin{cases} \alpha(1)\alpha(2) & (2) \\ (1/\sqrt{2})[\alpha(1)\beta(2)+\beta(1)\alpha(2)] & (3) \\ \beta(1)\beta(2) & (4) \end{cases}$$

Thus, the excited He configuration 1s(1)2s(2) leads to *four* states, one of which has a symmetric space wave function (equation 1), and three of which have antisymmetric space wave functions (equations 2–4). In a spherically symmetrical system at zero applied magnetic field, the latter three states have identical energies. They are said to be the components of a triplet state. The unique state is said to be a singlet state.

The total wave functions can be derived more elegantly by the method of Slater determinants[31], but the presentation here may be more accessible to those organic chemists whose contact with the formal part of quantum mechanics is infrequent.

Because the spin part of the singlet wave function is antisymmetric (equation 1), the total spin of the singlet is zero. It is proper to imagine the physical basis for this as being the cancellation of equal and opposite z-components of the spin angular momentum vectors, although it may be easier to remember that the total electronic spin S is made up of the algebraic sum of the uncompensated electron spins, each with $S = |\frac{1}{2}|$. In the singlet, each spin of $+\frac{1}{2}$ is compensated for by one of $-\frac{1}{2}$.

In the case of the triplet, two of the spin wave functions (in equations 2 and 4) represent additions of 'up' or 'down' z-components, whereas the third (in equation 3) represents a spin vector that is perpendicular to the z-axis. When placed in a magnetic field strong enough to quantize the energies of the triplet sublevels, these states separate because of the Zeeman effect and are designated T_{+1}, T_{-1} and T_0, respectively, where the subscripts are quantum numbers. It is the summation of two uncompensated like electron spins that results in a value of $S = 1$ for the triplet state and in the physically observable properties associated with paramagnetism.

To avoid confusion over the term 'energy of the triplet state', it is necessary to keep in mind that the Zeeman splittings of the triplet sublevels in the earth's magnetic field or even in the much higher field of an electron paramagnetic resonance spectroscopic experiment are very small (of the order of a fraction of a small calorie per mol) compared to most singlet–triplet separations (often 10000–20000 cal mol^{-1})[35]. For many chemical purposes, therefore, it does no harm to think of the 'singlet–triplet separation' as having one value rather than three.

The energies, E_1 and E_3, associated with the singlet and triplet states can be found by application of the Schrödinger equation. The singlet–triplet splitting emerges in a very natural way when the two-electron Hamiltonian is used, that is, when the full set of physical interactions (neglecting spin-orbit terms) in the three-particle He system (nucleus, electron (1) and electron (2)) is taken into account (equations 5 and 6)[36]. The energies $\bar{E}_3$ and $\bar{E}_1$ are expectation values (average energies), since $\psi_{s,a}\psi_{a,s}$ are one-electron wave functions and are not eigenfunctions of $H(1,2)$[33].

$$H(1,2)\psi_{s,a} = \bar{E}_1\psi_{s,a} \quad (5)$$

$$H(1,2)\psi_{a,s} = \bar{E}_3\psi_{a,s} \quad (6)$$

The solutions of equations 5 and 6 are given[33] by equation 7, in which the energies of the singlet and triplet are quadrisected into the components E_{1s}, E_{2s}, J and K. The terms E_{1s} and E_{2s} are the atomic orbital energies.

$$\bar{E}_j = E_{1s} + E_{2s} + J \pm K \quad (7)$$

The Coulomb integral has the form of equation 8, where r_{12} is the interelectronic distance, and the differentials $dv(1)$ and $dv(2)$ refer to the spatial coordinates of the electrons. Since all the terms in the integrand of equation 8 are positive, J is positive. As the name Coulomb integral implies, this energy term is electrostatic in nature and arises from the mutual repulsion of two charge clouds, one associated with electron 1 and described by 1s*1s, and the other associated with electron 2 and described by 2s*2s.

$$J = \int\int 1s^*(1)2s^*(2)(1/r_{12})1s(1)2s(2)dv(1)dv(2) \tag{8}$$

The exchange integral has the form of equation 9. Note that the two product functions in the integrand differ by an exchange of electrons, hence the name. The integral K gives the energy of interaction of an electron 'distribution' described by 1s*2s with another electron distribution of the same kind[33]. Although these are mathematical functions, not physically realizable electron distributions, the energy K is a real energy. An important purpose of the particular quadrisection in equation 7 is to divide up the energy so as to focus attention on the component responsible for the singlet–triplet splitting, namely K.

$$K = \int\int 1s^*(1)2s^*(2)(1/r_{12})2s(1)1s(2)dv(1)dv(2) \tag{9}$$

K is also an electrostatic term which turns out to be positive[36–38]. In the context of equation 7, this leads to the conclusion that $\bar{E}_1 > \bar{E}_3$, that is Hund's rule is obeyed. The energy separation between the singlet and the triplet is $2K$.

B. Physical Interpretation of Hund's Rule[39]

It is frequently stated that the energetic preference for the triplet state in excited He (and by extension, in other open-shell chemical systems) is the greater average separation of the electrons (r_{12}) which minimizes the interelectronic repulsion energy in that state. This circumstance is traced to the form of the space part of the wave function of the triplet, which is required to be antisymmetric by the Pauli principle, as already has been outlined (see equations 2–4).

A simple demonstration of the effect of spatial symmetry vs. antisymmetry is provided by the two-electrons-in-a-box model[40]. Imagine a one-dimensional box of length L containing two electrons whose position coordinates, x_1 and x_2, can be represented as fractions of L. The charge density in quantum mechanics is given by the square of the wave function, which will be ψ_+^2 for the symmetric space function of the singlet and ψ_-^2 for the antisymmetric space function of the triplet.

A contour diagram of the charge density distribution for the singlet shows two maxima, each of which occurs in a region where the two electronic position coordinates are equal (Figure 1a). In the case of the triplet, however, the charge density distribution peaks at points where the two electronic position coordinates are unequal (Figure 1b). In physical terms, the quantum mechanically enforced propinquity of the electrons in the singlet will result in a greater interelectronic repulsion energy. Another way of stating the matter would be to say that, at this level of approximation, the antisymmetric nature of the triplet wave function ensures efficient correlation of the electronic motions by keeping the electrons in the triplet farther apart, on the average, than is possible with the singlet. The separation between the two charge density distributions in the triplet is sometimes called a 'Fermi hole'.

This simple picture surely serves as a useful starting point for understanding the nature of the singlet–triplet splitting, but one should keep in mind that it is based upon an approximation, which is that the same set of atomic orbitals is used to compare the energies of open-shell singlet and corresponding triplet configurations. Qualitatively, the consequences of this approximation can be apprehended by dissection of the electronic energy of our model 1s2s configuration of He into its most important components. These consist

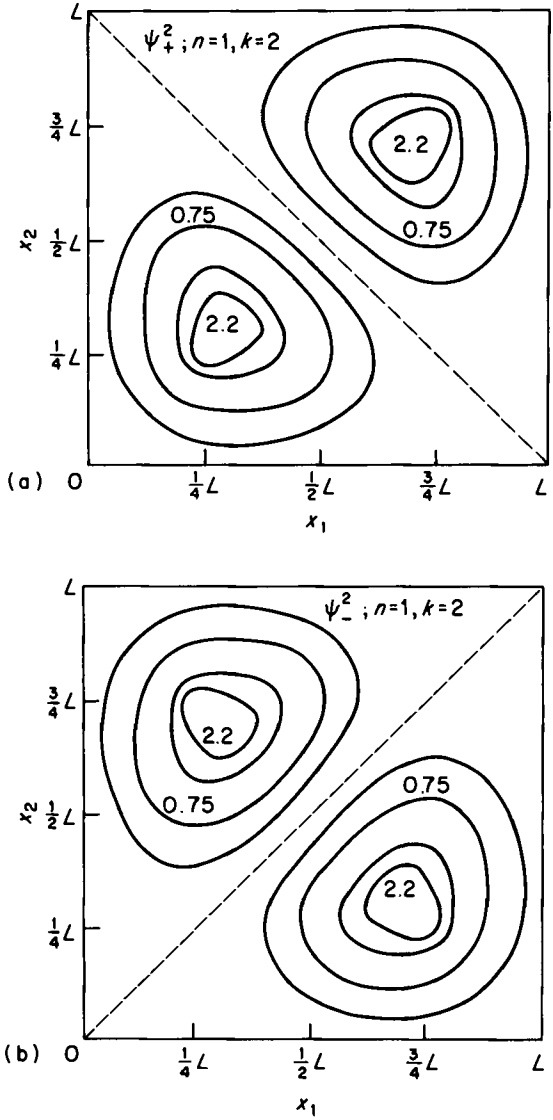


FIGURE 1. Contour diagrams of the charge density distribution for the singlet (a) and the triplet (b) of a hypothetical two-electrons-in-a-box system. *From Ref.* 35, *McGlynn, Azumi and Kinoshita,* Molecular Spectroscopy of the Triplet State, © 1969, *pp.* 69, 70. *Reprinted by permission of Prentice Hall, Englewood Cliffs, New Jersey*

of the two-electron portion (electron–electron repulsion) and the one-electron portions (kinetic energy and electron-nuclear attraction). Because of the approximation in which the atomic orbitals used for the singlet and triplet are the same, the one-electron components (kinetic energy and electron-nuclear attraction) remain the same for the two multiplets. As

was outlined above, the only energy difference between the two is in the two-electron components. This difference is generated because of the Pauli principle and is expressed in the form of the exchange energy, K.

At this point, it can be seen[43] that the approximation has led to a violation of the Virial Theorem, which may be stated as $2T = -V$, where T stands for kinetic energy, and V stands for potential energy. The theorem enforces a zero-sum rule on the total energy of the system and states that one cannot change the potential energy without a concomitant change in the kinetic energy. To satisfy the Virial Theorem, the decrease in potential energy when the singlet becomes the triplet must be accompanied by an increase in the kinetic energy. The result of this would be that the optimized orbitals of the triplet would be more contracted than those of the singlet. This effect increases the electron–electron repulsion in the triplet but also increases electron-nuclear attraction.

In other words, a higher order of theory than the approximation first used would recognize the balance of forces affecting the spatial extent of the wave function as the system 'attempts' simultaneously to minimize kinetic energy and electron–electron repulsion, which is favored by dilation of the wave function, and to maximize electron-nuclear attraction, which is favored by its contraction. Several calculations of atomic multiplet states, including those of our model system, the 1s,2s configuration of excited He, show that the electron-nuclear attraction is the dominant factor in determining multiplet stability[41-48]. In the triplet state, the orbitals are contracted to the point where electron–electron repulsion actually is greater than in the singlet, but the destabilization resulting from this increased repulsion is more than counterbalanced by the increased electron-nuclear attraction. It should be noted that this relationship holds even in one of the few atomic systems where Hund's rule is violated[44]. Thus, in the lowest multiplet states of Mg, where ^{1}D falls below ^{3}D, a calculation shows[44] that electron repulsion is greater in the lower energy ^{1}D state.

Colpa[43] has suggested an instructive reformulation of the physical basis of Hund's rule in terms of several crucial inequalities. First, one performs an SCF calculation in a two-electron system with two singly occupied orbitals, A and B, using for the singlet state a wave function of the type $(1/\sqrt{2})[A(1)B(2) + A(2)B(1)] \times$ spin function. The results of this (and further) calculations are expressed with the notation S for singlet energy and T for triplet energy. A superscript stands for a calculation done using orbitals optimized for the indicated state; a subscript signifies the type of calculation. On this basis, the result of the above calculation is denoted S^S_{SCF} (see Figure 2a).

Using these same orbitals (optimized for the singlet state), one then calculates T^S_{SCF}, the energy for the triplet state. Of course, had the calculation been done using the best triplet orbitals, one would have obtained a lower energy for the T state, T^T_{SCF}. T^S_{SCF} is then an upper limit for the 'true' (i.e. best within the approximation) triplet energy. Therefore, if we take into account the singlet–triplet splitting for each set of optimized orbitals (see Figure 2 and equation 7), we may write equation 10:

$$T^T_{SCF} \leqslant S^S_{SCF} - 2K^S_{AB} \tag{10}$$

which may be rearranged to equation 11:

$$2K^S_{AB} \leqslant S^S_{SCF} - T^T_{SCF} \tag{11}$$

Similarly, if one were to perform the calculation using the best triplet orbitals in the triplet wave function, one would obtain the triplet energy, T^T_{SCF} (see Figure 2b). Using triplet-optimized orbitals to calculate the singlet energy, one would obtain the energy S^T_{SCF}. Again, this is an upper limit to the 'true' singlet energy, S^S_{SCF}. Therefore, we have the inequality of equation 12:

$$S^S_{SCF} \leqslant T^T_{SCF} + 2K^T_{AB} \tag{12}$$

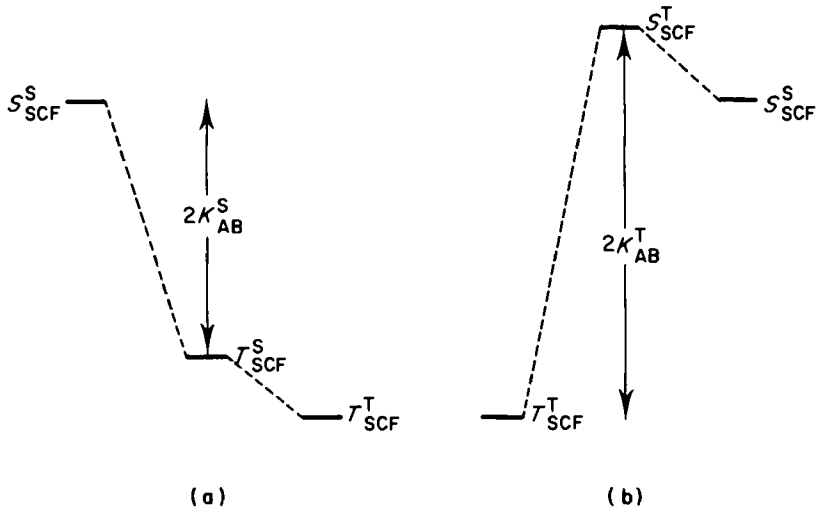


FIGURE 2. Relative energies of S and T states for different SCF calculations. K_{AB} is the exchange integral

Rearrangement of equation 12 gives equation 13:

$$2K^T_{AB} \geqslant S^S_{SCF} - T^T_{SCF} \tag{13}$$

Equations 11 and 13 now may be combined to give equation 14:

$$2K^S_{AB} \leqslant S^S_{SCF} - T^T_{SCF} \leqslant 2K^T_{AB} \tag{14}$$

In words, the singlet–triplet energy gap is larger than the exchange energy calculated with singlet-optimized orbitals and smaller than the exchange energy calculated with triplet-optimized orbitals. Since the exchange energy is necessarily positive[37], the 'true' singlet–triplet energy gap, $S^S_{SCF} - T^T_{SCF}$, must be positive, and Hund's rule is proved within this approximation. It is important that in this formulation, an assignment of the explicit origin of the difference in energy, that is, the relative contributions of electron–electron repulsion and electron-nuclear attraction, is not needed to derive the order of the states, which is attributable only to the fact that K is a positive quantity and that in calculating the energy of the spatially antisymmetric state, namely the triplet, we take the negative of K (see equation 7 and Figure 2).

For the present purpose, the effects of electron correlation have not been addressed. When this is done, the state of lower multiplicity, which is higher in energy, will be stabilized more than the state of higher multiplicity. This will have the effect of narrowing the S–T gap or even possibly inverting the order of states and leading to a violation of Hund's rule[49]. A further discussion, with emphasis on molecular rather than atomic systems, is given in Section III.F.

To strengthen the explication of Hund's rule, it may be useful to quote two succinct statements of the issues. According to Colpa and coworkers[45]

> . . . When we begin in an excited singlet state and go down in energy with frozen orbitals to an approximate triplet state, we use the argument that the triplet state has a lower energy solely because of its lower interelectron repulsion energy. The next step in our argument, the [orbital] relaxation, lowers the energy of the triplet state even further, but the electron repulsion may be raised so much

that there is no sign left of the original argument (lowering of repulsion) in the net result of the two steps taken together. In short, the second step strengthens the result of the first step but destroys the generality of the argument used in the first step.

To the same effect, McBride and Vary[50] point out

> First order stabilization [i.e., the decrease in energy of the higher multiplet due to the lesser extent of electron–electron repulsion assuming frozen orbitals] is very close to the true singlet–triplet difference, and its ultimate appearance in an unusual guise should not cloud the fact that the fundamental difference between the singlet and the triplet is the spatial antisymmetry of the latter, which keeps the electrons apart, other things being equal.

As long as the level of approximation is kept in mind, it would seem to be a matter of personal preference whether one chooses to ascribe the basis of Hund's rule to first-order electron–electron repulsion effects or to the more general formulation in terms of 'Pauli repulsion' as expressed by all of the components of the exchange integral K.

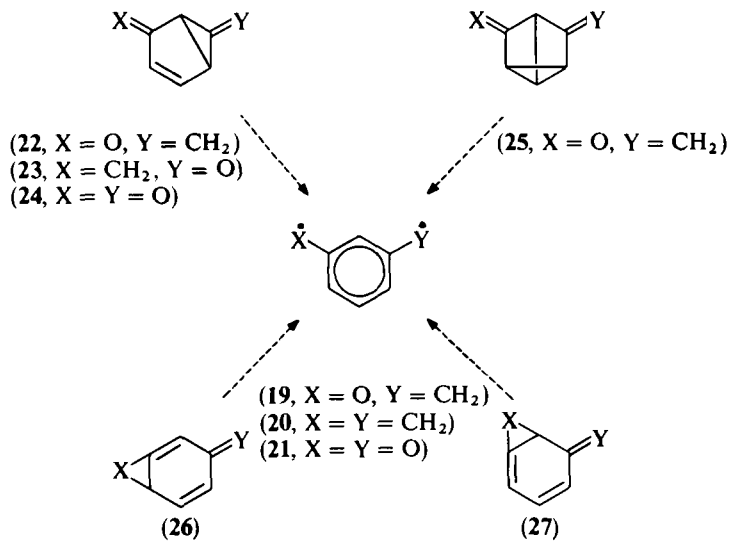
The profound and elegant systematization of atomic spectroscopy which culminated in Hund's rule was put forward 60 years ago[30]. The formulation of a simple qualitative understanding of its physical basis has developed slowly during the intervening time, and one must account the rule's author unduly modest when he remarks (in translation):

> The 'argument' for the validity of the rule (stronger antisymmetry of the space part of the eigenfunction is more favorable because of electron repulsion) first became apparent to me only later. Really, it should have been in *Z. physik*, **43**, 788 (1927). But I was just not that smart.[51]

III. THE *META*-QUINONE SERIES

A. Structure

General structural formulas for the biradical **19–21** and for the conceivable fully covalent isomers **22–27** of *m*-quinonoids are shown in Scheme 1. In the cases of **22**, **26** and



SCHEME 1

27, only one of a pair of isomers is shown: the other may be derived by interchange of X and Y. Structures **24** and **25** are equivalent to the original *m*-quinones hypothesized by Zincke (**1** and **2**). In principle, the biradical **19** could be derived by cleavage of one bond of **22**, **26** or **27**, or of both transannular bonds of **25**. Other fully covalent connectivities can be imagined, but they would violate Bredt's rule severely and are not shown. Structures **26** and **27** do not embody two exocyclic double bonds and thus have a dubious kinship to quinones. Although they are so far without example in the literature, Scheme I includes them as illustrations of potential alternative entry points onto the *m*-quinonoid energy surface.

Molecules of the group **22–27**, although they are expected to be strained and highly reactive, have conventional Kekulé structures and pose no special problems in valence theory. Structures **19–21**, however, are non-Kekulé species. They have enough atoms but not enough bonds to satisfy the standard rules of valence. These entities should be clearly differentiated from the more familiar reactive intermediates such as carbenes, carbanions, carbocations and radicals, which not only are bond-deficient but also are atom-deficient. Anticipating a later discussion, we note that the *m*-quinonoid non-Kekulé molecules are related in many ways to simpler biradicals such as trimethylenemethane (**28**) and tetramethyleneethane (**29**).

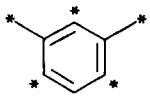
(**28**)

(**29**)

B. *meta*-Quinodimethane[32]

1. Theory

a. Hückel molecular orbital treatment. Theoretical description of *m*-quinonoids began in 1936 with Hückel's treatment[52] of the Schlenk–Brauns hydrocarbons and has continued to the present[28, 53–73]. As is the case with other biradicals[74], the *m*-quinonoid hydrocarbon **20** is characterized in the π-electron approximation by a pair of 'nearly degenerate', nominally non-bonding frontier molecular orbitals (NBMOs). Structures **20**, **28** and **29** are alternant, that is, the carbon atoms can be marked ('starred') in such a way that no two starred or unstarred positions are vicinal. For such systems (assumed for this purpose to be coplanar), Longuet-Higgins[56] showed by the application of Hückel π-electron theory that the number of NBMOs is always at least $N - 2T$, where N is the



(**20**)

(**28**)

(**29**)

number of π-electron centers, and T is the number of double bonds in the resonance structure with the maximum number of bonds. For most alternants, the number of NBMOs is actually predicted to be equal to $N - 2T$. The only significant exceptions occur in the 4n annulene cases (for example, cyclobutadiene), where there are typically two NBMOs despite the fact that $N - 2T = 0$. Thus, all three molecules **20**, **28** and **29**, should have two NBMOs.

The number of π electrons in the neutral form of each of these systems is enough to

provide double occupation for all the bonding MOs as the levels are filled by *aufbau*, but only two electrons are left to occupy the two NBMOs. There will be four zeroth-order configurations, two with single occupancy of each NBMO and either singlet or triplet spin configurations (Figure 3, a and b), and two with double occupancy of one or the other of the NBMOs (Figure 3, c and d). The latter two 'closed-shell' configurations will mix to produce two singlet configurations, whereas the 'open-shell' configurations will be distinguished by their spin as a singlet and a triplet.

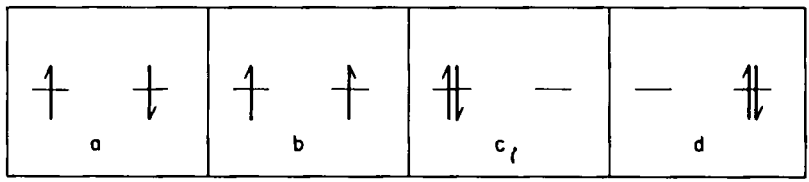


FIGURE 3. Zeroth-order states of a biradical. Configurations a and b correspond to 'open-shell' singlet and triplet, respectively, c and d are 'closed-shell' singlets

It now should be apparent why Longuet-Higgins's elegant theorem for predicting the number of NBMOs of alternant systems is significant. If Hund's rule applies to molecules, the diagram of Figure 3 would predict that the triplet would be the ground state of the neutral alternant system. In general, the total spin S of the ground state of such molecules will be half the number of NBMOs. The multiplicity, which is given by $2S + 1$, will be one more than the number of NBMOs.

Longuet-Higgins assumed that Hund's rule does apply to molecules, not only to atoms. Indeed, this assumption has a long history[51,75-80], which can be traced back almost as far as the atomic Hund's rule itself. The satisfying explanation on this basis of the long-known paramagnetism of the ubiquitous molecule O_2 was one of the earliest triumphs of the molecular orbital theory[75-80]. In retrospect, one may say that Hund's rule sometimes was applied to molecules uncritically, but it is easy to understand that the O_2 case must have swept aside any lingering doubt. The combination of Longuet-Higgins's theorem with Hund's rule thus leads to the prediction that *m*-quinodimethane (**20**) should have a triplet ground state. A similar conclusion for the specific case of the Schlenk–Brauns tetraphenyl derivative (**8**) was reached by Hückel[52], although he did not generalize the result.

These predictions, of course, are based upon a very approximate level of theory. Except for the few cases in which the molecular symmetry is high enough to enforce it, the NBMO degeneracy of non-Kekulé alternants is 'accidental' and vanishes in any higher level calculation[81-84]. When even the crudest consideration is given explicitly to electron repulsion, the energies of the nominal NBMOs split. For example, even an INDO calculation on *m*-quinodimethane (**20**) shows the frontier orbitals to be separated by $\sim 15\ \text{kcal mol}^{-1}$. It is not obvious that Hund's rule should apply to such a case. Hoffmann[85] has suggested that unless the gap between the frontier orbitals is 1.5 eV ($34\ \text{kcal mol}^{-1}$) or more at the extended Hückel level of theory, the triplet should be the ground state. Otherwise, it would be energetically advantageous to put both electrons in the lower orbital, since the electron repulsion so generated would not suffice to offset the orbital separation. In that case, the ground state would be described as a closed-shell singlet. Corresponding rules of thumb for higher levels of calculation are not available, and the prediction of the relative energies of the singlet and triplet in non-Kekulé molecules is a major undertaking in computational quantum mechanics. Hückel theory, even in its extended form, does not explicitly distinguish the singlet and triplet energies, since it is a one-electron theory[85]. As already has been discussed in Section III.B.1, the exchange

integral K, which determines the singlet–triplet splitting, emerges only when a two-electron (or multi-electron) Hamiltonian is used.

Since the analytical solution of the full Schrödinger equation for a molecule as large as *m*-quinodimethane (**20**) is not yet feasible, the task of theory becomes the choice of an approximate method. There are two older approaches, semiempirical[86] and *ab initio*[87]. More recently, a non-empirical Heisenberg Hamiltonian method has been applied to a few biradical systems[68].

b. Semiempirical treatments. The semiempirical molecular orbital methods all rely on a parameterization from experimental spectroscopic data to provide values for the needed core integrals and resonance integrals. Various levels of improvement can be achieved by configuration interaction (CI) calculations, in which singly, doubly, or even more highly excited electronic configurations are allowed to mix with the ground configuration. In most of the methods a reasonable molecular geometry is guessed by analogy to model structures.

The chief advantage of semiempirical MO methods for non-Kekulé problems are speed and economy. The disadvantages, however, are not to be overlooked. Perhaps the most fundamental of these is that the semiempirical nature of the wave functions means that they are not eigenfunctions of a correct molecular Hamiltonian but rather of an *effective* Hamiltonian. To derive energies, it is necessary to parameterize the integrals in order to include (implicitly) interelectronic effects. In such circumstances, the variational theorem does not apply, which has the serious consequence that one cannot be sure that a change of the parameterization scheme that leads to a lower calculated energy has necessarily produced an answer closer to the true energy.

Three semiempirical calculations of the energy separation between the lowest singlet and triplet states of *m*-quinodimethane are available. An SCF-CI calculation[60,61,88] with CI based on the singlet MOs using all singly and some doubly excited configurations leads to the conclusion that the triplet is the ground state by 7.8 kcal mol^{-1} [60]. Another approach[69] uses a full CI PPP (Pariser–Parr–Pople) calculation to predict a triplet ground state by 9 kcal mol^{-1}. Still another calculation[70] is based upon the INDO-S/CI program of Ridley and Zerner[89,90], which has been extensively checked[70] for reliability by comparison of its predictions to those of higher level theory or to experimental data for a number of non-Kekulé systems. Again, a triplet ground state for **33** is predicted. The lowest lying singlet state is $^1A_1$, which is calculated to be 15.0 kcal mol^{-1} above the $^3B_2$ ground state. Note that the $^1A_1$ state is largely of a closed-shell nature, despite the electron repulsion energy that one might imagine to be associated with a doubly occupied HOMO configuration. The reason for this can be found in the effect of CI. At the INDO/S level, before CI, the lowest singlet is found to be the open-shell type, $^1B_2$, but the CI treatment selectively stabilizes $^1A_1$[70].

It should also be noted that CI sharply diminishes the S–T gap in the INDO-S/CI calculation by the selective stabilization of the singlet. This can be traced to the fact that singlet configurations can be of either open- or closed-shell types, but triplet configurations must be open-shell. Thus, there are many more excited singlet configurations in any practical CI active space. If other factors are equal, mixing of configurations of like multiplicity will be more effective in lowering the energy of that multiplet.

c. Non-empirical treatment. The so-called non-empirical Heisenberg valence bond Hamiltonian approach[66] extracts the effective Hamiltonian H^{eff} from a high quality *ab initio* calculation on ethylene, using extended basis sets of double zeta plus d quality and a CI scheme involving up to 10^5 configurations. This procedure provides a model for the σ potential and the effective exchange integral between adjacent atoms which can be applied to other conjugated hydrocarbons. Since the method does not incorporate experimental data, it would not be correct to refer to it as 'semiempirical', yet it is not *ab initio* either in a direct sense. The method actually uses parameters derived from an *ab initio* calculation, so that it occupies a territory between the two older schemes. It also makes provision for

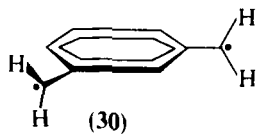
direct and efficient geometry optimization. This method predicts a triplet ground state for *m*-quinodimethane (**20**) 28 kcal mol^{-1} below the $^1A_1$ state. This separation is in the same direction as, but substantially larger than the values of 8, 9, 15 and 10 kcal mol^{-1} predicted by the semiempirical and *ab initio* methods.

d. Ab initio methods with large basis sets for a molecule as large as *m*-quinodimethane (**20**) require massive computational capacity and are far from commonplace. A major effort on **20**[67] employed the Dunning split valence basis functions and an extensive CI routine, after geometry optimization at the SCF level, to produce the predicted triplet ground state, 10 kcal mol^{-1} below the $^1A_1$ state. The (largely) open shell $^1B_2$ state is found[67] to be much higher in energy than the $^1A_1$ state, as is observed in the INDO-S/CI calculation[70].

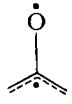
e. Prospects. Although the semiempirical methods often give quite reliable results for non-Kekulé molecules, there does not seem to be general agreement[91, 92] on whether they are to be regarded as substitutes for the much more expensive high-level *ab initio* theory. At least, they seem destined to be used as a guide to experiment, an indicator of what magnetic and chemical properties might be reasonably expected of new molecules, and an aid in the choice of synthetic non-Kekulé targets which may serve as tests of theory. The non-empirical method has not yet been extensively tested but should ultimately afford many interesting comparisons with other methods. One looks forward also to the expansion of computational power that will permit *ab initio* calculations for many more non-Kekulé systems.

f. Non-planar geometries. All of the above calculations on *m*-quinodimethane have imposed a planar geometry on the entire π-electron system. Superficially, this might be expected to be the most stable geometry since it preserves the conjugative stabilization. However, it is known[82, 93–97] from *ab initio* calculations on another conjugated biradical, specifically trimethylenemethane (**28**), that the electron–electron repulsion relieved by twisting one methylene group of the singlet is sufficient to overcome the loss of conjugation energy. This results in a closely matched pair of singlet states, of which one is planar and the other, usually at a slightly lower energy, is non-planar. The triplet states of conjugated biradicals prefer to preserve their planarity[57, 93–98]. The difference in the degree of preference for the planar configuration by the two multiplets can be understood in terms of the better electron correlation in the planar triplet, which accomplishes with the Fermi hole what can only be achieved by a structural distortion in the singlet[82, 99].

Dewar and Holloway[100] have recently proposed on the basis of MNDO-CI semi-empirical calculations that a biradical with the doubly twisted geometry (symmetry designation $^1B_2$) is the lowest energy singlet of the non-Kekulé molecule *m*-quinodimethane (**20**). The diagonalized MNDO force constant matrix shows this state to



(**30**)



(**31**)

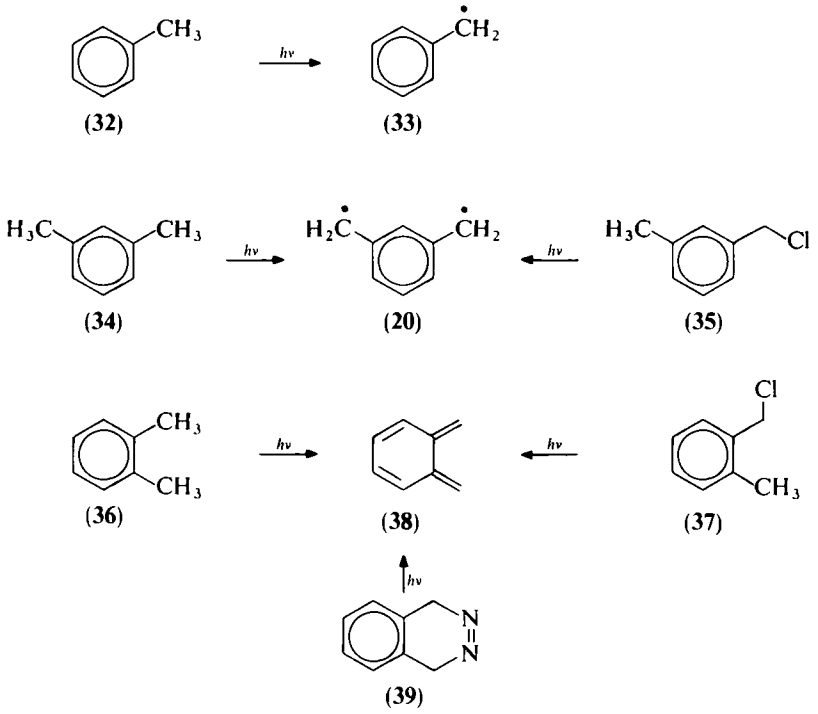
be in an energy minimum on the singlet surface. This is a most interesting result and opens the possibility that such species may contribute to the chemistry of *m*-quinodimethane. In the absence of experimental data, the reliability of this finding is difficult to evaluate, but it should be pointed out that a similar calculation[100] found planar singlet ($^1A_1$) oxyallyl (**31**) to be a saddle point on the energy surface, rather than a minimum, as was found in the most recent *ab initio* calculations of Osamura and coworkers[101].

2. Spectroscopy

a. Optical absorption and emission. Schlenk and Brauns[13] reported that the deep violet solution obtained by heating tetraphenyl-*m*-xylylene dichloride (**7**) in benzene with

copper–bronze showed an intense absorption band between 576 and 636 nm. A likely candidate for the absorbing species is tetraphenyl-*m*-quinodimethane (**8**), although the spectrum does not provide much structural information. However, modern techniques have contributed significantly in this regard.

The optical spectroscopy of the unsubstituted *m*-quinodimethane (**20**) was first studied by Migirdicyan[102]. Porter and Strachan[103] had shown that ultraviolet photolysis of



toluene (**32**) in rigid media was capable of cleaving a CH_2–H bond to give benzyl radical (**33**). This species was stable when thus trapped in the solid and could be observed by absorption spectroscopy. Extending these observations, Migirdicyan found that photolysis of *m*-xylene (**34**) or α-chloro-*m*-xylene (**35**) in methylcyclohexane glass at 77 K gave a common trapped species whose emission spectrum was entirely different from those obtained from the *ortho* counterparts **36** and **37**. Photolysis of the latter two species gave the Kekulé polyene *o*-quinodimethane (**38**), which Flynn and Michl[104] later independently generated from the diazene **39** and other precursors and showed to have the same spectroscopic properties.

A subsequent report[61] described the photolysis of *m*-xylene (**34**) in polycrystalline *n*-pentane (Shpolskii matrix), a medium that favors the observation of sharp vibrationally resolved electronic spectra. The photolysis produces both *m*-quinodimethane (**20**) and the *m*-methylbenzyl (*m*-xylyl) radical. Although the latter species has a strong fluorescence spectrum lying to the red side of 4740 Å, the fluorescence of **20** fortunately can be observed in the narrow wavelength range 4400–4700 Å. Figure 4 displays the two spectra shifted with respect to each other so that their 0, 0 bands coincide. Notice that the vibrational progressions are very similar. Moreover, the two main vibronic bands of *m*-quinodimethane (at 530 and 988 cm^{-1}) and those of *m*-methylbenzyl radical (at 521 and

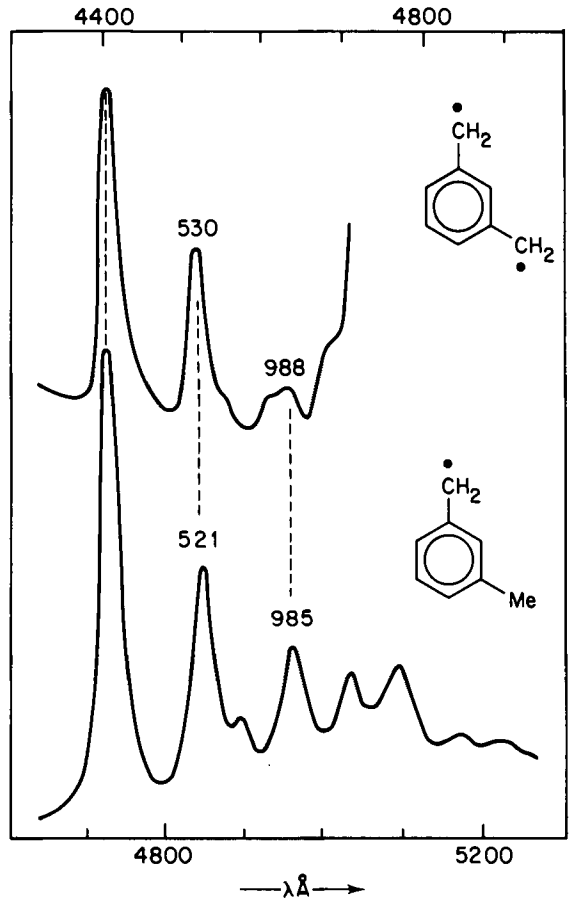


FIGURE 4. Fluorescence spectra of *m*-quinodimethane biradical (upper curve) and *m*-xylyl monoradical (lower curve, λ_{exc} = 3230 Å) produced by photolysis of *m*-xylene in pentane at 77 K. *Reproduced with permission from E. Migirdicyan and J. Baudet*, J. Am. Chem. Soc., **97**, 7400 (1975). *Copyright* (1975) *American Chemical Society*

985 cm^{-1}) have frequencies very similar to those of ground state vibrational modes of *m*-xylene. The optical spectroscopic data alone do not suffice to identify the spin states involved in the observed electronic transitions, and the quantum mechanical calculations[61] are not decisive in this regard. However, the subsequent experimental demonstration of a triplet ground state for **20** (see the next section) supports the assignment[105] of the electronic spectra to triplet–triplet transitions.

Further information on the excited triplet states of *m*-quinodimethane and its methylated derivatives is provided by site-selective laser fluorescence-excitation spectroscopy at 5–10 K. It is concluded that there are two close-lying excited states in these triplet molecules which can interact vibronically. Computational support (SCF MO/CI) for these assignments also is put forward[105–107].

b. Characterization of the spin state of non-Kekulé compounds. The experimental determination of the spin of the ground state of these species is not a routine matter. Techniques appropriate to the properties of specific molecules include chemical trapping, measurements of magnetic susceptibilities, chemically induced nuclear polarization and probably most often, electron paramagnetic resonance spectroscopy.

i. Magnetic susceptibility. The application of magnetic susceptibility measurements to the Schlenk–Brauns hydrocarbons has already been mentioned in Section II. A substance with one or more unpaired electrons will possess a permanent magnetic dipole moment because of the net electron spin. This causes it to have a positive magnetic susceptibility (paramagnetism) and therefore to be drawn into the more intense part of an inhomogeneous magnetic field[108, 109]. The paramagnetism will be proportional to the number of unpaired electron spins. However, the paired electrons in such a molecule (or any molecule) contribute a negative magnetic susceptibility (diamagnetism), which tends to push the sample out of the field. In most substances with net spin $S > 0$, the paramagnetism overbalances the diamagnetism, but a quantitative estimation of the paramagnetism requires that the observed net susceptibility be corrected for the diamagnetic contribution. The susceptibilities are usually measured with some form of Gouy balance, which is capable of determining the gain in apparent weight experienced by a paramagnetic substance in the magnetic field. For various reasons[108, 109], these measurements and corrections are difficult to carry out with a high degree of accuracy.

An even more serious problem with the magnetic susceptibility technique is that it is not sensitive to the structure of the paramagnetic species, since it measures only the net paramagnetism. Frequently (see below) the chemical or photochemical generation of a paramagnetic (e.g. triplet) species of interest is inadvertently accompanied by the formation of (often unidentified) radical impurities. The magnetic susceptibility measurement reports the total paramagnetism of the sample, a quantity from which it usually will not be possible to extract the information of interest, namely the paramagnetism of the triplet species.

ii. Electron paramagnetic resonance (EPR) spectroscopy[35, 110–115]. EPR spectroscopy, which became widely available in the 1950s, proved to be a powerful and decisive technique for characterization of the structure of paramagnetic species. Chemical substances with total electron spin $S > 0$ are paramagnetic and are required by quantum mechanics to exist in discrete spin substates in an applied magnetic field. The number of such substates (multiplicity) is given by $2S + 1$. Thus, a monoradical, with $S = \frac{1}{2}$, constitutes a doublet of states, usually referred to in abbreviated form as a 'doublet'. Although the outlines of EPR spectroscopy of doublet species probably are familiar to many chemists, a brief review will help to introduce the less familiar topic of EPR spectroscopy of high-spin species. The discussion that follows concerns entities that are adequately described by a time-independent spin Hamiltonian, a proviso that applies to the great majority (if not all) of the cases that will concern us here.

(*a*) *The Zeeman effect.* It should be obvious that substances with $S = 0$ cannot have EPR spectra, because a multiplicity of unity means that only one spin level exists at any field strength, and no other state can be populated by absorption of microwave radiation.

When $S = \frac{1}{2}$, two sublevels exist, whose energy separation increases with the strength (H) of the applied magnetic field (Zeeman effect, Figure 5). Because of the negative charge on the unpaired electron, the lower energy sublevel is the one with the electron's spin vector aligned against the field ($M_S = -\frac{1}{2}$), as can be seen from equation 15:

$$E = g\beta M_S H \tag{15}$$

The symbol g is the electronic g-factor, β is the Bohr magneton, H is the magnetic field strength and M_S is the spin quantum number of the doublet sublevel, which can take on the values $\pm\frac{1}{2}$. As H is increased, equation 15 predicts that the doublet sublevels should

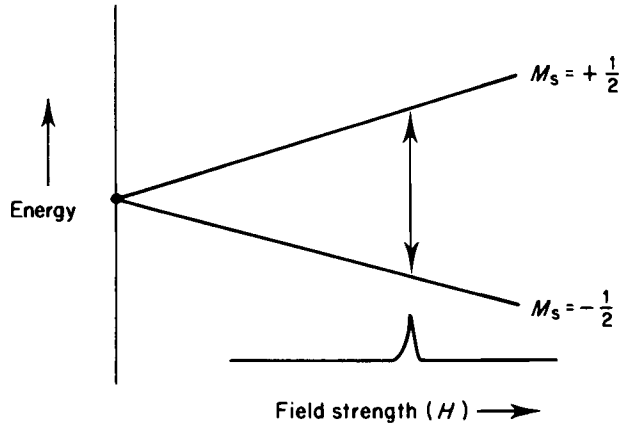


FIGURE 5. Energies of the sublevels of a doublet state as a function of field strength. The double-headed arrow shows the resonance condition for a particular microwave frequency. The transition represents a change in spin quantum number of $\Delta M_s = \pm 1$. *Adapted with permission from Ref.* 111, *p.* 13

separate in energy, the $M_S = -\frac{1}{2}$ state going down and the $M_S = +\frac{1}{2}$ state going up along lines whose slopes are $M_S g\beta$ (Figure 5).

The selection rule $\Delta M_S = \pm 1$, $\Delta M_I = 0$ (M_I is the nuclear spin quantum number) governs the transition. The ΔM_S rule is self-evident in the doublet case, but it applies also to higher spin systems. The probability of a transition depends upon the difference in populations of the two states, which usually (but not invariably) is controlled by a Boltzmann distribution.

For practical reasons, the resonance condition is met in a typical EPR experiment by holding the frequency of electromagnetic radiation constant and sweeping the field. Most of the experiments use X-band spectrometers, for which the typical operating parameters are a frequency in the microwave region (near 9 GHz) and a field strength up to about 10 000 gauss. At these field strengths, the sublevels are separated by a fraction of a small calorie per mol. A transition can occur, either by absorption of a microwave quantum by the lower state or by emission of one by the higher state, whenever the separation between the levels matches the energy of the quantum. Detailed information about the structure of the radical may be deduced from the hyperfine splitting of the electronic spin levels by the spin magnetic moments of the magnetically active nuclei (especially protons) in the molecule.

(*b*) *The spin–dipolar interaction and zero-field splitting.* In high-spin systems, in which two or more unpaired electrons are present, an additional complication is introduced, because each electron now is affected not only by the applied magnetic field but also by the field associated with the spin of the other unpaired electron(s). For reasons to be given, this is called the spin–dipolar interaction. The electron spin energies also are affected by another phenomenon, the spin–orbit interaction, but in most of the instances discussed here, this is a minor perturbation.

Although it adds conceptual complexity, the spin–dipolar interaction actually is a delightful boon, because it forms the physical basis for the so-called zero-field splitting (ZFS) of the sublevels of a high-spin molecular state. The ZFS is responsible for the characteristic features of multiplet EPR spectra which provide structural information

about the molecular carrier of the signal. A physical picture of the spin–dipolar interaction may be developed by following the discussion of El-Sayed[116].

It is useful to think of a spinning electron as generating a spin dipole. Since the dipoles of the unpaired electrons of a high-spin system all have the same directionality, the dipole–dipole coupling is repulsive. Imagine an atom in a triplet state in which the distribution of the two unpaired electrons is spherical (state symmetry designation ^3S). Assume the absence of an applied magnetic field. We may select arbitrarily three mutually perpendicular planes, YZ, XZ and XY. The spin of the two electrons may be quantized so that the component of the spin angular momentum in the direction perpendicular to the chosen plane is zero. For example, if the two electrons are considered to have their spin axes confined to the XY plane, the component of spin angular momentum along the Z direction is zero. The quantum state so defined may be called the T_Z zero-field state. Similarly, the T_Y and T_X zero-field states correspond to magnetic sublevels in which the two unpaired electrons are spinning in (that is, have their spin axes confined to) the XZ and YZ planes, respectively, and have zero components of spin angular momentum in the Y and X directions. Because of the spherical symmetry of the electron distribution, the average distance of the two parallel spins in the different planes is the same. Therefore, the repulsive magnetic dipolar interaction between the two electrons is independent of the plane that happens to contain their spin angular momentum vectors. Consequently, the zero-field states T_Z, T_Y and T_X all have the same energy (Figure 6a) in the absence of an applied magnetic field.

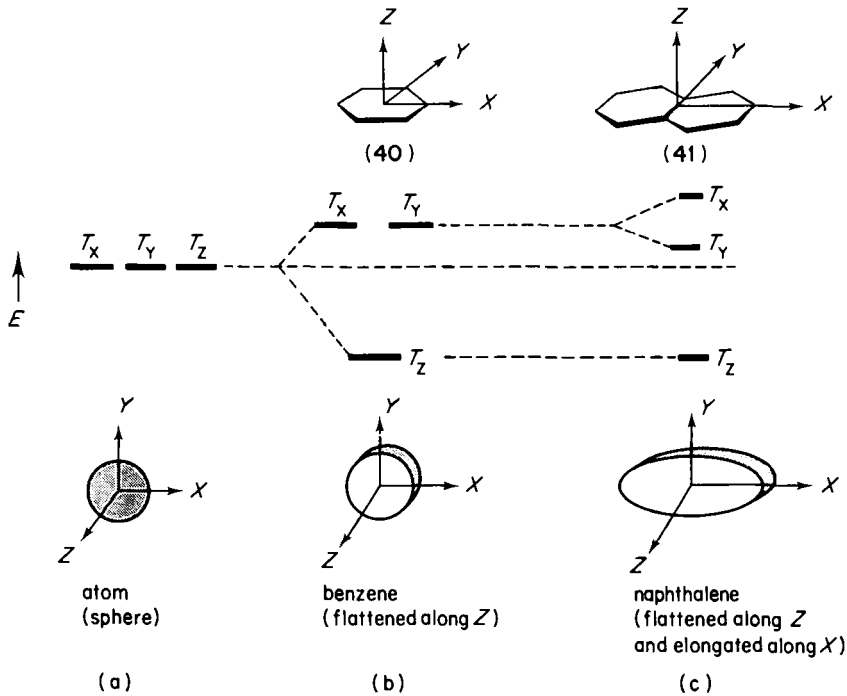


FIGURE 6. The origin of zero-field splitting in molecules. The average distance, and thus the magnetic dipolar couplings, will depend upon the plane that contains the spin angular momentum vectors of the two electrons. In the states T_X, T_Y and T_Z, these planes are respectively, YZ, XZ, and XY. The energy scale is schematic. *Taken from M. A. El-Sayed, Ref.* 116, *and copied with permission*

When two electrons with unpaired spins are present in a molecule rather than in a ^3S state of an atom, the spherical symmetry of the electron distribution is broken. In the triplet state of benzene **40** (Figure 6b), for example, the electron distribution can be modeled by the flattened tablet of Figure 6b. The average distance of the two parallel spins in plane YZ is the same as that in plane XZ, but the separation is greater in plane XY. Consequently, the state T_Z is stabilized by the resulting diminished dipolar repulsion, whereas states T_Y and T_X are destabilized. This splitting of the state energies is the zero-field splitting. It results directly from the anisotropic nature of the electron spin dipolar coupling in the molecule. In other words, the molecular geometry has quantized the spin levels. A moment's reflection makes obvious the potential utility of the converse form of this reasoning to deduce elements of molecular structure of high-spin molecules from ZFS data.

The flattening shown in Figure 6 is oblate and tends to spread out the electron distribution in the plane of the two equivalent axes (X and Y) and compress it along the unique direction. If the distortion were to be imposed in a prolate sense, by stretching the sphere along the unique axis Z, it would have the effect of concentrating the electron distribution in the XY plane, thereby raising the energy of T_Z and lowering that of T_X and T_Y. The state ordering shown in Figure 6 corresponds to a positive D-value (see below), whereas the prolate distortion would lead to a negative D-value. Examples of the latter kind in molecular triplets are not common, but several cases exist in radical pairs immobilized in rigid media[50,117].

Figure 6b shows that a two-fold degeneracy of spin states at zero field persists in a hypothetically hexagonally symmetric benzene triplet as a consequence of the directional equivalence of the X and Y axes. This degeneracy is characteristic of any triplet species whose geometry embodies a magnetically isotropic plane (e.g. XY in Figure 6b) and an axis perpendicular to it of three-fold or higher symmetry.

Actually, the EPR and ENDOR spectra of the $^3B_{1u}$ photoexcited state of benzene (C_6H_6) in C_6D_6 host crystal cannot be interpreted in terms of species with the expected D_{6h} symmetry[118-120]. It appears that in this molecule and also in triplet mesitylene[118], under the stated conditions, slight geometric distortions lower the symmetry. The discussion based on Figure 6 therefore is idealized.

The remaining degeneracy vanishes when the molecule's shape is further distorted by elongation along one of the axes X or Y. Figure 6c shows the energies of the zero-field spin sublevels of naphthalene triplet, **41** (Figure 6c), whose π-electron distribution can be modeled by the lozenge shape obtained by elongation along X.

(*c*) *EPR spectroscopy of high-spin systems.* EPR is the most widely used technique for measuring the ZF energy separations. The details of procedures for extracting the ZFS parameters, D and E, from EPR systems of high-spin molecules have been reviewed[35,110-115] and need not be repeated here, but for a qualitative understanding of these experiments, it will be useful to call attention to a few important elementary concepts.

We return to our simple atomic triplet system with a spherically symmetrical electron distribution. As we saw in Figure 6a, the three triplet levels are degenerate at zero field. What would happen if this species were placed in a magnetic field whose lines of force lie along the Z-axis? Then the electrons whose spin vectors are in the XY plane (perpendicular to Z) would remain with equal energy in all directions in this plane, but because of the negative charge on each electron, those in the YZ and XZ planes would be of higher energy when aligned with the field and of lower energy when aligned against it. Quantum mechanically, the energy is again given by equation 15, but now, M_S is the spin quantum number of the triplet sublevel, which can take on the values -1, 0 and $+1$ corresponding to spin alignments against, perpendicular to, and with the field direction. As H_Z is increased from zero, equation 15 predicts that the triplet sublevels should separate in energy. One of them, characterized by $M_S = 0$, will maintain its zero-field energy, but the $M_S = -1$ and

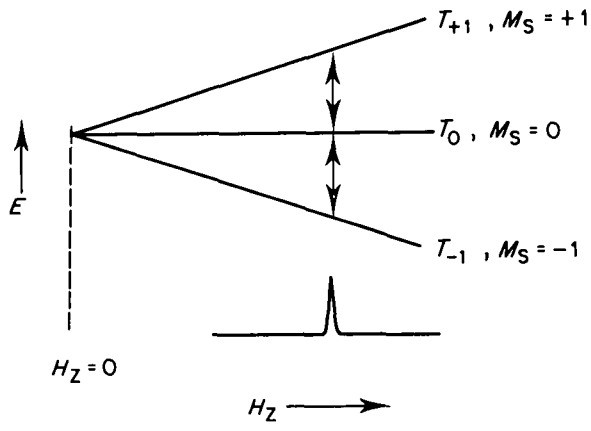


FIGURE 7. Zeeman splitting of the electronic spin sublevels of a spherically symmetrical triplet in a magnetic field of strength H_Z. The 'allowed' $\Delta M_S = \pm 1$ transitions coincide

$M_S = +1$ states will go down and up, respectively, along lines whose slopes are $M_S g\beta$ (see Figure 7). Because of the spherical symmetry, the splitting pattern will be identical to that in Figure 7 when the external magnetic field is applied along the X or Y axis. Thus, the EPR spectrum of an immobilized spherically symmetrical triplet will be isotropic.

As already has been mentioned in connection with doublet spectra, the selection rule for an EPR spectroscopic transition is $\Delta M_S = \pm 1$. Because the splitting of the spherically symmetrical triplet sublevels of Figure 7 is symmetrical about the zero-energy line, the $\Delta M_S = \pm 1$ transitions between either nearest-neighbor pair of levels will coincide, so that only one line will be observed.

This simple picture is changed in a triplet molecule where the electron distribution no longer is spherically symmetrical. As we have seen, this produces a separation of the triplet sublevels, even at zero field. Imagine that we have a rigidly oriented triplet benzene molecule and we apply a magnetic field, H_Z. What happens to the zero-field energies as the field is increased? To answer this question, we must be aware that (except for the case of a linear molecule in a field parallel to the axis), the zero-field states are not eigenfunctions of the high-field spin Hamiltonian. The high-field eigenfunctions are the basis functions of the triplet state, T_{-1}, T_{+1}, and T_0, but the zero-field eigenfunctions are mixtures of the basis functions (equations 16 and 17).

$$T_X = 1/\sqrt{2}\,(T_{-1} - T_{+1}) \tag{16}$$

$$T_Y = i/\sqrt{2}\,(T_{-1} + T_{+1}) \tag{17}$$

$$T_Z = T_0$$

Although the triplet basis functions are well described with the spin quantum numbers $M_S = \pm 1, 0$, this is not true of the zero-field states.

As the field increases, the major cause of the energy separation between the states gradually shifts from the molecular quantization associated with the spin–dipolar interaction to the field quantization associated with the Zeeman effect. Correspondingly, the zero-field eigenfunctions T_X, T_Y and T_Z evolve into the high-field eigenfunctions $T_{\pm 1}$ and T_0. This process is depicted in Figure 8. Note that the state T_Z which is destined to become T_0, does not change its energy. This property is similar to that of the T_0 state in the

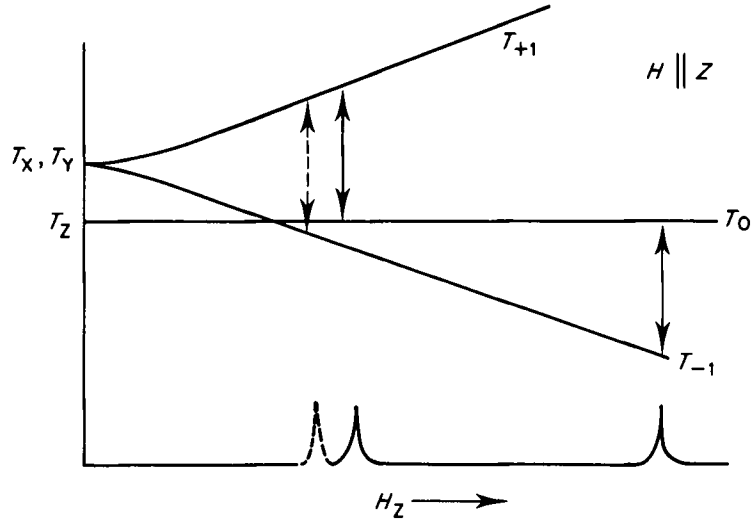


FIGURE 8. Zeeman splitting of the electronic spin sublevels of a triplet with $\geqslant$ 3-fold rotation axis (e.g. benzene) in a magnetic field of strength H_z. The $\Delta M_s = \pm 1$ transitions occur at different field strengths

spherically symmetrical system of Figure 7. The states T_X and T_Y which ultimately become $T_{\pm 1}$ are split symmetrically by the Zeeman effect, but because their zero-field energies are different from that of T_Z, the energy separation that corresponds to the microwave frequency occurs at a different field strength for T_{+1} and T_{-1}. Thus, two transitions will be observed at the positions marked by the full arrows, where the energy of the microwave just fits between sublevels whose spin quantum numbers differ by one unit (hence the name '$\Delta M_S = \pm 1$ transitions'). Note that there is one other position (marked by the dashed arrow) at which a fit can be made, but it connects two levels that differ by $\Delta M_S = 2$. This transition is formally forbidden if it falls at a field position high enough to make M_S a 'good' (i.e. well-defined) quantum number. Full field quantization may occur when the zero-field splitting in the triplet is very small, but frequently, it is not achieved throughout the experimental region, and the $\Delta M_S = \pm 2$ transitions are seen as a (usually weak) resonance at a field approximately half that of the center of gravity of the $\Delta M_S = \pm 1$ transitions. These 'half-field transitions' are especially diagnostic of a triplet state, because by definition only such a species has the three sublevels required for ΔM_S to change by two units.

If the magnetic field is imposed along one of the other two equivalent axes of the hypothetical benzene triplet, i.e. perpendicular to the Z axis, the Zeeman splitting shown in Figure 9 is observed. Note that the two $\Delta M_S = \pm 1$ transitions occur at field positions different from those in Figure 8. Therefore, for oriented samples of an axially symmetric triplet a total of four EPR lines may be expected, two in each of the canonical orientations. It is an extremely useful quirk of nature that these four lines also can be observed in randomly oriented samples in which the axes of the triplet molecules are disposed at all possible angles to the applied field (see below).

Using the principles outlined for the Zeeman effects in the axially symmetric case, it is quite straightforward to sketch the state energies as a function of field strength (Figure 10)

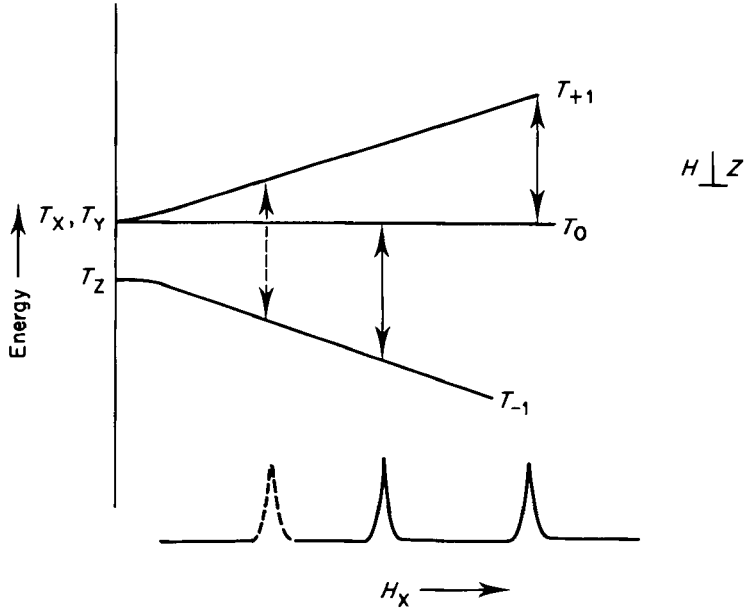


FIGURE 9. Similar to Figure 8, with the applied field perpendicular to the Z axis

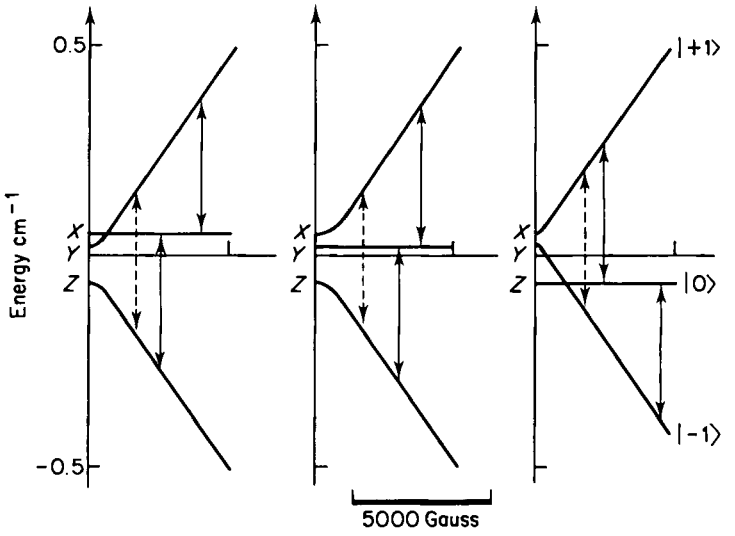


FIGURE 10. Zeeman splitting of the electronic spin sublevels of the triplet state of a molecule with $D > 0$, $E < 0$, and $|D| \neq 3|E|$. An example is naphthalene (see Figure 6c). *Reproduced with permission from A. Carrington and A. D. McLachlan*, Introduction to Magnetic Resonance, *2nd edn, Harper and Row, New York*, 1978, *p.* 121

expected for the three canonical orientations of the non-symmetrical case, e.g., naphthalene, whose zero-field energies are shown in Figure 6c.

It turns out that only two parameters, D and E, are needed to characterize the zero-field splittings. If the spin–dipolar approximation is appropriate for the spin system under observation (i.e. if spin-orbit coupling can be neglected) the parameter D measures the average propinquity of the spin dipoles. It is inversely proportional to the cube of the distance between them. The parameter E is related to the molecular symmetry. E is necessarily zero for an axially symmetric case (see Figures 4b and 8) but may be accidentally zero in other cases as well. The signs of D and E, which determine the state orderings, are not available directly from the EPR spectra, and, the parameters usually are reported in absolute magnitudes, $|D|$ and $|E|$. In the special circumstance that $|D| = 3|E|$, the spectrum collapses from six lines to three. These relationships are summarized in Table 1, where the number of lines listed is the sum of those observable in the three canonical orientations.

TABLE 1. Characteristics of EPR spectra triplets

Molecular symmetry	Number of lines from dipolar coupling
Axially symmetric	4
Unsymmetric $\lvert D\rvert \neq 3\lvert E\rvert$	6
Unsymmetric $\lvert D\rvert = 3\lvert E\rvert$	3

The first observations of the EPR transitions of a canonically oriented triplet molecule were reported in a landmark paper by Hutchison and Mangum[121]. By incorporating a small amount of naphthalene in a host single crystal of durene[122] and irradiating the sample in the EPR microwave cavity, they were able to obtain orientationally dependent spectra of excited triplet naphthalene from which the principal molecular axes could be deduced. The success of such experiments depends upon the similarity in shape between the guest and host molecules, which permits substitution of the guest in the crystal lattice of the host.

Superficially, it might be imagined that observation of EPR spectra of randomly oriented triplet molecules would be difficult. The effective magnetic field (H_{eff}) at one of the electrons (e_1) in such an experiment when the field is applied in a fixed direction (H_z), is given by equation 18,

$$H_{eff} \approx H_z + \frac{\mu_e (3\cos^2\theta - 1)}{r^3} \tag{18}$$

where θ is the angle between the applied field and the vector connecting the two electronic spin dipoles (e_1 and e_2) and r is the scalar magnitude of the vector (see Figure 11). The uncertainty principle acts to ensure that when the triplet molecules are tumbling rapidly on the time-scale of the EPR transition, the angularly dependent second term of equation 18 averages to zero, which has the effect of eliminating the spectroscopic consequences of the dipolar coupling. However, when the molecules are fixed, even if randomly oriented, the anisotropic contributions to H_{eff} still exist. Therefore, characteristic EPR spectra of high spin molecules in powders or frozen glassy or polycrystalline media can be observed, as was first noted by Burns[123] for the inorganic species Cr^{3+} ($S = 3/2$) and Mn^{2+} ($S = 5/2$), and for organic triplets by Yager and coworkers[124].

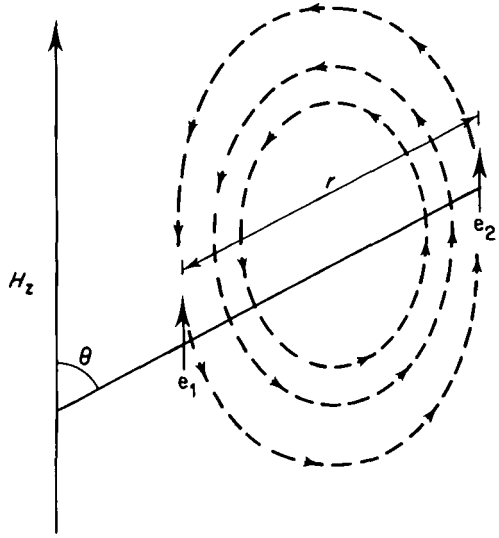


FIGURE 11. Spin–dipolar interaction of two electrons in an applied field H_z. The diagram shows magnetic lines of force emanating only from one side of electron 2, but a similar set is to be imagined on the other side

Although it is true that in a randomly oriented sample, all orientations (θ) of the interelectronic vector with respect to the applied field are equally probable, it does not follow that their contributions to H_{eff} are equal, because this contribution depends not directly on θ but rather on $3\cos^2\theta - 1$. It is a property of this function (see Figure 12) that its value changes very little near $\theta = 0°$ and near $\theta = 90°$. Near each of these angles there will be an unusually wide range of orientations all of which correspond to almost the same value of $3\cos^2\theta - 1$. These angles therefore tend to 'gather' resonances because the probability of a transition there is much higher than elsewhere. It is this 'lumpy' distribution of transition probabilities that preserves the spectral anisotropy, despite the 'smooth' distribution of orientations. These 'turning points' correspond to the transitions that would be observed in canonically oriented spectra, so that the aspects of the spectra predicted in Table 1 apply also to the randomly oriented case.

(*d*) *Ground state multiplicity from EPR spectroscopy*[125]. Although a substantial body of literature exists[126] on the experimental determination of the absolute and relative energies of the lowest singlet and triplet photochemically excited states of ordinary closed-shell molecules, very few measurements of these energies are available for biradical or multiradical low-lying or ground states. The reasons for this difference are not difficult to find, since the standard optical spectroscopic techniques and photosensitization experiments that provide the requisite data for closed-shell systems do not apply to the open-shell cases. Not only is the size of the singlet–triplet separation in biradicals usually difficult to determine, but even the ordering of the states is by no means straightforward.

In principle, the ordering and separation of the states should be accessible through the temperature dependence of the paramagnetism of the triplet. According to the Curie law, the paramagnetism (I) is inversely proportional to the absolute temperature (equation 19, where C is a constant). In some cases, the relationship has a non-zero intercept

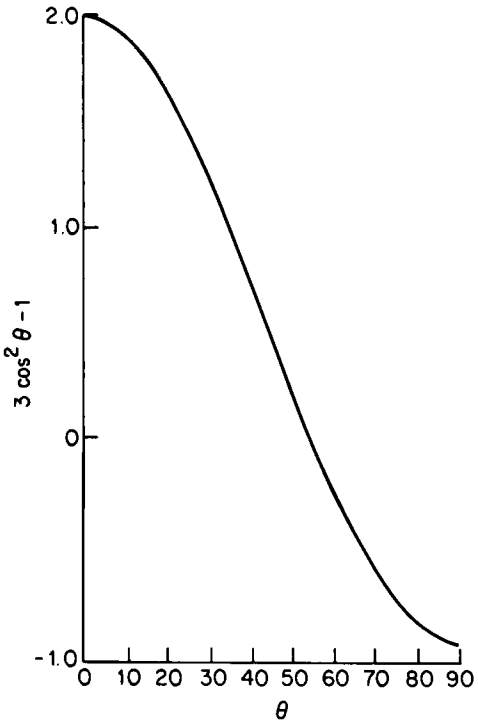


FIGURE 12. The value of the function $3\cos^2\theta - 1$ changes very little near $\theta = 0°$ and near $\theta = 90°$

(Curie–Weiss law), but this need not concern us here[109].

$$I = C/T \tag{19}$$

Although like any paramagnetic substance, the triplet follows the Curie law, the concentration of triplet will change with temperature (unless the singlet–triplet gap is accidentally zero). The behavior of a singlet–triplet pair in a Curie law study is predictable from thermodynamic considerations combined with the Curie law.

Consider a triplet and a singlet in thermal equilibrium and separated by an energy $\Delta E = E_T - E_S$. From the Boltzmann distribution of the population of states and the statistical factor of 3 in favor of the triplet, the relative concentration of the triplet in a given sample can be expressed as in equation 20, and the Curie law as in equation 21[127].

$$[\text{triplet}]_{\text{rel}} = \frac{3[\exp(-\Delta E/RT)]}{1 + 3[\exp(-\Delta E/RT)]} \tag{20}$$

$$IT = C[\text{triplet}]_{\text{rel}} \tag{21}$$

Because of the high chemical reactivity of non-Kekulé compounds, most of the EPR spectroscopic studies have been carried out on samples generated photochemically in isolation media at low temperature. Qualitatively, it is sometimes concluded that the ground state is triplet if the EPR signal persists in the dark at the lowest readily achievable temperature (usually 4.2 K, the boiling point of helium). This conclusion embodies the

assumption that relaxation to the ground spin state will occur rapidly compared to the rate at which the investigator's patience evaporates. Moreover, the Boltzmann distribution ensures some concentration of the triplet species at equilibrium, even when the ground state is singlet. For example, if the triplet energy is 100 cal mol^{-1} greater than that of the singlet, the equilibrium mixture at 4.2 K will contain the triplet species to the extent of about 2 parts in 10^5. In a typical sample, this might correspond to an absolute concentration in the range of 10^{-8} M, which might be detectable by EPR spectroscopy[128].

In principle, the shape of the Curie plot is capable of giving a more quantitative measure of the sign and the magnitude of ΔE. The simplest case is one in which the triplet is favored as the ground state (ΔE is negative). With a large negative ΔE, the concentration of the triplet will change over the experimental temperature range by only an insignificant amount, and the Curie plot will be linear. If ΔE is small and negative, upward curvature of the Curie plot at low temperature might be expected, as the triplet concentration increases at the expense of the singlet. Actually, however, this curvature is almost imperceptible, and plots for the cases $\Delta E = -5$ to -50 cal mol^{-1} are essentially linear below 70 K. Of course, if $\Delta E = 0$, equations 20 and 21 require the plot to be linear.

If the singlet is the ground state and $\Delta E \geqslant +2000$ cal mol^{-1}, it may be difficult to observe any signal below 77 K because of insufficient triplet concentration. For a smaller gap, exemplified in Figure 13, where $\Delta E = +50$ cal mol^{-1} under appropriate experimental conditions, the curvature between 77 K and 12 K should be detectable (and in a very few cases[126], has been). However, the maximum near 16 K, which is the most dramatic region of such a curve (Figure 13) may not be easy to characterize because saturation of the EPR transitions at or just below this temperature begins to become pronounced. This imparts its own curvature to the Curie plot. Saturation usually can be recognized by a deviation

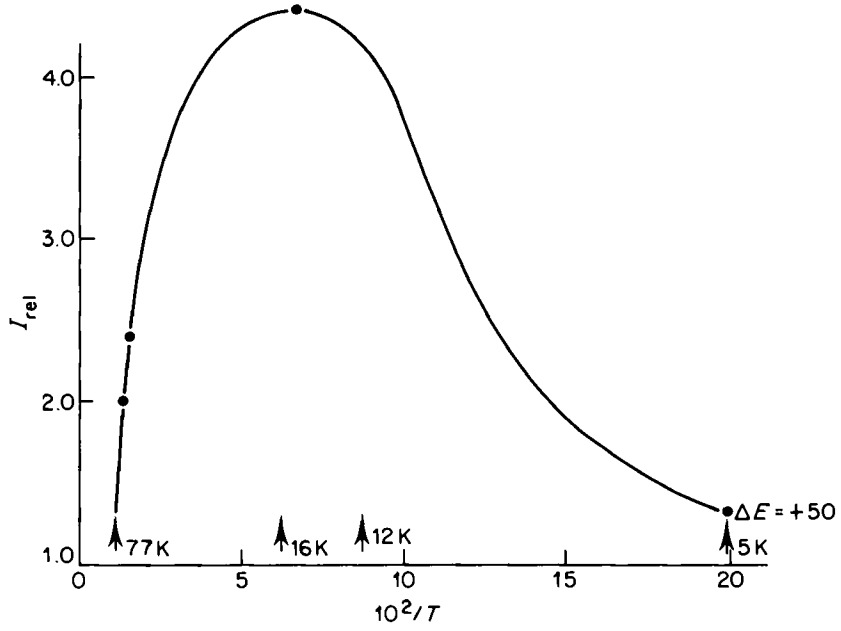


FIGURE 13 Relative EPR signal intensity as a function of reciprocal temperature (Curie plot) for a species whose triplet state lies above the singlet by 50 cal/mol

from linearity of the plot of I vs. square root of microwave power (at constant temperature)[111]. Smaller positive values of ΔE will lead to plots down to 16 K that appear linear within the experimental error.

As Figure 14 shows, the region above 77 K (boiling point of liquid nitrogen) can be essentially uninformative. Values of ΔE between + 100 and − 100 cal mol^{-1} give nearly linear plots. Larger positive values show curvature, but the relative intensity changes are small. For $\Delta E = +200$ cal mol^{-1}, for example, I_{rel} changes only 30% between 77 K and 130 K, so that the experimental error in each point becomes a significant fraction of the total range.

Measurements at temperatures higher than those of Figure 14 may be useful, if the chemical stability of the system permits (a big if!). In this region, one can populate thermally a higher triplet from a ground state singlet to a significant extent. For example, when $\Delta E = +2000$ cal mol^{-1}, the triplet will constitute about 2% of the total biradical concentration. Unfortunately, the Boltzmann effect of temperature, which raises the triplet population, is partially offset by the Curie effect of temperature, which lowers the paramagnetism. Figure 15 shows the lag between relative triplet concentration and the relative EPR signal intensity in this region.

The literature contains a number of qualitative assignments of triplet ground states based upon linear Curie plots in the region above 77 K. Although there is a strong likelihood that the assignments are correct in most cases, one should bear in mind that the range of circumstances in which the Curie plot can be used as the basis of a convincing assignment is quite limited and that measurements in the cryogenic region (< 77 K) are imperative.

The need for a more reliable, more broadly applicable method for the determination of

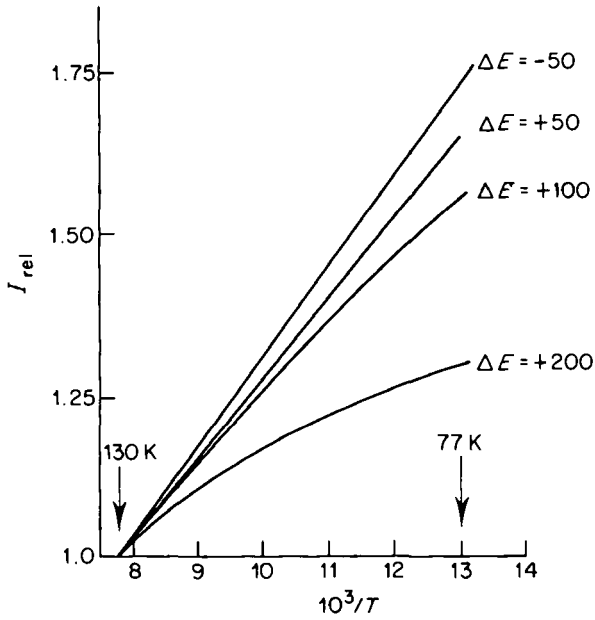


FIGURE 14. Relative EPR signal intensity (I_{rel}) as a function of reciprocal absolute temperature. The indicated values of $\Delta E = (E_T - E_S)$ are in cal mol^{-1}

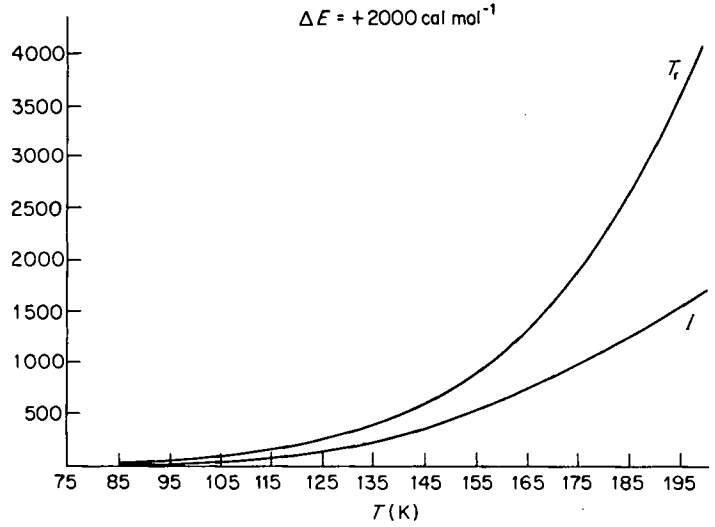


FIGURE 15. Relationship between absolute temperature and relative triplet concentration (T_r) or relative EPR signal intensity (I) for a singlet–triplet equilibrium system when $\Delta E = +2000$ cal mol^{-1} (singlet ground state)

ΔE should now be obvious. Perhaps no other single development would do more to advance the study of non-Kekulé molecules.

iii. Structural characterization of high spin m-quinonoids from the ZFS parameters D and E. The assignment of structure to high-spin states of non-Kekulé compounds would be facilitated by a reliable method for calculation of the ZFS parameters of the EPR spectrum. A quantitative comparison of predicted and observed ZFS requires an accurate knowledge of the electronic spin-density distribution, which in general is not readily available without wave functions derived from an *ab initio* molecular orbital calculation using a large basis set and extensive configuration interaction[129,130].

In the spin–dipolar approximation, the Hamiltonian H_{SS} may be expressed in equation 22:

$$H_{SS} = \hat{S}\cdot\hat{D}\cdot\hat{S} = \frac{g^2\beta^2}{2}[\hat{S}_x, \hat{S}_y, \hat{S}_z] \begin{bmatrix} \frac{r^2-3x^2}{r^5} & \frac{-3xy}{r^5} & \frac{-3xy}{r^5} \\ \frac{-3yx}{r^5} & \frac{r^2-3y^2}{r^5} & \frac{-3yz}{r^5} \\ \frac{-3zx}{r^5} & \frac{-3zy}{r^5} & \frac{r^2-3z^2}{r^5} \end{bmatrix} \begin{bmatrix} \hat{S}_x \\ \hat{S}_y \\ \hat{S}_z \end{bmatrix} \quad (22)$$

The terms of equation 22 are defined as follows: $\hat{S}$ is the total spin operator of the two electrons ($= \hat{S}_1 + \hat{S}_2$), D is a traceless second rank tensor, $\hat{S}_i$ is the component of the total spin operator in the i-direction ($i = x, y$ or z), g is taken to be the g-factor of the free electron ($g_e = 2.0023$), β is the Bohr magneton, r is the interelectronic distance, and x, y, and z are the respective components of the interelectronic distance in a coordinate system that in principle may be arbitrarily oriented relative to the molecular framework.

The matrix elements of $\boldsymbol{D}$ are averaged over the electronic wave function. $\boldsymbol{D}$ is diagonalized to ${}^{d}\boldsymbol{D}$ by rotation of the arbitrarily chosen Cartesian coordinate system until it is parallel to the coordinate system defined by the spin–dipolar interaction, namely the principal axes of $\boldsymbol{D}$. This rotation of the coordinate axes causes the off-diagonal elements of $\boldsymbol{D}$ to become equal to zero after averaging over the electronic wave function. The diagonal elements D_{ll} ($l = X$, Y, or Z) of ${}^{d}\boldsymbol{D}$ are the negatives of the relative energies of the three triplet sublevels in the absence of an applied magnetic field. For the coordinate system in which $\boldsymbol{D} = {}^{d}\boldsymbol{D}$, the ZFS parameters D and E take the simple forms of equations 23 and 24.

$$D = \frac{3g^2\beta^2}{4}\left\langle \frac{r^2 - 3z^2}{r^5} \right\rangle \tag{23}$$

$$E = \frac{3g^2\beta^2}{4}\left\langle \frac{y^2 - x^2}{r^5} \right\rangle \tag{24}$$

In a theoretically rigorous calculation[129–132], high-quality *ab initio* wave functions would be used to obtain the expectation values in these equations. Such calculations have been carried out for the excited triplet states of benzene and naphthalene and for the ground triplet state of trimethylenemethane[130,131] at various levels of approximation. The expansion of the expectation value $\langle \psi H_{SS} \psi \rangle$ of the spin operator (ψ is the triplet wave function) sometimes can be simplified by neglect of the two-center and multicenter exchange integrals[131]. Calculation of the expectation value then requires the evaluation of a number of two-center Coulomb integrals over the entire wave function. However, even in its simplified form, the application of these methods to large non-Kekulé molecules of low symmetry is still a formidable task.

A semiempirical way of dealing with this difficulty has been examined[133–142]. It is based upon an approximation of the wave functions suggested by McWeeny[143], in which the positions of two point-half-charges, placed at the most probable distance of the electron from the nucleus in a 2p atomic orbital, replace ϕ_i, the atomic orbital function in ψ. The orbital interactions involved are shown in Figure 16. From idealized geometries and several different semiempirical methods for obtaining the wave functions, useful results have been obtained for a number of molecules of the *m*-quinone series as well as for several other cases[142]. The predictions for the *m*-quinonoids are presented in Table 2 along with the available experimental data.

The details of the extraction of accurate ZFS parameters from the observed spectra are described elsewhere[110–114], but an illustration of an approximate method based on the

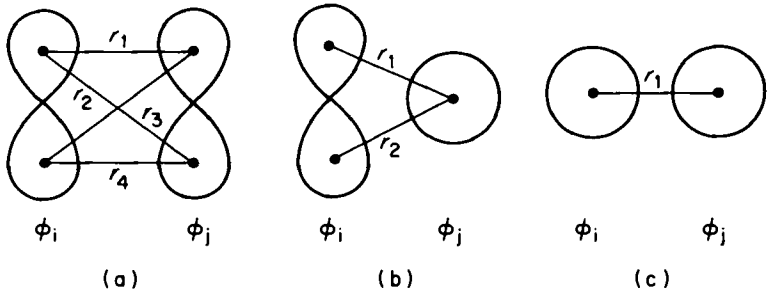


FIGURE 16. Orbital interactions used in approximate calculations of ZFS in triplet species. The diagrams show interactions in (a) p, p; (b) s, p; (c) s, s. The atomic orbital ϕ_i in the wave function ψ is approximated, according to McWeeny[143], by the position of a point-half-charge at the most probable distance of the electron from the nucleus in a 2p atomic orbital

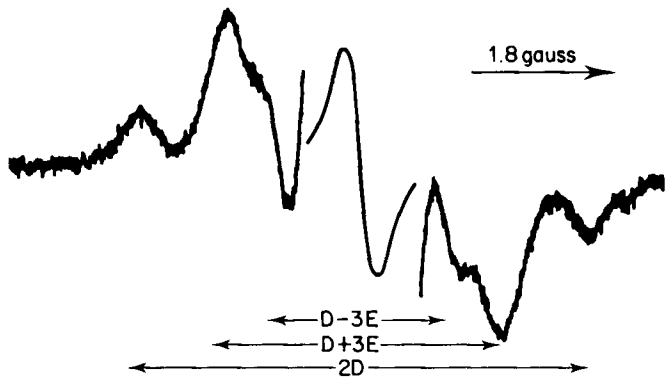


FIGURE 17. EPR spectrum of **8** in toluene glass at 173 K. The ZFS parameters are $|D|/hc = 0.0064\ cm^{-1}$, $|E|/hc = 0.0056\ cm^{-1}$. *Reproduced with permission from Ref.* 136

separations of the pairs of lines in a randomly oriented sample is given in Figure 17, which shows the spectrum[136] of the Schlenk hydrocarbon tetraphenyl-*m*-quinodimethane (**8**). A similar but not identical spectrum ($|D| = 0.0079\ cm^{-1}$, $|E| \leqslant 0.0005\ cm^{-1}$) is reported in an independent study[144].

The best calculational fit to the $|D|$ value for **8** is obtained on the assumption that the biradical is non-planar, with the benzhydryl moieties both twisted by 90° with respect to the central ring[136]. The other calculated values of Table 2 were based upon the assumption of planar molecular geometries.

Although the calculations of E fluctuate badly around the observed values (a deficiency found in higher level calculations also[131]), the calculated $|D|$ values in Table 2 are uniformly higher than the corresponding experimental values (where available) by about a factor of 2. The same factor applies to several comparisons (not shown here) in the trimethylenemethane and tetramethyleneethane series[140]. It seems likely that the empirical correction should be applied to $|D|$ values calculated for other members of these series, but it would be prudent to keep in mind that the physical basis for this apparently consistent discrepancy is not understood and that the range of reliability of the method is therefore not well demarcated.

The predictions nevertheless are useful for the anticipation of trends in $|D|$ as a function of structural change. For example, the calculations predict a trend in $|D|$ for the simple *m*-quinomethanoids **20** < **19** < **21** in agreement with experiment for the two available cases. This probably results from the increasingly concentrated electron density distribution caused by the electronegative oxygen atoms, which increases the average propinquity of the unpaired electrons. Similar trends are seen in the benzo series **43** < **45** or **44** < **47**. On the other hand, the comparable trend in the experimental data for the 1,8-naphthoquinonoids **48** < **49** is barely perceptible. Nevertheless, 1,8-naphthoquinone biradical itself (**50**) is predicted to have a large $|D|$ value, almost as large as that of *m*-quinone biradical (**21**). It should be emphasized that all of these calculations are based upon the spin–dipolar coupling approximation. Especially in the heteroatom-substituted systems, spin-orbit effects may contribute in the actual molecule, and the observed $|D|$ values may differ significantly from those predicted here.

The calculation produces the expected diminution in $|D|$ value when the electron density is spread over a broader area, as is observed experimentally in the available cases (compare **20** > **43**, **19** > **44** or **45**, **21** > **47**, and **42** > **46**).

TABLE 2. Calculated[a] and experimental ZFS parameters[g] for *m*-quinonoid non-Kekulé compounds

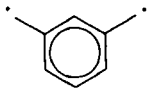
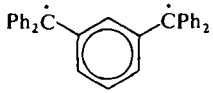
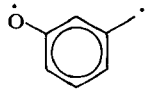
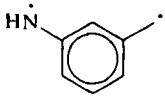
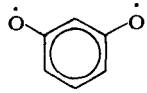
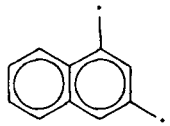
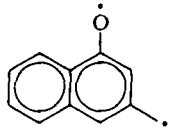
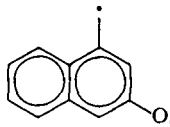
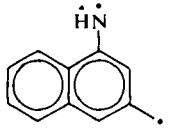
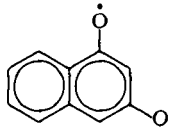
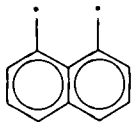
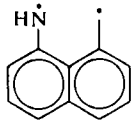
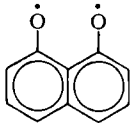
Compound		Experimental		Calculated	
		$\|D\|/hc$	$\|E\|/hc$	$\|D\|/hc$	$\|E\|/hc$
	(20)	0.011	$\leqslant 0.001^{h-j}$	0.0323[b] 0.0371[d] 0.0338[e] 0.0378[f]	0.0047[b] 0.0028[d] 0.0035[e] 0.0025[f]
	(8)	0.0064[o] 0.0079[p]	0.00056[o] $\leqslant 0.0005^{p}$	0.0079[n]	0.00036[n]
	(19)	0.0266[j]	0.0074[j]	0.0543[c] 0.0572[f]	0.0087[c] 0.0099[f]
	(42)			0.0459[f]	0.00427[f]
	(21)			0.0873[d] 0.0871[f]	0.0068[d] 0.0037[f]
	(43)			0.0262[b] 0.0320[d]	0.0023[b] 0.0012[d]
	(44)	0.0204[k]	0.0052[k]	0.0438[d] 0.0477[f]	0.0076[d] 0.0081[f]
	(45)			0.0390[d] 0.0388[f]	0.0089[d] 0.0099[f]
	(46)			0.0393[f]	0.00387[f]
	(47)			0.0708[d]	0.0052[d]

TABLE 2. (*Contd.*)

Compound		Experimental $\|D\|/hc$	Experimental $\|E\|/hc$	Calculated $\|D\|/hc$	Calculated $\|E\|/hc$
	(48)	0.0218[l] 0.024[m]	0.0021[l] 0.001[m]	0.0401[b] 0.0377[d]	0.0076[b] 0.0111[d]
	(49)	0.0255[q]	0.0008[q]	0.0356[d]	0.0111[d]
	(50)			0.0756[d]	0.0154[d]

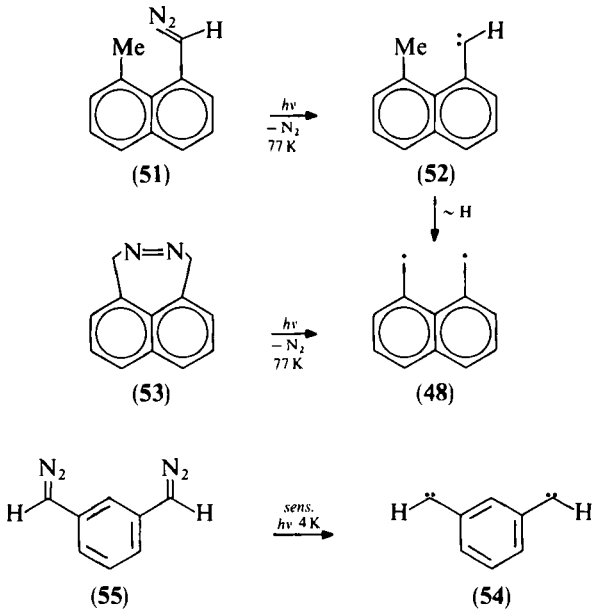
[a] Except for 8, calculated in Refs 139, 140, 142, assuming molecular planarity and using wave functions from the indicated method (footnotes *b–q*).
[b] Simple Hückel. [c] CNDO closed-shell singlet. [d] CNDO open-shell triplet. [e] INDO closed-shell singlet. [f] INDO open-shell triplet. [g] Absolute values in cm^{-1}. [h] Ref. 145. [i] Refs 146, 147. [j] Ref. 139, 140. [k] Refs 140, 148. [l] Ref. 149. [m] Refs 150, 151. [n] Calculated for a non-planar configuration in Ref. 136. [o] Ref. 136. [p] Ref. 144. [q] Ref. 151.

C. Chemistry of *m*-Quinonoids

1. Synthesis and reactions of m-quinodimethane

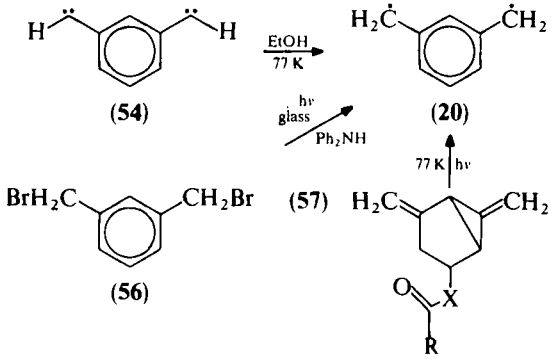
Although Migirdicyan and co-workers[61, 102, 105–107] identified the *m*-quinodimethane biradical **20** from the emission and excitation spectra of irradiated *m*-xylene preparations (see Section III.B.2.a), another attempt[145] to observe **20** by EPR spectroscopy under these conditions failed. Wright and Platz[145] made the first EPR observation of **20** using a different synthetic technique, which had been developed originally by Platz[152] in another context. The key reaction is a hydrogen transfer to a carbene from a nearby C–H bond as exemplified for an intramolecular case in the formation of 1,8-naphthoquinodimethane (**48**) from the photolysis at 77 K of 8-methyl-1-diazomethylnaphthalene (**51**), presumably via the carbene **52**. The EPR spectrum of **48** obtained in this way matched that of the triplet species obtained[149] from the diazene **53**. The carbene could not be isolated, even at 4 K. Senthilnathan and Platz[150] suggest that at low temperatures, the hydrogen transfer reaction occurs by quantum mechanical tunneling through a potential barrier.

An intermolecular variant of this hydrogen transfer leads to *m*-quinodimethane **20**[145]. The Bell Laboratories group[153] had generated the bis-carbene (**54**) by photolysis of the diazo compound (**55**). The bis-carbene (**54**) was stable at cryogenic temperatures and showed a beautifully detailed ESR spectrum which was identified as that of the quintet state of this species. Wright and Platz[145] reasoned that it might be possible to reduce **54** to the *m*-quinodimethane biradical **20** by hydrogen transfer from a more reactive medium. Indeed photolysis of the bis-diazo compound **55** in ethanol glass at 22 K gave the characteristic quintet spectrum of **54**, but when the temperature of the sample was raised to



77 K, the quintet spectrum faded and was replaced by a new spectrum of a randomly oriented triplet species, $|D| = 0.011\ cm^{-1}$, $|E| \leqslant 0.001\ cm^{-1}$, to which the structure **20** was assigned. The ZFS parameter $|D|$ is in reasonably good agreement with the predicted value[139] provided the empirical correction factor of 0.5 is applied to the latter (see Table 2). That a hydrogen transfer from the solvent is involved in the transformation of **54** was established by the observation that the quintet spectrum at 77 K is stable in ethanol-d_6 or perfluoroalkane glasses[145].

Significantly, the same spectrum of biradical **20** was obtained by Wright and Platz[145] by photolysis of *m*-xylylene dibromide (**56**) in the presence of diphenylamine (**57**). A completely different preparation of the same species was subsequently reported by Goodman and Berson[146, 147], who generated it from either of the ketones **58** or **59**, or the



(**58**, X = CH_2, R = Me)
(**59**, X = CH_2, R = Ph)
(**60**, X = O, R = Ph)

benzoate **60** (see below). Neither group has been able to observe the $\Delta M_S = 2$ transition, but this is not surprising in view of the small $|D|$ value (see Section III.B.2.b).

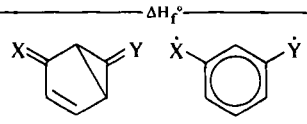
Although the EPR spectrum of **20** is not observed[145] under the conditions (photolysis of *m*-xylene in an alkane matrix, 77 K) which permitted detection of its optical emission spectroscopy[61] (see Section III.B.2.a), an EPR spectrum similar to that of **20** is generated[145] by photolysis of mesitylene (1,3,5-trimethylbenzene) in an alkane matrix. Presumably, the carrier of the EPR signal is 5-methyl-1,3-bis-methylenebenzene, a methyl-substituted **20**. Reasons for the differences in behavior between *m*-xylene and mesitylene remain to be elucidated.

The EPR signal intensity of *m*-quinodimethane is linear with $1/T$ over the range 30–77 K[145]. The triplet therefore is the ground state or within a few small calories of it. This result is compatible with the triplet ground state predicted by theory (see Section II.B.1).

Three methods of generating and detecting *m*-quinodimethanes in fluid solutions have been devised. All use the same overall strategy as the original covalent → biradical *m*-quinonoid valency tautomeric change (**22** → **19**, see below) designed for the preparation of *m*-quinomethane, the oxy analog of *m*-quinodimethane (**20**)[27].

However, the thermochemical-kinetic properties of the covalent–biradical pairs necessitate some significant changes in technique when the **22** → **19** type of reaction is adapted to the hydrocarbon case, **61** → **20**. Table 3 shows the relative energies of some of the covalent–biradical valency tautomeric parts in the *m*-quinone series[140]. Although these estimates are rough, they leave no doubt that the ring-opening, covalent → biradical, is thermochemically much more favorable in the hydrocarbon case **61** → **23**, (Table 3, entry 4) than in the monoketone case **22** → **19** (Table 3, entry 2). The reason for this is primarily the large dissociation energy of the carbonyl group's π bond (~ 88 kcal mol^{-1}), which stabilizes the covalent cyclic form in the ketone case.

TABLE 3. Relative energies (in kcal mol^{-1})[a] of the covalent and biradical forms of *m*-quinonoid valency tautomers[b]



No.	X	Y	Covalent	Biradical	ΔH_f^0 (biradical) $-\Delta H_f^0$ (covalent)
1	O	O	− 4.4	5.8	10.2
2	O	CH_2	44.1	39.9	−4.2
3	CH_2	O	41.4	39.9	−1.5
4	CH_2	CH_2	90.2	70.0	−20.2

[a] The standard heat of formation values (ΔH_f^0) are calculated using the group equivalents of Benson[154] and the assumption that the strain energy in the covalent form is 45 kcal mol^{-1} estimated by analogy to other systems[155]. No correction for the spin state is included. The values shown are in kcal mol^{-1}.

[b] Adapted from Ref. 140 with permission.

Moreover, the covalent bicyclic hydrocarbon **61** should be less stable kinetically than the covalent oxygen analog **24**. The latter compound is a stable species and survives distillation or gas chromatography. Below 80°C it undergoes thermal reactions in which the rate-determining step is the ring-opening **22** → **19** only slowly, with the indicated Arrhenius parameters of Table 4[156]. In contrast, the hydrocarbon **61** is unknown. A rough estimate[157] based on analogies to model systems[158, 159] suggests an activation energy of

TABLE 4. Arrhenius activation parameters

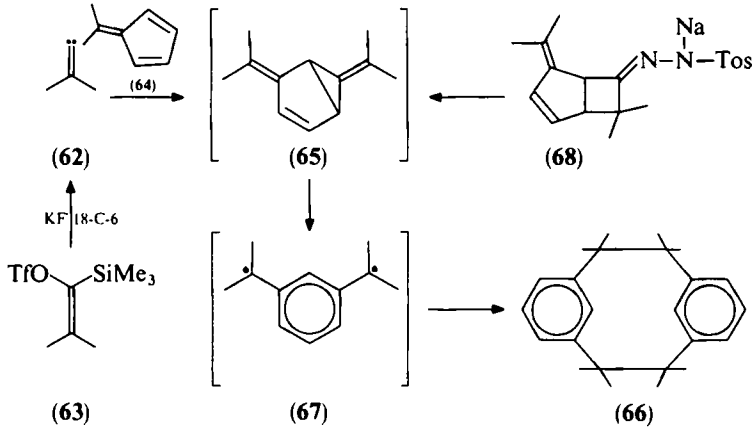
		E_a (kcal mol^{-1})	log A (A in s^{-1})
 (22) (19)	obsd.	30.6	14.0
 (61) (20)	est.	10	14

only 10 kcal mol^{-1} for the ring-opening, which if correct would correspond to a lifetime in the microsecond range for **61** at room temperature (assuming $\Delta S^{\ddagger} \approx 0$ cal mol^{-1} deg^{-1}). Obviously, special methods are needed to study this system.

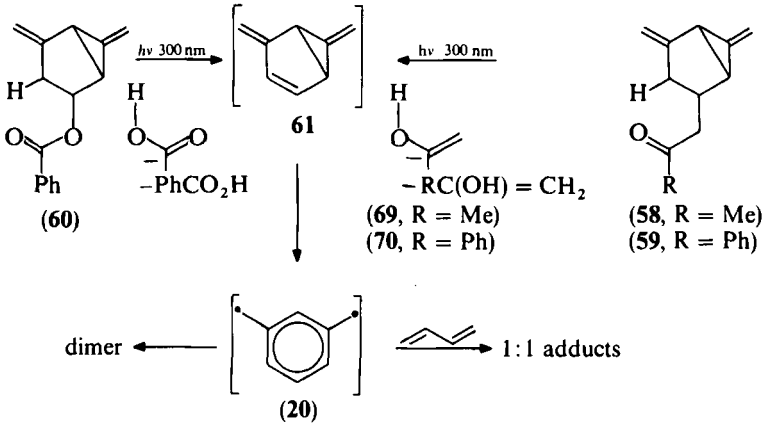
In one of these, dimethylvinylidene (**62**), generated by the potassium fluoride induced decomposition[160] of the silylated enol triflate **63**, reacts in CCl_4 or tetrahydrofuran solution with 6,6-dimethylfulvene (**64**) to give a 20% yield of the octamethyl-2,2-metacyclophane **66**[161]. A reasonable interpretation is that the carbenoid addition generates the tetramethyl derivative (**65**) of hydrocarbon **61**. Thermal ring-opening of **65** to tetramethyl-*m*-quinodimethane (**67**), followed by dimerization of the latter, would lead to the metacyclophane (**66**).

The same unstable hydrocarbon **65** probably is the intermediate in the thermal decomposition of the sodium tosylhydrazone **68**, which gives a 17% yield of the 2,2-metacyclophane (**66**)[162].

Neither of these synthetic methods has been applied to the generation of a *m*-quinodimethane biradical under conditions that would permit its chemical interception or its observation by EPR spectroscopy. Indeed, it might not be easy to find a trapping agent for biradical **67** that would be compatible with carbene **62**.



A third approach accomplishes both of these objectives by the generation of the covalent hydrocarbon **61** and from it the parent *m*-quinodimethane **20** in Norrish type II photofragmentations of the ester **60** or the ketones **58** or **59** (Scheme 2).

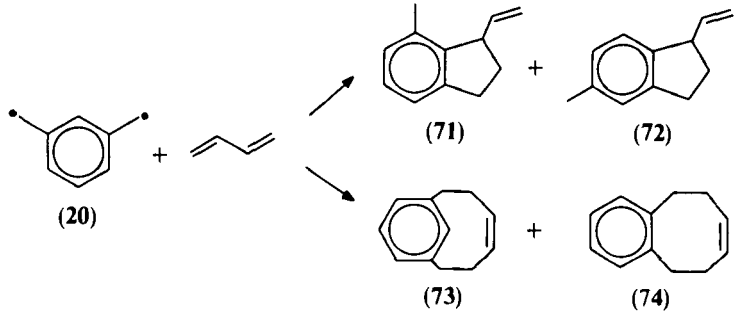


SCHEME 2

Photolyses of the ester **60** or the phenyl ketone **59** in 2-propanol glass at 77 K give rise to the characteristic six-line EPR signal of *m*-quinodimethane biradical **20**[146, 147], essentially identical (except for a different doublet impurity pattern) with that generated by the bis-carbene reduction route of Wright and Platz[145] (**54** → **20**). These reactions constitute a second and a third independent synthesis of **20** and serve to strengthen its assignment as the carrier of the EPR triplet signal. Upon warming the matrix, 2,2-metacyclophane was identified in the reaction mixture [146, 147].

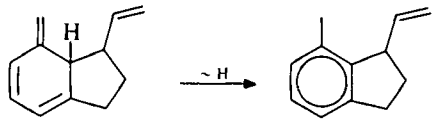
Solution phase photolyses of the methyl ketone **58** or phenyl ketone **59** presumably again resulted in the elimination of the enol of the fragment ketone (**69** or **70**) and formation of the bicyclic *m*-quinomethanoid **61**. Although the enol of acetophenone (**70**, Scheme 2) was identified by low temperature nuclear magnetic resonance (NMR) spectroscopy of a solution that had been irradiated at −78°C, the spectrum did not reveal any trace of the hydrocarbon **61**, which thus appears to be thermally (or photochemically) unstable under the conditions of its birth[146, 147].

In the absence of added trapping agents, the photolysis of methyl ketone **50** shown in Scheme 2 leads to 2,2-metacyclophane in low yields (5–15%), resulting from dimerization



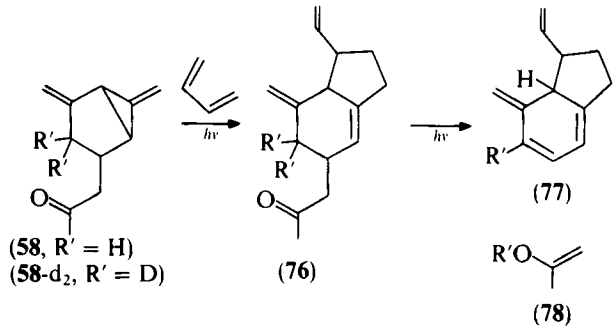
of *m*-quinodimethane biradical **20**. However, this species can be intercepted by incorporation of any of a variety of conjugated dienes or α,β-unsaturated carbonyl compounds in the reaction mixture. Photolysis of the methyl ketone **58** in the presence of a large excess of butadiene gives a 40–60% yield of four 1:1 adducts, whose structures are **71–74**.

Products **71** and **72** result from a 1,2-addition of **20** to a double bond of the diene and presumably arise from a primary prearomatic adduct, e.g. **75**, by a hydrogen shift. Product **73** results from a 1,4-addition to the diene, and product **74** results from a secondary photolysis of **73**[163].



(75) (71)

Several lines of evidence support the sequential mechanism of Scheme 2: Norrish type II photofragmentation of ketone **58** or **59** produces hydrocarbon **61** and then biradical **20**, which ultimately is captured by cycloaddition to 1,3-butadiene. The already described observation of acetophenone enol in the photolysis mixture strongly suggests the occurrence of some sort of Norrish type II reaction. However, this finding alone does not suffice to exclude an alternative mechanism (Scheme 3), in which cycloaddition of



(58, R' = H)
(58-d_2, R' = D)

(76)

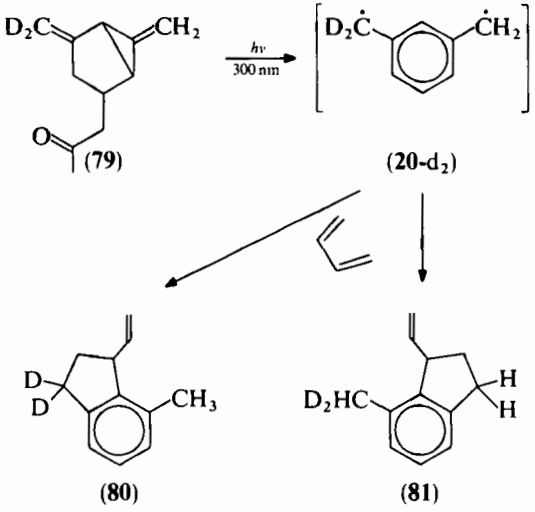
(77)

(78)

SCHEME 3

butadiene hypothetically occurs first, followed by Norrish type II photoelimination. Further experiments showed that the mechanism of Scheme 2, which involves the biradical **20**, is to be preferred to that of Scheme 3, which bypasses **20** entirely. The choice is made by noting that the Scheme 3 mechanism consumes ketone by a direct cycloaddition pathway (**58** → **76**), whereas the Scheme 2 mechanism consumes ketone in a Norrish type II process involving a hydrogen transfer. The Scheme 2 mechanism therefore predicts a primary deuterium isotope effect on the quantum yield for consumption of the ketone (**58** vs. **58**-d_2), but the Scheme 3 mechanism predicts only a very small secondary isotope effect. The observed value, $\phi_H/\phi_D \sim 2.2$ for the singlet photoprocess, is compatible only with the first prediction and, moreover, is very similar in magnitude to isotope effects in singlet Norrish type II reactions in other systems[146, 147]

A second piece of evidence favoring Scheme 2 comes from an isotopic position labeling experiment (Scheme 4) starting with the ketone **79**, deuterium-substituted in only one of

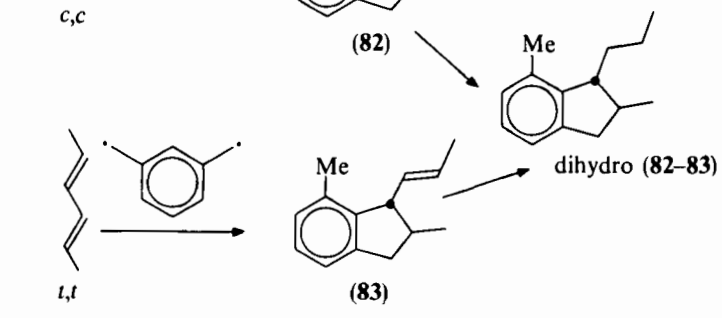


SCHEME 4

the two exocyclic methylene groups. The butadiene adduct from **79** contains deuterium essentially equally distributed between the benzylic methylene group and the methyl group, as would be required if the bilaterally symmetrical intermediate *m*-quinodimethane **20**-d_2 were on the reaction pathway[146, 147].

2. *Mechanism of the cycloadditions*

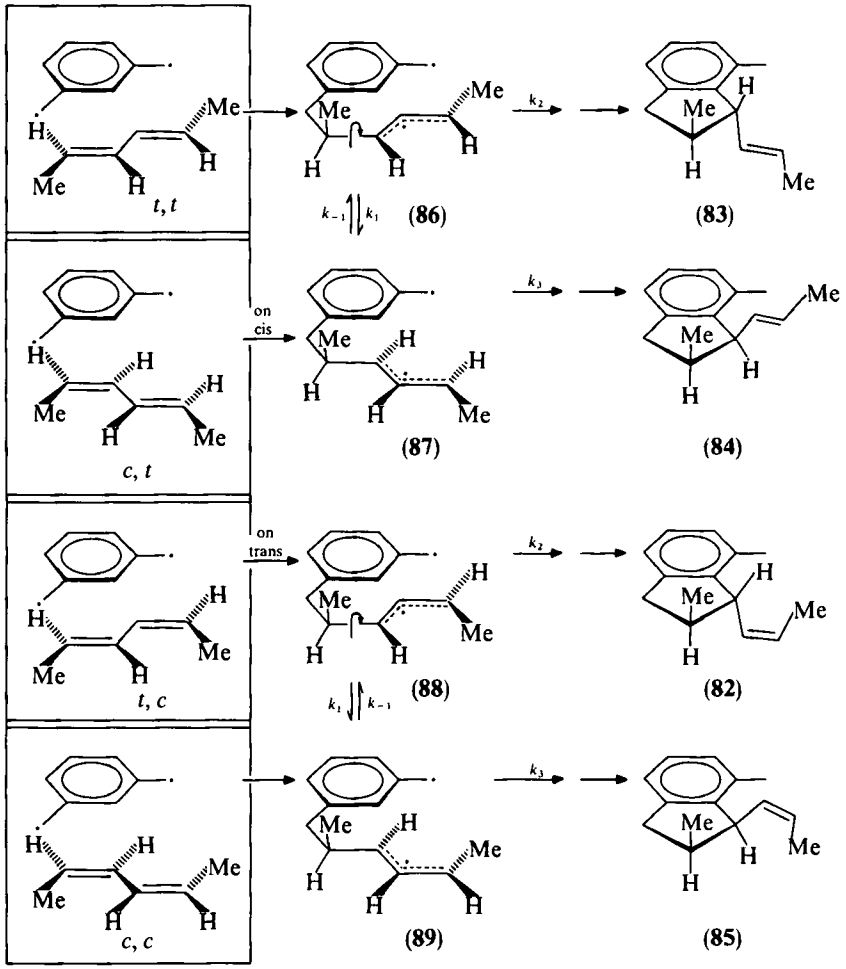
Both the 1,2 and the 1,4 cycloadditions of **20** to *cis,cis*- and *trans,trans*-2,4-hexadienes are most easily interpreted as stepwise rather than concerted processes. Either pure diene gives mixtures of stereoisomeric 1,2-adducts in which the original stereochemistry of the unreacted diene double bond is completely preserved, but that of the reacting double bond is not carried over into the product. These results are exemplified in Scheme 5, which shows



SCHEME 5

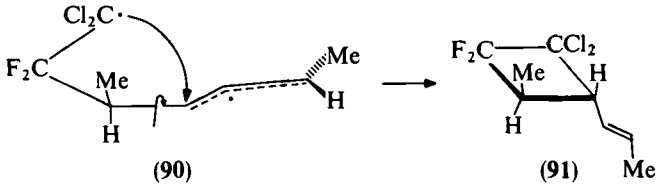
that in *both* of the dominant 1,2-*ortho* adducts, **82** and **83**, from *cis,cis* (*c,c*)- and *trans,trans* (*t,t*)-2,4-hexadiene, respectively, the stereochemistry of the ring substituents is *trans*. The adducts differ only in the side-chain stereochemistry, and each can be reduced to a common dihydro derivative, dihydro **82–83**[147].

Scheme 6 shows the suggested[147] stepwise mechanism applied to the reactions with the three 2,4-hexadienes. Addition of the biradical to the diene (say *trans, trans*) gives an adduct biradical (**86**), which can either cyclize to product **83**, or suffer internal rotation to another adduct biradical (**87**). Cyclization of **87** gives a stereoisomeric adduct **84**. The adduct biradical is assumed to preserve stereochemistry around the allylic unit, in analogy to model systems. Application of the same scheme to *cis,cis*-2,4-hexadiene predicts the formation of two new stereoisomeric adducts, **82** and **85**, whereas all four adducts should be formed from *cis,trans*-2,4-hexadiene, since that diene has two non-equivalent sites for 1,2-cycloaddition. The experimental data[147] are fully in accord with this scheme.



SCHEME 6

The competition between cyclization and internal rotation (Scheme 6) may be analyzed quantitatively[147] by treatment of the data with the steady-state approximation, a procedure copied directly from that used by Montgomery and coworkers[164] in a study of the additions of 1,1-dichloro-2,2-difluoroethene to the 2,4-hexadienes. Those reactions also involve a biradical adduct intermediate (e.g. **90**) in which a similar internal rotation vs. cyclization competition controls the relative stereochemistry of the ring carbons in the cyclobutane product (e.g. **91**).

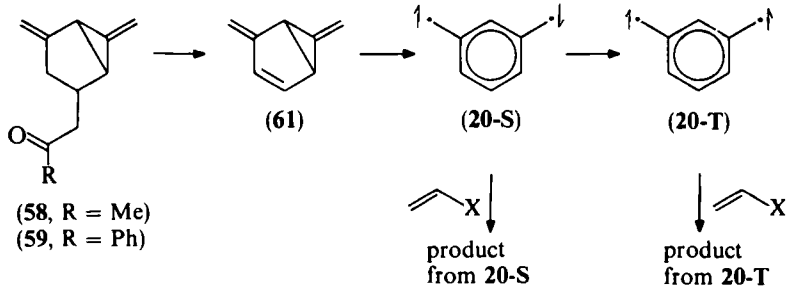


(90) (91)

The analysis employs the assumption that common k_2 and k_3 values apply to the intermediates from stereoisomeric precursors. Applied to the additions of the *m*-quinodimethane biradical it permits the extraction of the competition ratios of Scheme 6, k_1/k_2 and k_{-1}/k_3, which turn out to be in remarkable agreement with the corresponding ratios in the 1,1-dichloro-2,2-difluoroethene additions. In both systems, the ratios may be expressed as $k_1/k_2 = 11.5 \pm 1.5$ and $k_{-1}/k_3 = 2.5 \pm 0.3$. The original paper[147] discusses the possibility that an 'entropy-controlled' cyclization may be the common feature that is responsible for the similarities in the competition ratios.

The Norrish type II photofragmentation which leads to biradical **20** (Scheme 2), when carried out in the presence of a large excess of diene, should occur in the n, π^* singlet state of the ketone precursor **58** or **59**. This could proceed adiabatically via singlet **61** to singlet **20** (**20-S**), which therefore is likely to be the first-formed *m*-quinodimethane biradical intermediate. However, as we have seen, singlet **20** is unstable with respect to triplet, **20-T**, and therefore should decay to it forthwith.

Scheme 7 shows this mechanism in which two sequentially formed reactive intermediates each can give rise to products by reaction with an olefin. If the intersystem crossing (isc) **20-S** → **20-T** is irreversible, the intermediates form a cascade of energy states, with the higher energy state being populated earlier in the mechanism. If the isc is fast and reversible, the intermediates may be said (preserving the aqueous analogy) to constitute a pool of energy states. Taken at face value, the theoretical calculations, which place **20-T** 10 kcal mol^{-1} below **20-S** (see Section III.B.1.d), suggest that the pool mechanism cannot be important, since the **20-T** → **20-S** reaction would be too slow to meet the requirement of



SCHEME 7

rapid reversible isc. Therefore, a cascade mechanism seems probable. Capture of **20-S** then would have to compete with isc. The competition would be dependent on the concentration of the trapping agent, since trapping is bimolecular, whereas isc is unimolecular. Provided that the ratios of rate constants were suitable, it might be possible to manipulate at will the fraction of the product derived from **20-S** or **20-T** by changing the concentration of the trapping agent. The use of dilution effects for this type of analysis is well known from the chemistry of carbenes, nitrenes and trimethylenemethanes[165, 166].

Experimentally, however, little or no dilution effect on the product ratios is observed in reactions of the *m*-quinodimethane system[146, 147]. This result does not necessarily exclude the cascade mechanism (Scheme 7), since it could be caused by a slow rate of capture of the first intermediate **20-S**, or an exceptionally fast rate of isc, or a product distribution from **20-T** that is the same as that from **20-S**.

The effect of added oxygen has provided another device for distinguishing singlet from triplet biradical chemistry in cycloadditions. The triplet state of 2-isopropylidene-cyclopentan-1,3-diyl, a trimethylenemethane derivative, is selectively scavenged by O_2, leaving the singlet to form its characteristic cycloadducts with olefinic trapping agents[165, 166]. In the case of the *m*-quinodimethane system, however, O_2 is without effect on the product composition[146, 147].

The negative results of the application of these two test criteria to biradical **20** leaves the investigators (for the present, at least) without a means of assigning the spin state of the reactive species[146, 147]. Currently, the mechanism of cycloadditions of **20**, rather than being characterized as a cascade or a pool, more accurately might be described as a swamp, blanketed by a miasma of ignorance, into whose murky depths our senses cannot yet penetrate.

D. *m*-Quinomethane and *m*-Naphthoquinomethane

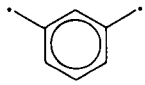
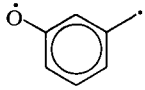
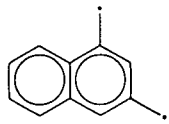
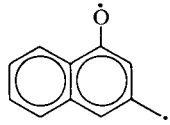
1. Theory

At the simple Hückel π-electron level of calculation, the frontier orbitals of the hydrocarbon system *m*-quinodimethane are exactly degenerate. When combined with Hund's rule, this leads to the prediction of a triplet ground state (see Section III.B.1) in accord with the experimental observations (see Section III.C.2). However, rejoicing over this concordance should not be unrestrained, because the degeneracy vanishes at any level of theory that takes into account two-electron effects. As we have seen (Section III.B.1) it is not clear whether Hund's rule should be applied, although a *post hoc* justification for doing so comes from the results of the best *ab initio* calculations, which confirm the expectation of a triplet ground state.

What then should we predict for the spin of the ground state of the *m*-quinomethane non-Kekulé system **19**? At the INDO/1 level of calculation, the two frontier orbitals are separated by some 67 kcal mol^{-1}. Surely, one would think that so large a separation would place this molecule well outside the category of substances with degenerate or nearly degenerate orbitals to which one applies the recipe: 'If the separation of the molecular orbitals is sufficiently small, Hund's rule requires the triplet to be the ground state'[74]. Rather, one might expect the closed-shell zwitterionic singlet state, with both frontier electrons occupying the lower frontier orbital, to be preferred.

A higher level semiempirical calculation (INDO/S-CI)[70], however, predicts that although the most stable singlet is in fact one of largely closed-shell character (with small coefficients on the open-shell configurations in the CI wave function), the triplet state is the ground state and lies 12 kcal mol^{-1} lower than the singlet (Table 5). INDO/S-CI predicts[70] a similar result for the naphtho derivative **92**: the lowest singlet is of largely closed-shell character, but the triplet is more stable by about 17 kcal mol^{-1}.

TABLE 5. Relative energies of low-lying states of non-Kekulé molecules calculated by INDO/S-CI[70]

		E (kcal mol^{-1})
 (20)	$^3B_2$	0.0
	$^1A'$	15.0
 (19)	$^3A'$	0.0
	$^1A'$	12.0
 (43)	$^3A'$	0.0
	$^1A'$	14.7
 (92)	$^3A'$	0.0
	$^1A'$	17.0

These non-intuitive predictions (retrodictions, actually) are confirmed by the experimental findings that both **19**[27, 140, 167] and **92**[140, 148], when generated photochemically from the covalent *m*-quinonoid precursors in glassy media at low temperatures, persist in the dark as paramagnetic species (see Figure 18) whose signal intensities follow the Curie law. These molecules therefore very probably have triplet ground states. Similarly 1-imino-8-methylenenaphthalene (**49**) has a triplet ground state, as judged by the same experimental criteria[151]. These findings stress the importance of electron repulsion effects in determining the state orderings in non-Kekulé molecules. One-electron theories, even when parameterized to include such effects, simply cannot be relied upon to deal with this problem, and it is not until CI is included that one approaches a proper account of the relative energies.

Moreover, the calculational and experimental results just described provide some quantitative justification for the assertion[63] that heteroatom-for-carbon substitution should not change the state ordering predicted for the hydrocarbon. In fact, INDO/S-CI predicts not only that the order of the states should survive a heteroatomic perturbation but also that their energy separation should not change much. This can be seen in the comparisons (Table 5) **20** vs. **19** and **45** vs. **92**.

What is the physical basis for these calculational results? Qualitatively, the splitting of the NBMOs at the one-electron level of theory (e.g., simple Hückel) is produced by the changes in the Coulomb and resonance integrals associated with the heteroatomic

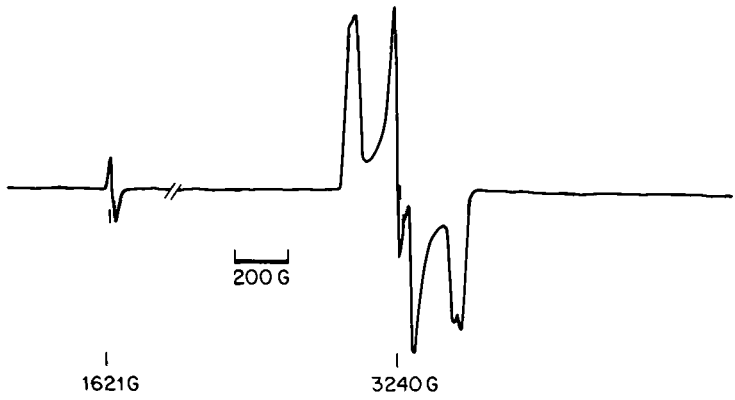
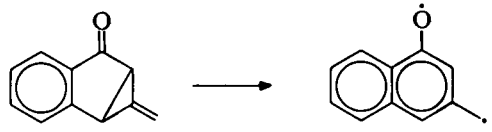


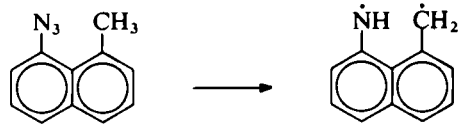
FIGURE 18. EPR spectrum of the triplet state of 3-methylenenaphthalene-1-oxy (**92**) obtained by irradiation of a 2-methyltetrahydrofuran matrix of ketone **93** at 77 K. The small absorption near 3245 G is due to cavity background. Note the $M_S = \pm 2$ transition at 1621 G. The triplet ZFS parameters are (in cm^{-1}) $|D|/hc = 0.0204 \pm 0.0002$ and $|E|/hc = 0.0052 \pm 0.0004$. The fit of the spectrum can be achieved only with the use of an anisotropic g- tensor, i.e., one in which the g-factor along one direction (coincident with the C–O bond) is significantly different from the free-spin value because of spin-orbit perturbation by the oxygen atom. *Reproduced with permission from D. E. Seeger, E. F. Hilinski and J. A. Berson,* J. Am. Chem. Soc., **103**, 720 (1981). *Copyright* (1981) *American Chemical Society*

perturbation. Because of the neglect of electron repulsion effects at this level, the aufbau principle forces double occupation of the lower-lying frontier level and hence a singlet ground state. If electron repulsion effects are large enough, however, the first-order NBMO splitting will play a minor role in determining the ordering and separation of the

(22) (19)



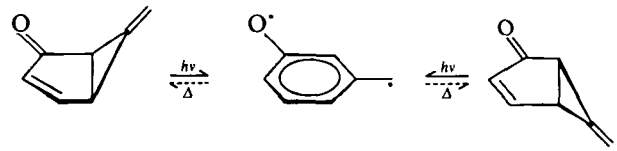
(93) (92)



(49)

states. Evidently, this is the case in the systems studied here, and by implication, in many others. The usual criterion for the application of Hund's rule, namely that the frontier orbitals be degenerate or nearly so, can be misleading.

One might hope to effect thermally a reversal of the photochemical ring-opening **22** → **19** detected by EPR spectroscopy, since entry 2 of Table 3 shows the biradical **19** to be only 4.2 kcal mol^{-1} lower in energy than the covalent structure **22**. Unless a substantial additional barrier is added on to this energy gap, thermal cyclization of **19** should occur well below room temperature. An attempt[140] to observe this reaction made use of the optical activity of **18**, which would be lost (**18a** → **18b**) during the photochemical–thermal cycle via achiral biradical **19**. Thus, a sample of optically active **18a** was cooled to 77 K in a glassy

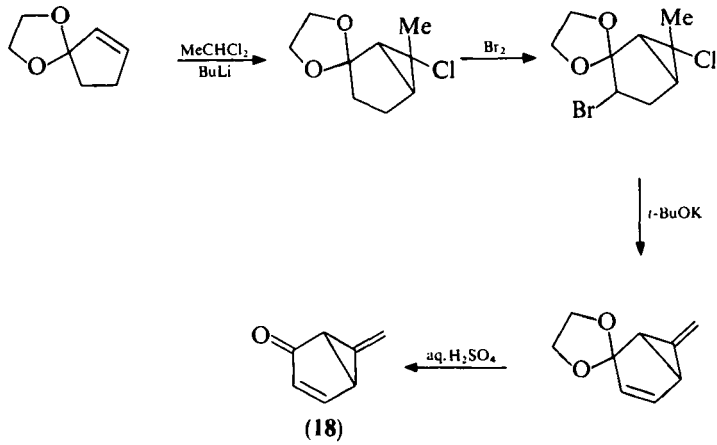


(18a) **(19)** **(18b)**

matrix, photolyzed (6% conversion to **19** by an EPR 'spin count') and the matrix was thawed by warming to room temperature. The sample was subjected to ten successive such cycles, but the optical activity of the ketone recovered from the reaction mixture was the same as that of the starting material. Although the products of the photoreaction are unknown, the result suggests that thermal return of the aromatic biradical **19** to the bicyclic ketone **18** is at least inefficient compared to side reactions that may occur during the warm-up part of the cycle and may be slow in the absolute sense because of a substantial energy barrier. Further experiments (see Section III.C.2) on the kinetics of the addition reactions of **18** support the hypothesis of a large barrier.

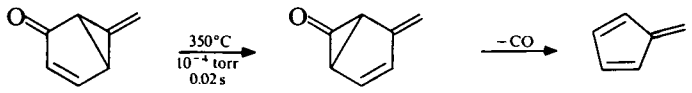
2. *Chemistry*

As would be expected from the thermochemical relationships of Table 3 (Section III.B.3), the ketone **18** seems to be much more stable than its unknown hydrocarbon counterpart **61**. Compound **18** can be prepared by the sequence shown and is



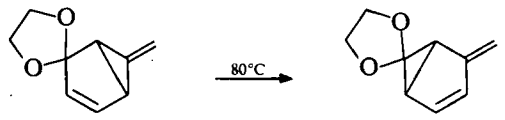
(18)

stable up to about 80°C in solution. At higher temperatures, it gives rise to a mixture of products which have not yet been identified. Flash vacuum pyrolysis of **18** gives fulvene, a product which may arise via a two-step sequence: 1,3-sigmatropic rearrangement to the

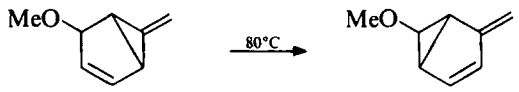


(**18**) (**94**)

cyclopropanone **94** followed by cheletropic decarbonylation[168, 169]. Although **94** has not been detected in this rearrangement, the corresponding structural change has been observed directly in the ketal **95**[140, 170] and methyl ether **96**[170].



(**95**) (**97**)



(**96**) (**98**)

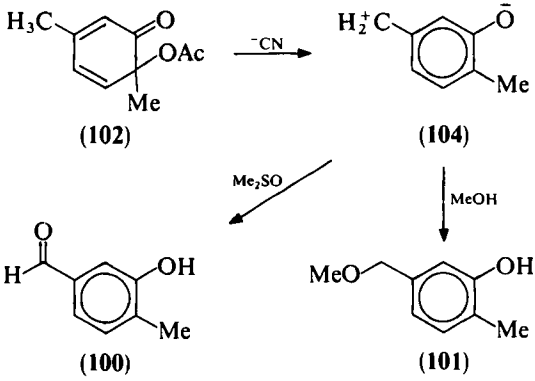
Stereochemical studies[170] implicate vinyltrimethylenemethane biradicals as true intermediates in the latter two rearrangements. Optically active ketal **95** gives completely racemic rearranged ketal **97**, hypothetically by way of the achiral intermediate **99**, and either epimer of the ether **96** gives the same mixture of epimers of **98** (predominantly the *syn*-methoxy isomer). The expected intermediate from the comparable cleavage of the bridge bond of **18** would be the non-Kekulé biradical **19**, or its zwitterionic counterpart.

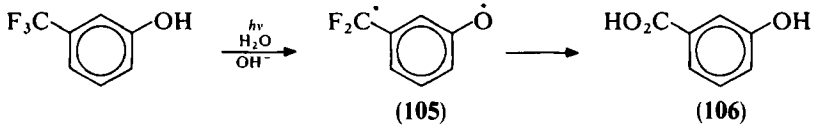
(**99**) (**19**)

The first proposal of the occurrence of such a species in a solution phase reaction was made in 1964, when Leitich and Wessely[171] explained the formation of products **100** and **101** in the reactions of the acetoxydiene (**102**) as arising from the zwitterionic form **104**.

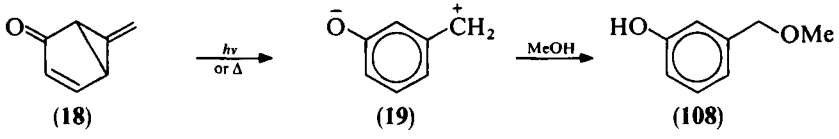
Subsequently, Seiler and Wirz[172] proposed the *m*-difluoromethylenephenoxyl biradical **105** as the key intermediate in the photohydrolysis of *m*-trifluoromethylphenol to *m*-hydroxybenzoic acid (**106**).

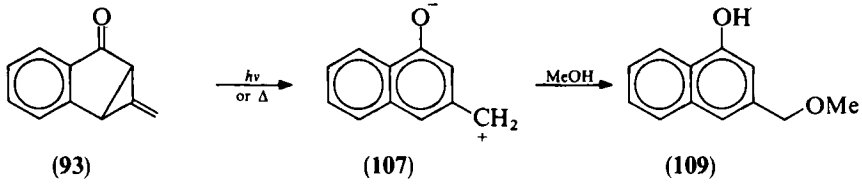
Capture of the zwitterionic species **19** and **107** of the *m*-quinomethane and *m*-naphthoquinomethane series is implied by the thermal and photochemical alcoholysis reactions of **18** and **93**, which give *m*-hydroxybenzyl ethers **108**[27, 140] and **109**[140, 148].





These are not the types of products that would have been expected if the reactive intermediate behaved like an ordinary free radical, which should have displayed redox chemistry initiated by abstraction of hydrogen from the α-OH position of the alcohol.



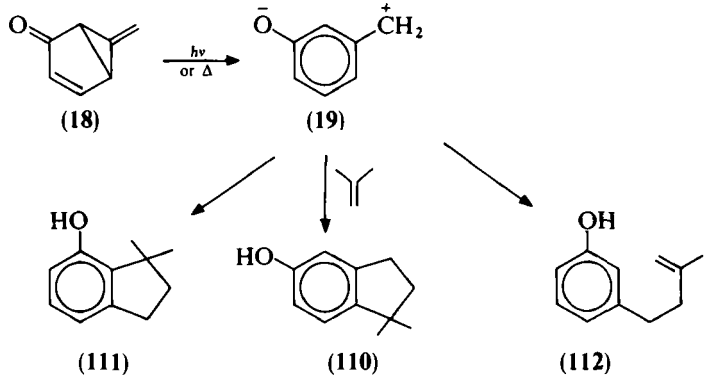


Similarly, the thermal or photochemical cycloaddition of **18** occurs smoothly with dienes or electron-rich olefins but not with electron-deficient ones[156, 167]. The products are 5- or 7-hydroxyindans, e.g. **110** and **111**. Also formed is the monocyclic olefin **112**.

Superficially, these reactions might be formulated as a Diels–Alder reaction and a vinylogous ene reaction, respectively, in which a σ bond plays a π-like role. However, these analogies imply a bimolecular mechanism, which is incompatible with the kinetics of the thermal reactions[156].

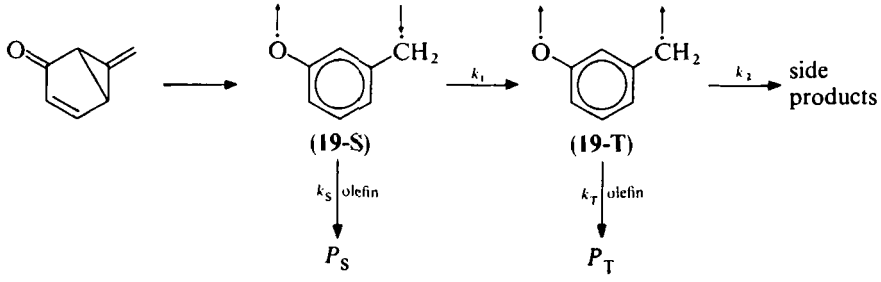
The thermal disappearance of the enone **18** is a first-order process, the rate being independent of the concentration of trapping agent (MeOH or isoprene). This suggests that *unimolecular* formation of a reactive intermediate is the rate-determining step. The Arrhenius parameters, $\log A$ (A in s^{-1}) = 14.0, E_a = 30.6 kcal mol^{-1}, are consistent with a spin-conservative transition state and a high barrier separating the reactant enone **18** from

a singlet intermediate. Although practical circumstances make difficult an isothermal comparison of the behavior of the reactive species generated thermally (110°C) and photochemically (0°C), the product compositions from the two sets of conditions are the same and imply that a common reactive intermediate is involved.



(18) (19) (111) (110) (112)

The formation of a singlet as the initial intermediate which is less stable than the triplet ground state (see Section III.B) establishes the conditions for a cascade mechanism. Attempts to test for the cascade of intermediates using the usual[165, 166] effects of dilution and O_2 on the product composition fail. Both tests give essentially negative results, as is also the case with the hydrocarbon biradical *m*-quinodimethane (Section III.D). Again, one cannot exclude the existence of the cascade mechanism on this basis. This can be verified by an examination of the kinetic form of the ratio of products from the singlet and triplet intermediates, P_S and P_T, expressed in equation 25. The rate constants are defined as shown in the reaction scheme, and k_2 may contain a term in concentration of another reactant.

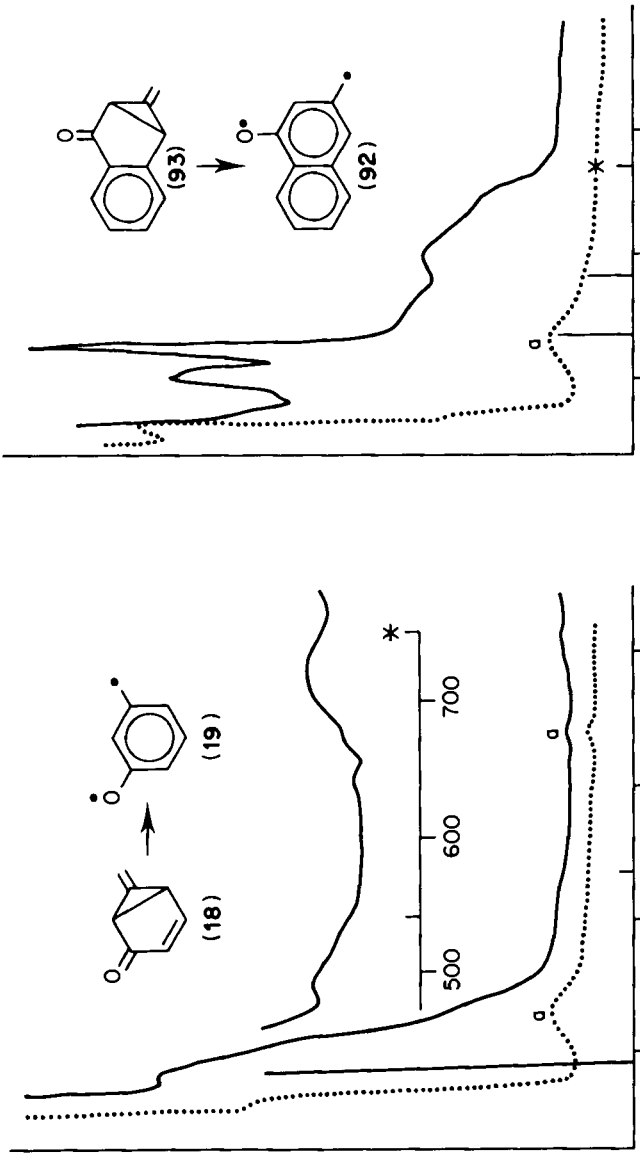


$$P_S/P_T = \frac{k_S[\text{olefin}]}{k_1} + \frac{k_S k_2}{k_1 k_T} \tag{25}$$

If the rate constant (k_T) for the capture of the triplet is small relative to that leading to side products (k_2), the product ratio always will be dominated by the concentration-independent term, and there will be no dilution effect.

It is possible, however, to construct a strong presumptive case for the singlet as the reactive intermediate based upon a correlation of optical and EPR spectroscopy of immobilized species with time-resolved spectroscopy of the transients in fluid media.

The photochemical generation of the triplet ground states of *m*-quinomethane (**19**) and *m*-naphthoquinomethane (**92**) in glassy media has been described in the preceding section.



FIGURES 19 and 20. Optical spectra of preparations of *m*-quinomethane (**19**, Figure 19) and *m*-naphthoquinomethane (**92**, Figure 20) triplet states in EtOH glass at 15 K obtained by irradiation of ketones **18** and **93**, respectively. The vertical bars mark the locations (nm) and relative intensities calculated by INDO/S-CI theory. In Figure 19, the vertical scale is expanded for the uppermost curve. Asterisks (*) mark the predicted locations of the longest wavelength n, π^* band . . . . before irradiation; ——— after irradiation for one minute at 220–440 nm. The features marked 'a' are baseline artifacts. *Reproduced with permission from D. E. Seeger, P. M. Lahti, A. R. Rossi and J. A. Berson*, J. Am. Chem. Soc., **108**, 1251 (1986). *Copyright* (1986) *American Chemical Society*

Accompanying the appearance of the characteristic EPR signals of these biradicals are bands in the visible region of the optical absorption spectrum (Figures 19 and 20)[173]. If the large singlet–triplet splittings predicted by theory (Section III.E) are even approximately correct, the singlet will be present in too small a concentration to contribute to the optical absorption, which therefore must be ascribed essentially completely to the triplet.

Although the longest wavelength feature of the spectrum of *m*-quinomethane triplet (Figure 19) lies too far to the blue to escape being overlapped by the strong absorption tail of the starting ketone (**18**) and hence is not suitable for time-resolved spectroscopy, the *m*-naphthoquinomethane triplet has a well-defined maximum near 500 nm (Figure 20) which can be used for this purpose. In low-temperature isolation media the position of this band is insensitive to the polarity of the matrix[173].

The same species is deduced to be the second of two successive transients formed in the solution-phase picosecond flash photolysis of the ketone **93**[174]. This transient (called B) has an absorption maximum near 500 nm whose position is also insensitive to solvent polarity (Figure 22). It is long-lived on the picosecond time-scale. The primary photoproduct from the flash photolysis of **93** is a different species (A) which has a solvent-sensitive spectrum (Figure 21) and which decays to B by first-order kinetics with a solvent-sensitive lifetime of 0.25–2.74 nanoseconds. Transient A also can be intercepted by a large excess of methanol in a second-order process to give **109** which can compete with its decay to B.

The data are interpreted in terms of a cascade mechanism, in which A and B are identified, respectively, with the *m*-naphthoquinomethane zwitterionic singlet **107** and its biradical triplet counterpart[174]. Since the descriptive chemistry of *m*-quinomethane matches that of *m*-naphthoquinomethane, it seems highly likely that a similar cascade exists in both systems.

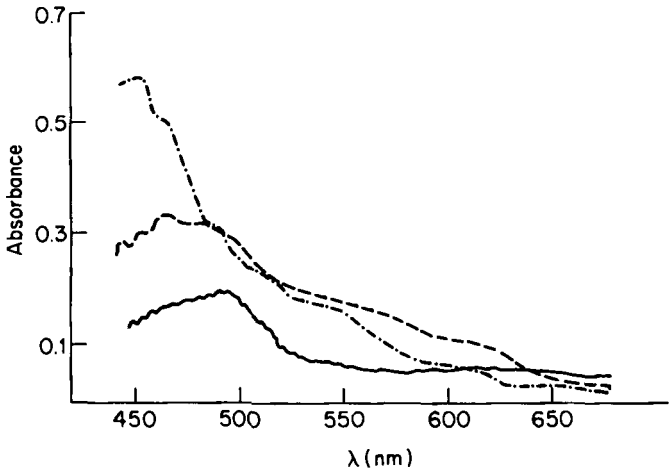


FIGURE 21. Spectra observed 25 ps after 355 nm excitation of ketone **93** in cyclohexane (——), benzene (– – –) and acetonitrile (–·–·–). *Reproduced with permission from J. L. Goodman, K. S. Peters, P. M. Lahti and J. A. Berson*, J. Am. Chem. Soc., **107**, 276 (1985). *Copyright* (1985) *American Chemical Society*

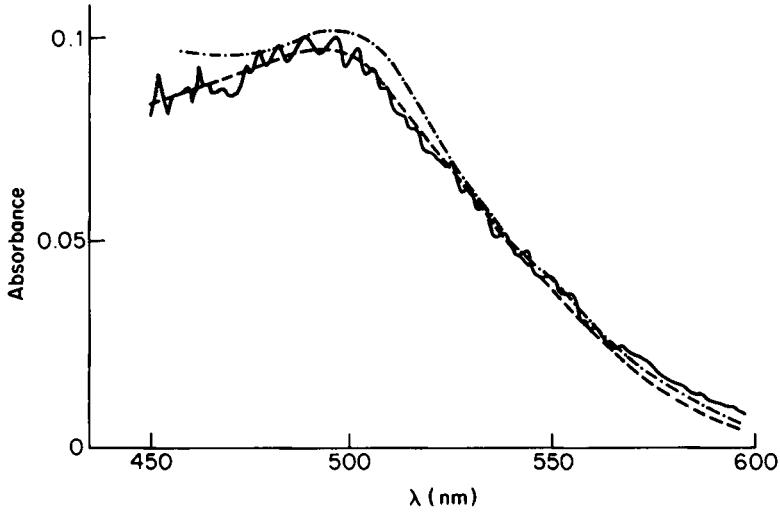
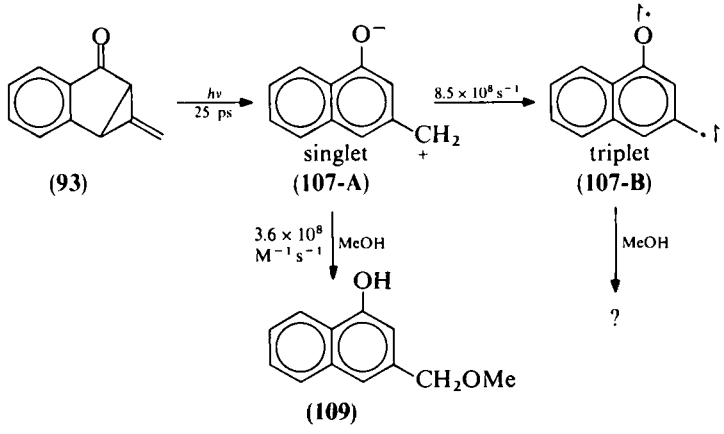


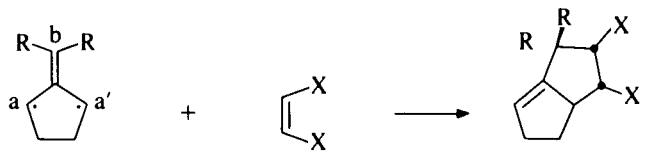
FIGURE 22. Spectra observed 9 ns after 355 nm excitation of ketone **93** in cyclohexane (——), benzene (– – –) and acetonitrile (· · ·). *Reproduced with permission from J. L. Goodman, K. S. Peters, P. M. Lahti and J. A. Berson*, J. Am. Chem. Soc., **107**, 276 (1985). *Copyright* (1985) *American Chemical Society*



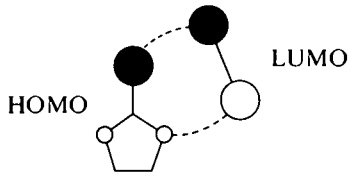
3. Stereochemistry and regiochemistry of m-quinomethane cycloadditions

The cycloadditions of the trimethylenemethane (TMM) biradicals 2-methylenecyclopentane-1,3-diyl (**113**) and 2-isopropylidenecyclopentane-1,3-diyl (**114**) show all the signs expected of concerted reactions[165, 166]. They are stereospecifically *cis* and regiospecifically fused (reaction at a + b rather than at a + a').

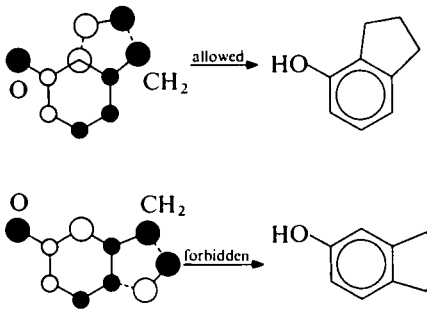
The regiospecificity has been ascribed[165, 166, 175, 176] to phase matching of the TMM HOMO and the olefin LUMO at the reactive sites (**115**). An extension of this reasoning to the case of *m*-quinomethane closed-shell singlet suggests that, if the reaction is to be concerted, only the orientation leading to the *ortho* product is allowed, whereas that leading to *para* product is forbidden. If these factors were determinative, the *ortho* adduct would be formed concertedly and stereospecifically, but the *para* adduct would be formed



(**113**, R = H)
(**114**, R = Me)



(**115**)

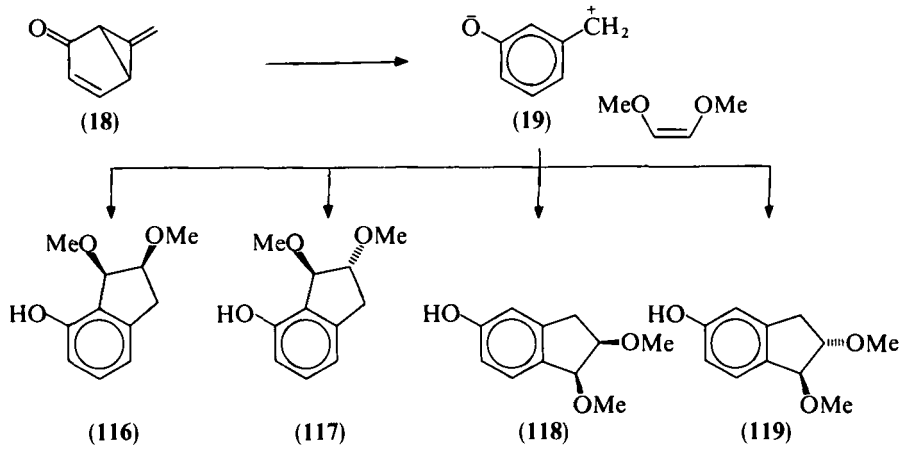


by a stepwise mechanism, which would lead to some loss of stereospecificity. The anticipated switch in stereospecificity would clearly signal a change in mechanism. However, as Table 6[167] shows, the cycloadditions of *m*-quinomethane to *cis*-1,2-dimethoxyethene show no significant differences in stereospecificity between the *ortho* and *para* adducts.

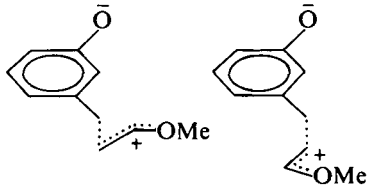
Although the overall stereospecificities of cycloaddition are somewhat lower with the 2,4-hexadienes than with *cis*-1,2-dimethoxyethene (e.g. 6:1 in the *ortho-cis* case as compared to 17:1), the stereospecificities in the *ortho* adduct series again do not differ significantly from those in the *para* series. With neither kind of trapping agent does the product stereospecificity depend markedly upon the orientation of the addition, a finding that argues against a dominant reaction under orbital symmetry control of a concerted *ortho* process[167].

TABLE 6. Product ratios in the reaction of **24** with *cis*-1,2-dimethoxyethene at 115°C

Product ratio	Solvent	
	Benzene	MeCN
o-cis/o-trans (**116/117**)	17.0 ± 0.6	17.1 ± 0.1
p-cis/p-trans (**118/119**)	13 ± 3	14.7 ± 1
ortho/para [(**116** + **117**)/(**118** + **119**)]	3.2 ± 0.2	1.5 ± 0.1



Solvent polarity has little effect on the *cis/trans* product ratios (Table 6) in the reaction with *cis*-1,2-dimethoxyethene. On the other hand, the *ortho/para* ratio responds noticeably, with the relative amount of *para* product increasing in the more polar solvent, MeCN. The effect may be rationalized as a selective stabilization of the more polar 'extended' transition state **121** relative to the less polar 'coiled' transition state **120** in a polar solvent[167]. This solvent effect is reminiscent of the increased preference for *endo* vs. *exo* stereochemistry of the Diels–Alder reaction with increasing solvent polarity, which was interpreted in a similar way[177].



E. Bis-*m*-Quinomethanes

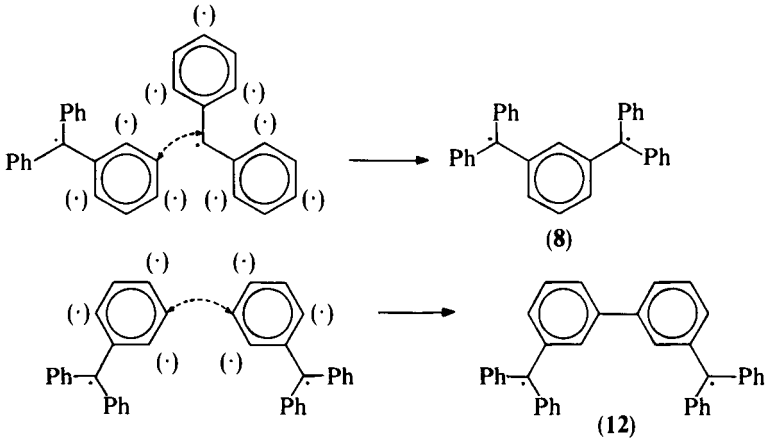
1. Theory

The intrinsic interest in non-Kekulé molecules as examples of a highly unconventional form of matter would justify an unstructured examination of their synthesis and behavior. Such a program would be intellectually respectable in the same sense as was the exploration of aromatic chemistry of the late nineteenth century. One intuits that new chemical reactions and physical properties wait to be discovered in this field, and no more sophisticated motivation is needed. Nevertheless, because of their potential or actual open-shell nature, non-Kekulé molecules represent engaging theoretical problems (see Section III.B). The experimental organic chemist therefore finds motivation beyond the descriptive one in the design and construction of new non-Kekulé systems to stimulate the development of theory.

This interaction between theory and experiment actually began early in the study of non-Kekulé molecules. Section II has described briefly the observation of Müller and Bunge[29] that the two hydrocarbons **14** and **18** of Schlenk and Brauns[13,14] are paramagnetic, as

would be predicted from their half-filled degenerate NBMOs, if Hund's rule applied to molecules.

However, in the same year, 1936, Hückel[52] pointed out that good theoretical reasons existed to apply Hund's rule to **8** but not to the apparently closely related **12**. His argument derives from the recognition of fundamentally disparate connectivity patterns in the two molecules. Specifically, one can consider **12** to have been formed by a union at the *meta* positions of two triphenylmethyl fragments, whereas **8** is formed by a union at a triphenylmethyl *meta* position and a benzhydryl methine position.



Because the carbon atoms at the **12**-forming union have zero HMO coefficients (the sites are 'inactive'[28]), the exchange interaction will be small. The quantum mechanical reasoning that leads to this conclusion is straightforward.

Assume that the interaction of the two triphenylmethyl fragments, A and B, can be modeled by the interaction of the two single electrons in the triphenylmethyl HMO NBMOs, orbital χ_{10} in each case. Denote NBMO χ_{10} on fragment A as orbital a and that on fragment B as b. Each HMO χ_j made up of $\pi-$AOs ϕ_i may be expressed as in equation 26.

$$\phi_i = c_i p_\pi \tag{26a}$$

$$\chi_j = \sum_i \phi_i \tag{26b}$$

where c_i is the coefficient of the ith carbon p orbital in the π system. Expansion of the exchange integral (see equation 9) gives rise to products of the form in equation 27

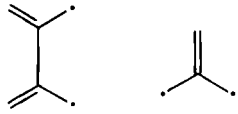
$$\mathrm{a(1)b(1)} = \left(\sum_i \phi_i\right)\cdot\left(\sum_k \phi_k\right) \tag{27}$$

where the summations over i and k represent the linear combinations of atomic orbitals that constitute the HMOs a and b. To a first approximation, products between terms of the two summations can make a contribution to the exchange energy only if the terms refer to carbon atoms that are adjacent and have non-zero coefficients. But the only linkage between the fragments A and B is the *meta–meta* junction in **12**. Since this junction links two sites with zero coefficients, the exchange energy vanishes at this level of approximation, and the normal basis for the application of Hund's rule vanishes with it. The argument is qualitative, since at a higher level of theory, the π coefficients at the junction will not be precisely zero. Moreover, the case of an inactive–active connection (as in trimethylene-

methane, **28**) would be indistinguishable from that of an inactive–inactive one if the argument were to be taken literally. Nevertheless, the major point remains, namely, that an inactive–inactive junction in a π fragment analysis leads to the prediction of a small singlet–triplet gap.

> Given the paucity of related experimental data and the primitive state of molecular quantum theory at the time, the immediate recognition[52] that **8** and **12**, although superficially similar in structure, were likely to be fundamentally disparate in magnetic properties, can only be regarded as remarkable[173].

Oddly, Hückel's prescient paper of 1936 seems to have made little impact. Longuet-Higgins does not cite it in his very influential work of 1950[56] and it is clear that he makes no distinction between non-Kekulé molecules with inactive–inactive connections and those without. For example, he applies Hund's rule to predict triplet ground states for both tetramethyleneethane (**29**) and trimethylenemethane (**28**), which are the parent substances of the former and the latter categories, respectively.

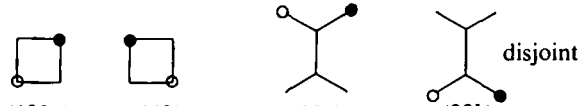


(29) **(28)**

In fact, it took more than 40 years before attention was redirected to the problem Hückel had addressed in 1936. The seminal papers are those of Borden and Davidson[62], Misurkin and Ovchinnikov[64] and Ovchinnikov[63], which were followed by numerous other contributions[65–72, 178–180]. These theoretical studies have strengthened the conceptual basis for identifying which π-conjugated molecules might violate Hund's rule.

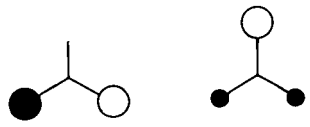
In the Borden–Davidson formalism[62], if the NBMOs are (or by linear combinations can be) confined to separate regions of the molecule, they are said to be disjoint. This property, to first order, erases the Coulombic repulsion that usually destabilizes the singlet in π-conjugated biradicals.

Disjoint character is exemplified by the NBMOs of cyclobutadiene (which is formally not a non-Kekulé molecule) and tetramethyleneethane (which is). The separation of the two NBMOs of cyclobutadiene to non-identical regions of the molecule is illustrated in **122a** and **122b**, and the corresponding NBMOs of tetramethyleneethane are shown as **29a** and **29b**. This property of separability of the NBMOs means that to first order, the peaks of



(122a) **(122b)** **(29a)** **(29b)**

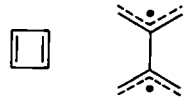
the two electron distributions in the singlet state of either of these disjoint systems are as well separated as those in the triplet. This is to be contrasted with the more usual non-disjoint type of biradical, exemplified by trimethylenemethane, whose NBMOs **28a** and **28b** cannot be confined to separate atoms by any linear combination.



(28a) **(28b)**

A sufficient (see tetramethyleneethane) but not a necessary (see cyclobutadiene) criterion for disjoint character is met if the molecule can be constructed by inactive–inactive union of two radical fragments[62]. This is the intellectual bridge between Hückel's early insight and the more rigorous, computationally buttressed modern formulation.

At the SCF level of theory, the singlet and triplet states of a disjoint system are degenerate. A higher-order effect, dynamic spin polarization, then can selectively stabilize the singlet and produce a violation of Hund's rule. Two examples of this have been confirmed computationally at a reasonably high level: a square planar cyclobutadiene (**122**)[180–182] and planar tetramethyleneethane (**29**)[62].



(122) (29)

The physical basis of dynamic spin polarization[180, 183–185] can be understood as an extension of the more familiar static spin polarization[81, 186–192]. In allyl radical, for example, simple HMO theory predicts zero spin density at C(2) because the NBMO ψ_2 has a node at that site. However, the EPR spectrum of allyl[193] shows a finite coupling constant (4.06 G) of the electron with the proton at C(2) (see Figure 23). This can be explained at a

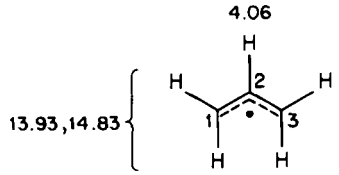


FIGURE 23. Proton hyperfine coupling constants in allyl radical (in gauss). *Reproduced with permission from Ref.* 110, *p.* 91

higher level of theory by taking electron correlation into account. One way of showing the interactions is to assign different orbitals, $\psi_1(\alpha)$ and $\psi_1(\beta)$, to the electrons of opposite spin in the lowest occupied π MO, ψ_1 (see Figure 24). Assume (arbitrarily) that the single electron in ψ_2 has α spin. This electron polarizes the electrons in ψ_1, that is, causes a perturbation in their spatial distribution, so as to minimize the energy. There are two conceivable polarizations: type A concentrates α spin at C(2) and β spin at C(1) and C(3), whereas type B concentrates the spins in the opposite sense. Both types of polarization will minimize the electron repulsion by localizing the electrons of ψ_1 to different sites. However, the type B polarization is preferred, because it concentrates electrons of like spin (α) at common sites (C(1) and C(3)), whereas type A polarization concentrates electrons of opposite spin at those sites. The physical basis of the preference for type B polarization is the same as that of Hund's rule (Section II.B): the exchange energy will favor the parallel spin configuration at a given site. The result is that, although most of the spin density does reside at C(1) and C(3) in the allyl radical, as would be predicted just from the electron distribution in ψ_2, a finite amount of spin density resides at C(2) because of the polarization of the electrons in ψ_1, and the spin at C(2) is opposite to that of C(1) and C(3).

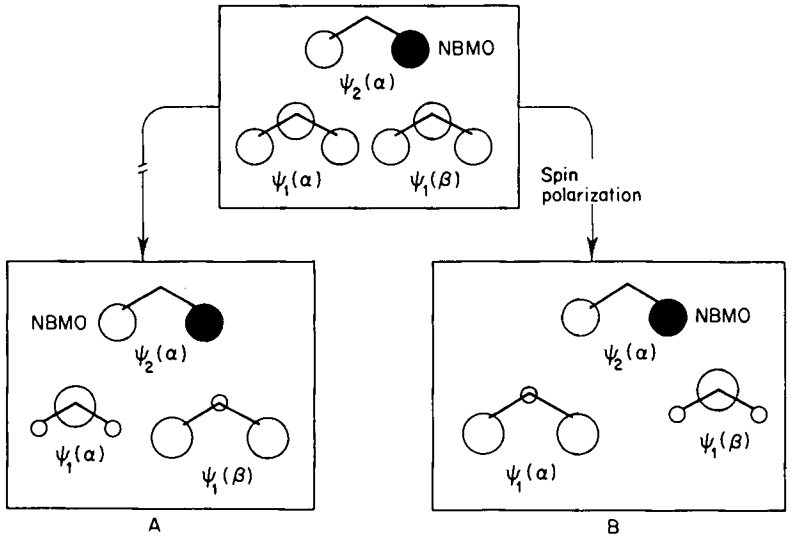


FIGURE 24. Two conceivable spin polarizations of the ψ_1 π electrons of allyl radical ψ_2 odd electrons. Type A is less favorable than type B

This static spin polarization arises from the existence of a net spin in the allyl radical, whereas in a singlet state of a biradical, e.g. **29**, or a 4n polyene, e.g. **122**, there is no net spin. However, a proper quantum mechanical description of such species employs configuration interaction, in which the ground electron configuration mixes with excited configurations, many of which have singly occupied orbitals. The electrons in such orbitals polarize the electrons in lower energy orbitals in the same way as described for allyl, so that the effect is similar. Hence the name[180] 'dynamic spin polarization'. Although a similar polarization might be imagined for the triplet, it turns out that the polarization is much less than in the singlet[180] and, in fact, to first order, there is no polarization in the triplet[185]. The net result is that dynamic spin polarization will conduce to a singlet ground state, in violation of Hund's rule, in disjoint π-electron molecules.

In the formalism of Ovchinnikov[63], a similar result can be obtained for the case of alternant π-conjugated molecules. These conform to a rule that each atom of the π system can be assigned a parity by starring in such a way that no two starred or unstarred positions are adjacent. Using a Heisenberg Hamiltonian within a valence-bond theoretical framework, Ovchinnikov[63] derived a formula which states that the total spin of the ground state will be given by half the difference between the numbers of starred and unstarred π centers (equation 28):

$$S = (n^* - n)/2 \tag{28}$$

Obviously, when $n^* = n$, the total spin is zero, and the ground state is singlet. Since it has been shown[62] that such equal parity systems are disjoint, but that not all disjoint alternant systems have equal parity, the $S = 0$ cases of Ovchinnikov are a subcategory of disjoint molecules.

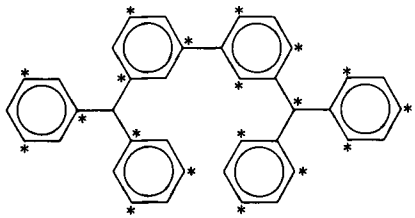
The Ovchinnikov formulation[63] is especially attractive since it requires no calculations and reduces the task of finding candidate structures for low-spin ground states to a simple enumeration. How this works should be immediately obvious from the starring diagrams for trimethylenemethane (**31**) and tetramethyleneethane (**32**). Note that equation 28 is

(28) (29)

$S = (3-1)/2 = 1$ triplet $S = (3-3)/2 = 0$ singlet

proposed[63] to hold even in heteroatom perturbed π-conjugated systems, an assumption that, as we have seen (Section III.B), is supported both computationally and experimentally.

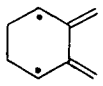
Although reasons to expect Hund's rule violations thus have been recognized for more than 50 years, Nature has so far frustrated attempts to verify these predictions. Part of the blame may be placed upon the already described difficulties of identifying unstable species with singlet ground states. Moreover, the obvious simple candidates, cyclobutadiene (**122**) and tetramethyleneethane (**29**) test the theory only if they exist in idealized geometries, square planar for **122** and planar for **29**. The weight of evidence is against these geometries for **122**[194, 195] and **29**[95, 196, 197]. Similarly, the Schlenk–Brauns hydrocarbon **18**, has been assigned a triplet ground state on the basis of the adherence of its EPR signal intensity to the Curie law[198]. It seems probable that **12** is non-planar, so that its nominally equal-parity nature is not a reliable basis for predicting a low-spin ground state.



(12)

$S = (19-19)/2 = 0$

The tetramethyleneethane derivative **123** presumably is planar or nearly so, but the experimental evidence so far does not seem to permit an unequivocal assignment of the ground state[199–202].

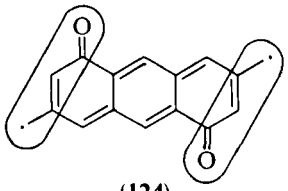


(123)

The currently available EPR techniques for measuring ground-state singlet-triplet energy separations (ΔE) do not work in most cases because curvature in the Curie plot usually is indiscernible (see Section III.B.2b). This forces the issue to be cast in binary form: is Hund's rule obeyed or not? It should be apparent, however, that two very different kinds of biradical, a non-disjoint triplet with a large ΔE and a disjoint one with a small ΔE, both might hide behind a 'linear' Curie plot. Hückel's conjecture then would be correct but experimentally unverified. At present, a historical accident makes us dependent upon an actual violation of Hund's rule for an experimental proof.

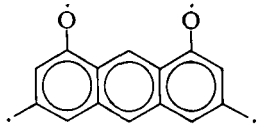
2. Experiment

Recent studies have used the bis-*m*-quinomethanoid **124** to test the equal parity criterion for low-spin ground states[203-205]. The biradical **124** has overall C_{2h} symmetry. As an equal parity system, it should have a singlet ground state. It is related to the simplest disjoint biradical tetramethyleneethane (**29**) in the sense that the Hückel NBMO electron density is confined to the two (ringed) pentadienyl moieties disjointly. The rigid conjugated framework prevents twisting about the connection between them. The isomeric molecule **125** has overall C_{2v} symmetry. It is non-disjoint and formally a tetraradical, for which the qualitative spin rule predicts a quintet ground state. Tetraradical **125** therefore serves as a control system to test the application of Hund's rule to a non-disjoint case closely related to the disjoint test **124**.



(124)

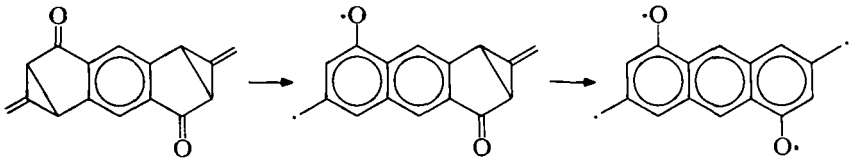
$S = (9-9)/2 = 0$



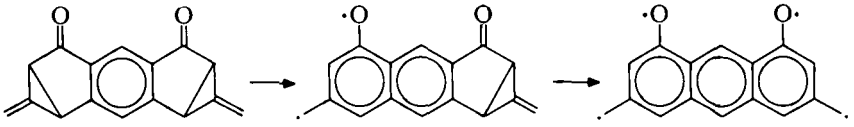
(125)

$S = (11-7)/2 = 2$

The synthesis of **124** and **125** are effected by successive photochemical ring-cleavages, **126** → **127** → **124** and **128** → **129** → **125**, of samples immobilized in rigid media. The



(126) **(127)** **(124)**



(128) **(129)** **(125)**

sequence of events can be monitored by both optical and EPR spectroscopy (Figures 25 and 26). Cleavage of one bridge bond in either **128** or **126** gives either of the orange species (Figures 25 and 26, respectively) formulated as substituted *m*-naphthoquinomethanes **129** and **127**. By analogy to *m*-naphthoquinomethane itself (Section III.E), these species are expected to be triplets and are in fact observable as such by EPR spectroscopy (Figures 27 and 28). The $|D|/hc$ values for **129** and **127**, $\sim 0.020\ cm^{-1}$, are in good agreement with that of *m*-naphthoquinomethane, $|D|/hc = 0.0204\ cm^{-1}$.

Irradiation at wavelengths beyond 420 nm of the immobilized sample of **129** causes the optical spectrum responsible for the orange color to fade and be replaced by a new absorption spectrum (Figure 25) associated with a visible red–purple color. A parallel change occurs in the EPR spectrum, as the primary photoproduct, the triplet **129**, is

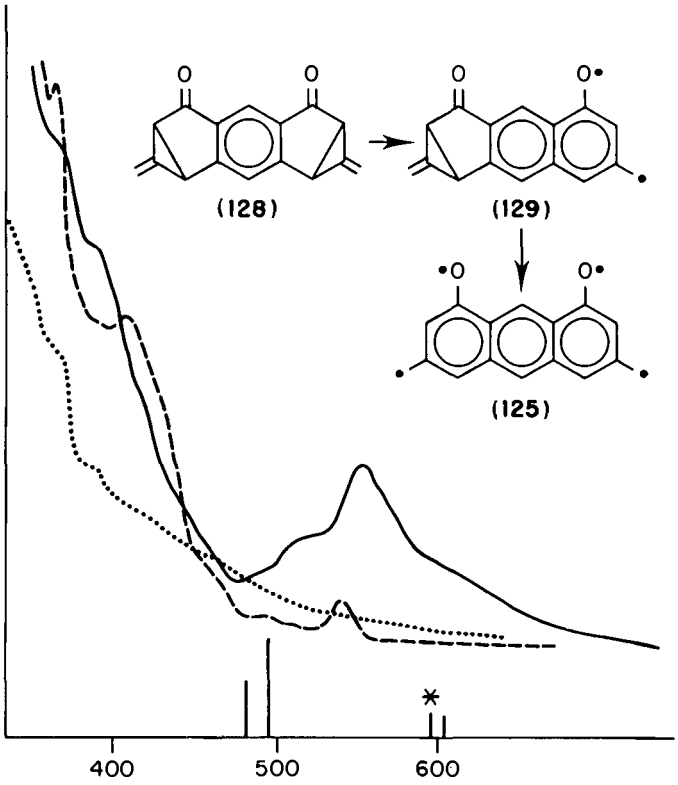


FIGURE 25. Optical spectra at 16 K in EtOH glass obtained by irradiation of the diketone **128** at 220–440 nm to give the triplet **129** and then at > 425 nm to give the quintet **125**. (· · ·) before irradiation; (– – –) primary photolysis product **129**; (——) secondary product **125**. Transitions shown by vertical bars are calculated for **125**. *Reproduced with permission from D. E. Seeger, P. M. Lahti, A. R. Rossi and J. A. Berson*, J. Am. Chem. Soc., **108**, 1251 (1986). *Copyright* (1986) *American Chemical Society*

converted to a new species, the quintet C_{2v} tetraradical **125** (Figure 27). The quintet is the ground spin state of the tricyclic structure **125**, as judged from a linear Curie plot between 15 and 70 K. Aside from the intensity variation, the EPR spectrum does not change in this temperature range, which is interpreted to mean that no nearby state of different multiplicity is populated or depleted. Similarly, the optical spectrum is temperature-insensitive. As expected, Hund's rule applies to this non-disjoint case.

Similar irradiation of the immobilized sample of the primary photoproduct **127** in the C_{2h} series causes the orange color to change to red–purple (Figure 26) and the triplet EPR spectrum to be replaced by that of another triplet species with a much smaller ZFS, $|D|/hc = 0.0025\ cm^{-1}$ (Figures 28 and 29). This is consistent with the much greater average separation of the unpaired electrons in **124** as compared to **127**. The Curie plot is linear between 15 and 70 K. Again, neither optical nor EPR spectroscopy gives evidence of a variable contribution from any other species in this temperature range. Thus, either the singlet and triplet are accidentally almost exactly degenerate ($\Delta E \leqslant 0.024\ kcal\,mol^{-1}$), or

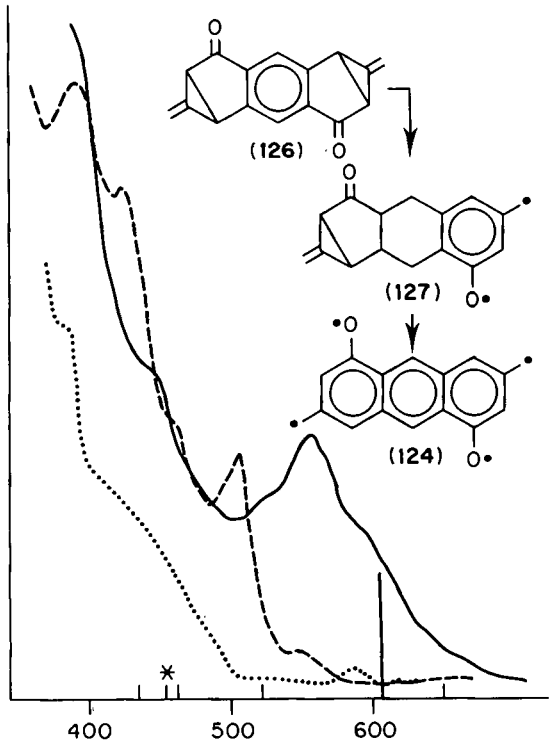


FIGURE 26. Similar to Figure **25** for the process **126** (· · ·) → **127** (---) → **124** (——). Transitions shown by vertical bars are calculated for **124**. *Reproduced with permission from D. E. Seeger, P. M. Lahti, A. R. Rossi and J. A. Berson,* J. Am. Chem. Soc., **108**, 1251 (1986). *Copyright* (1986) *American Chemical Society*

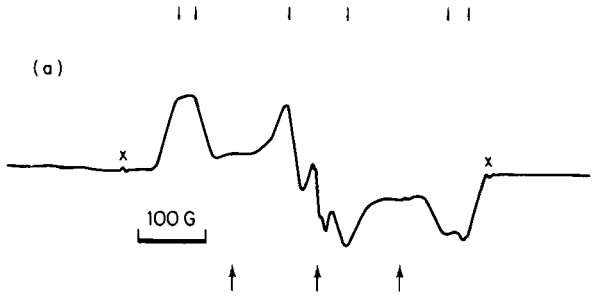


FIGURE 27. EPR spectra from photolysis of diketone **128** in 2-methyltetrahydrofuran (2-MTHF) glass at 36 K. The lines and arrows mark the positions of transitions associated with the triplet state of biradical **129** and the quintet state of tetraradical **125**, respectively. The symbol X marks absorption by H atoms. All the spectra were recorded with the same spectrometer control settings. (a) After 30 s irradiation at 305 nm $\leqslant \lambda \leqslant$ 525 nm; (b) after 10 m at $\lambda > 425$ nm; (c) after 35 m at $\lambda > 425$ nm; (d) after 180 m at $\lambda > 425$ nm. *Reproduced with permission from D. E. Seeger, P. M. Lahti, A. R. Rossi and J. A. Berson,* J. Am. Chem. Soc., **108**, 1251 (1986). *Copyright* (1986) *American Chemical Society*

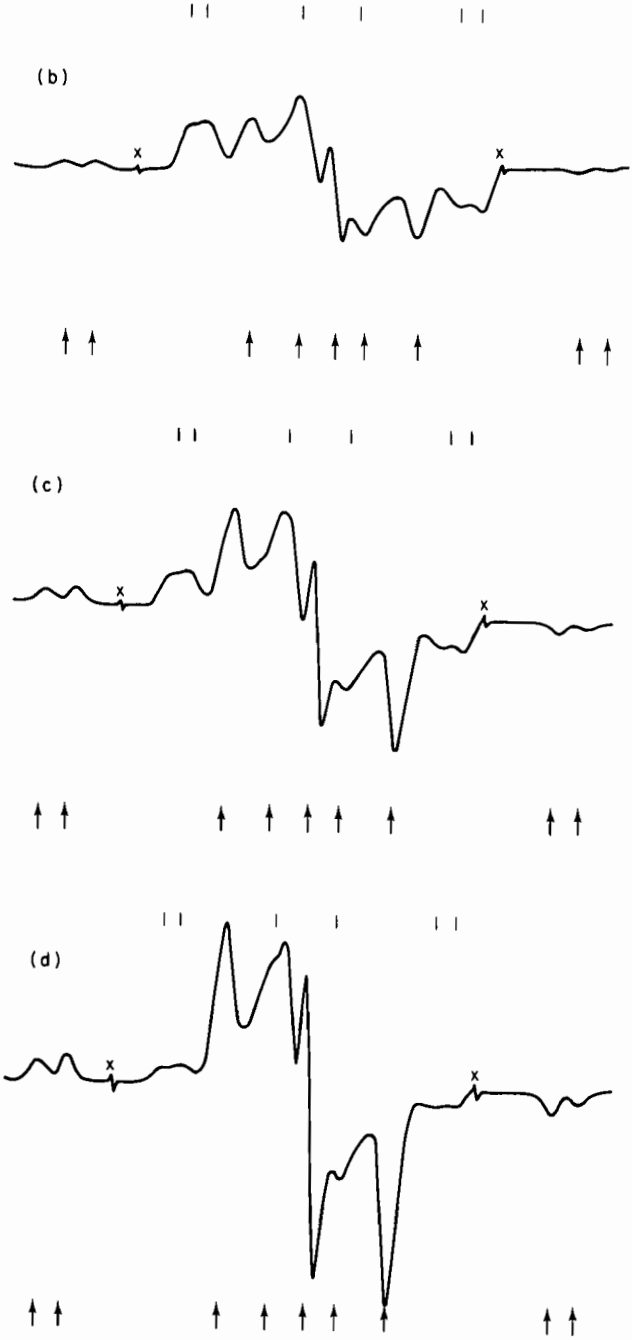


FIGURE 27. Continued

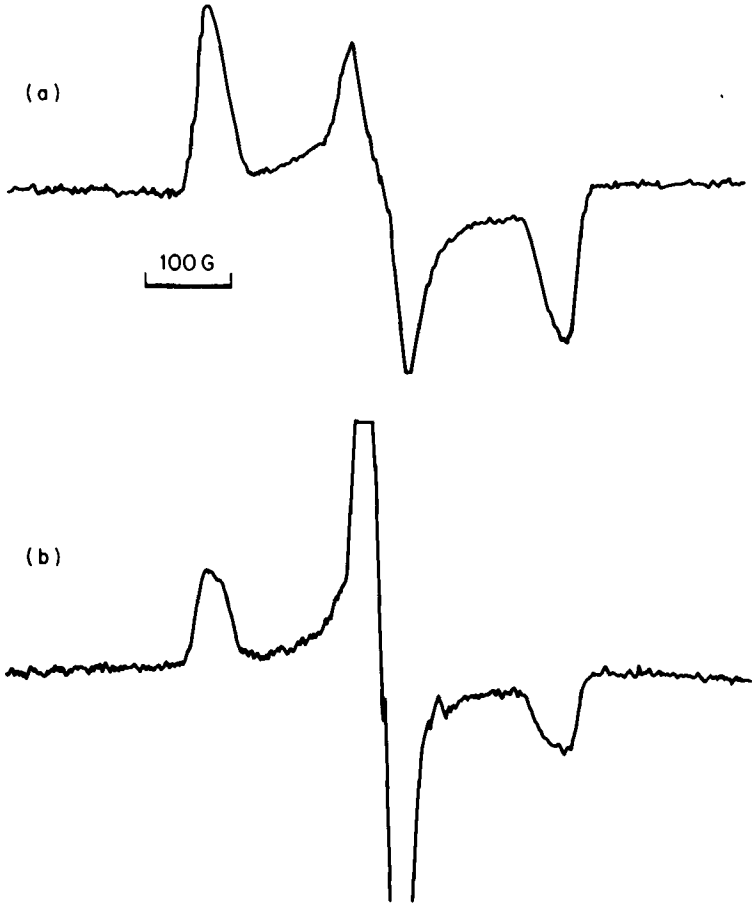


FIGURE 28. EPR spectra obtained from photolysis of diketone **126** in 2-MTHF glass at 77 K. Spectra (a)–(c) were recorded with the same spectrometer settings. Spectrum (d) is of the same preparation as (c), except that the *x*-axis has been expanded and the *y*-axis contracted. (a) After 30 s, $305 \leqslant \lambda \leqslant 525$ nm. The spectral contribution of a small amount of secondary photoproduct has been digitally subtracted. (b) After 4 m further photolysis, $\lambda \geqslant 425$ nm. (c) After 81 m, $\lambda \geqslant 425$ nm; (d) same preparation as (c) with altered scale. *Reproduced with permission from D. E. Seeger, P. M. Lahti, A. R. Rossi and J. A. Berson*, J. Am. Chem. Soc., **108**, 1251 (1986). *Copyright* (1986) *American Chemical Society*

more probably, the triplet is the ground state[173, 204, 205]. Thus, a high-spin ground state seems to be preferred, despite the disjoint character of the NBMOs associated with the equal-parity connectivity pattern of the C_{2h} biradical **124**.

The apparent breakdown of the qualitative theories in the case of **124** makes it clear that other factors can sometimes override disjoint character. There can hardly be any doubt that the main idea of the qualitative theories is correct, namely that the exchange interaction of the SOMO electrons in equal-parity (therefore disjoint) π-conjugated non-Kekulé molecules is small, and hence that a singlet should be the ground state or a very low-

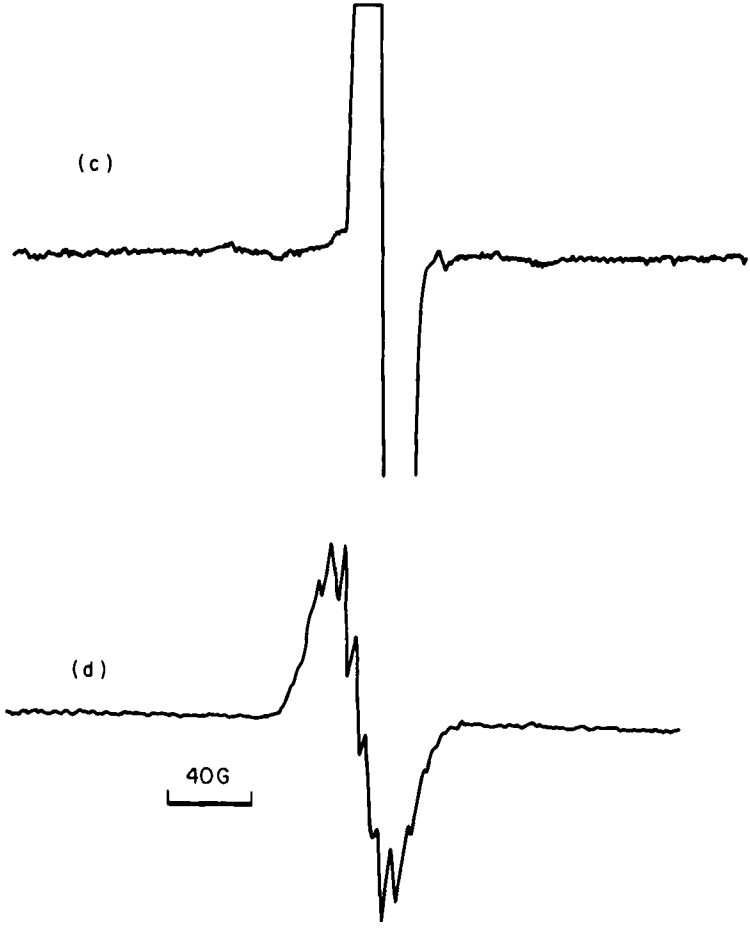


FIGURE 28. Continued

lying excited state. The problem at present is to perceive the structural features of formally disjoint test molecules that act to restore some of the exchange coupling and thereby contaminate the desired pure test situation.

In this connection, it is encouraging to note the outcome of an INDO/S-CI calculation[70], which places the triplet of **124** 4.3 kcal mol^{-1} lower in energy than the singlet, in qualitative agreement with the experimental observations. Although at this stage, these theoretical results cannot be said to have elucidated the underlying physical reasons for the unexpected adherence of this particular disjoint system to Hund's rule, they offer some basis for confidence that INDO/S-CI calculations may provide hints on which non-Kekulé molecules would constitute useful tests of spin state order and spacing. An example of such utility is given in the following section.

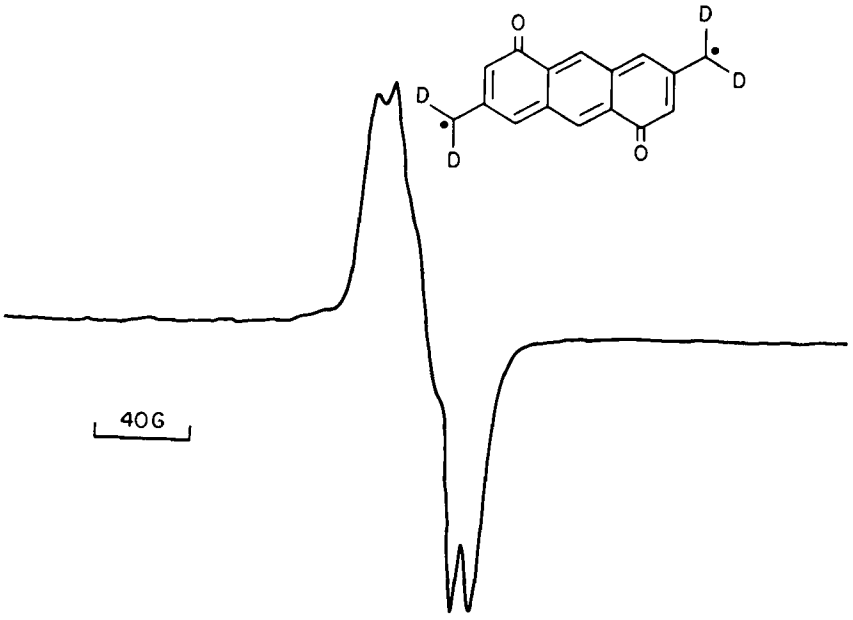
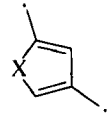


FIGURE 29. Secondary EPR spectrum obtained (similarly to that of Figure 27d) from the photolysis of **126**-d_4. The triplet ZFS parameters are $|D|/hc = 0.0025\,cm^{-1}$ and $|E|/hc = 0.0009\,cm^{-1}$. *Reproduced with permission from D. E. Seeger, P. M. Lahti, A. R. Rossi and J. A. Berson*, J. Am. Chem. Soc., **108**, 1251 (1986). *Copyright* (1986) *American Chemical Society*

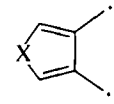
F. 2,4- and 3,4-Dimethylenefuran and 3,4-Dimethylenethiophene

1. Theory

Analogous to the relationship of the *m*-quinonoids to benzene is that of the 2,4- and 3,4-dimethylene derivatives, **130–135**, to the five-membered heterocyclic aromatics furan, thiophene and pyrrole. These non-Kekulé substances are of special interest because the



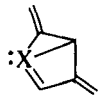
(**130**, X = NH)
(**131**, X = O)
(**132**, X = S)



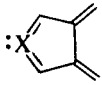
(**133**, X = NH)
(**134**, X = O)
(**135**, X = S)

odd number of ring members makes them non-alternant, so that Ovchinnikov's parity criterion for the spin of the ground state does not apply. INDO/S-CI calculations[70, 71] provide some insight on the properties that might be expected of these substances and are supported by *ab initio* calculations[206–208], which give similar predictions.

It should be clear from inspection of **130–135** that no non-ionic full-valence structure for these substances can be written without expansion of the octet of the heteroatom (**136** and **137**). Although this may be conceivable for the case of X = S, it is conventionally not



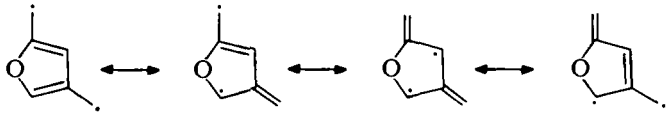
(136)



(137)

acceptable for atoms of the first row (N, O). In this sense, then the latter two systems can be considered to be of the non-Kekulé type.

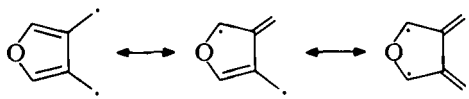
In simple resonance terms, the contributing structures to the 2,4-dimethylene group, **130–132**, include, in addition to zwitterionic structures, a group of structures in which the odd electrons are assigned to different positions (e.g. **138–141**). The last two of these, **140** and **141**, emphasize the relationship of this system to trimethylenemethane (**31**). Similarly,



(138) (139) (140) (141)

(31)

the resonance forms of the 3,4-dimethylene system (e.g. **142–144**) suggest a relationship to tetramethyleneethane (**29**). To the extent that these analogies are valid, that is, if the oxygen

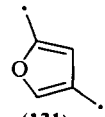
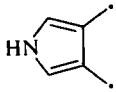
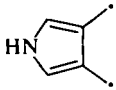
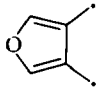
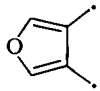
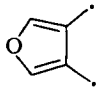
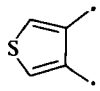


(142) (143) (144)

(29)

(or other heteroatom) introduces little perturbation, one might expect the ordering of the spin states in the 2,4-system to be the same as that in trimethylenemethane (triplet ground state), and that in the 3,4-system to be the same as in the tetramethyleneethane (singlet ground state). As Table 7 shows, the calculations predict exactly this result.

TABLE 7. Energies of some non-Kekulé molecular states

Structure	State	Calc. method	Relative energy (kcal mol^{-1})	Ref.
 (131)	$^3A''$ $^1A''$	INDO/S-CI	0.0 13.3	70
 (133)	$^1A_1$ $^3B_2$	INDO/S-CI	0.0 4.3	206
 (133)	$^1A_1$ $^3B_2$	*a*	0.0 5.8–6.4	208
 (134)	$^1A_1$ $^3B_2$	INDO/S-CI	0.0 0.5	70
 (134)	$^1A_1$ $^3B_2$	*b*	0.0 4.4	207
 (134)	$^1A_1$ $^3B_2$	*c*	0.0 2.2–2.6	208
 (135)	$^1A_1$ $^3B_2$	INDO/S-CI	0.0 0.4	206
 (136)	$^1A_1$ $^3B_2$	INDO/S-CI	0.4 0.0	206
 (136)	$^1A_1$ $^3B_2$	*d*	0.0 1.4–1.6	208

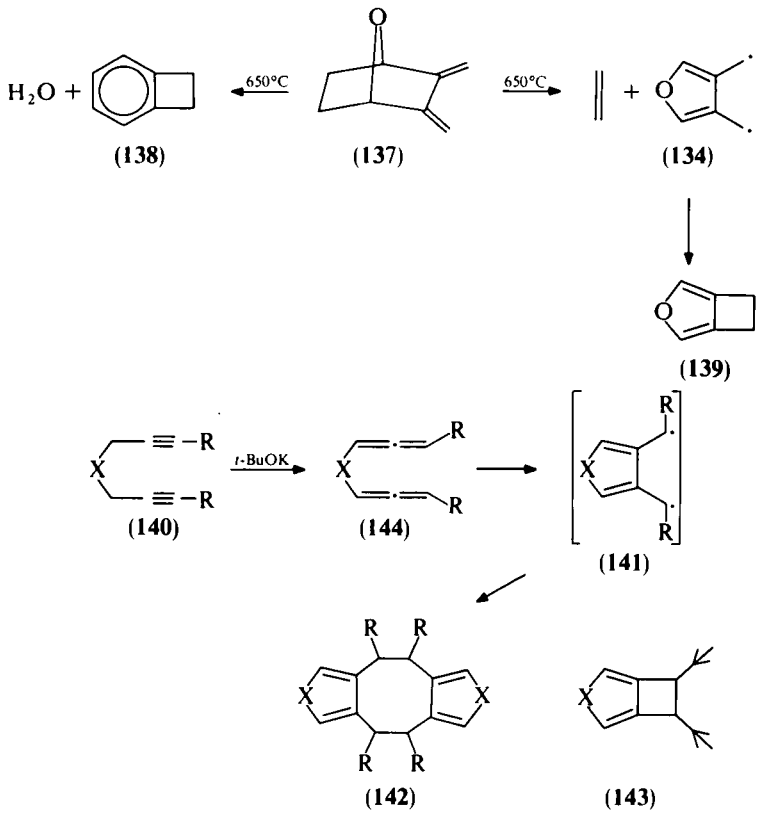
[a] Split valence (SV) SDTQ CI in the space of the conceptual minimal π basis set (5.8); SV multireference S CI in the full π space (6.4). [b] STO-3G/3-21G SDTQ CI, at 3-21G UHF triplet geometry. [c] SV SDTQ CI and SV MRSD CI. With polarization functions on the heavy atoms (SVP), the value is 1.7. [d] SV SDTQ CI (1.5), SV MRSD CI (1.6), SVP SDTQ CI (1.4).

In the 3,4-bismethylene series, the INDO-S/CI calculations consistently show a 2–3 kcal mol^{-1} less severe violation of Hund's rule than the *ab initio* results, but both calculations agree that the singlet should be the ground state or at worst a very low-lying excited state. On the other hand, the 2,4-bismethylenefuran (**131**) shows a decided preference for the triplet. For reference, Table 7 shows results of calculations on the cyclic hydrocarbon tetramethyleneethane (**136**), for which the INDO-S/CI and *ab initio* methods closely bracket a zero singlet–triplet gap.

2. *Chemistry of 3,4-dimethylenefuran and 3,4-dimethylenethiophene*

Vogel and Hardy showed that pyrolysis of 2,3-bismethylene-7-oxabicyclo[2.2.1]heptane (**137**) proceeded by two competitive pathways, one to give water and benzocyclobutene (**138**) and the other to give ethylene and 3-oxabicyclo[3.2.0]hepta-1,4-diene (furanocyclobutene; **139**). They pointed out the possibility that 3,4-bismethylenefuran biradical (**134**) might be an intermediate in the latter pathway[209].

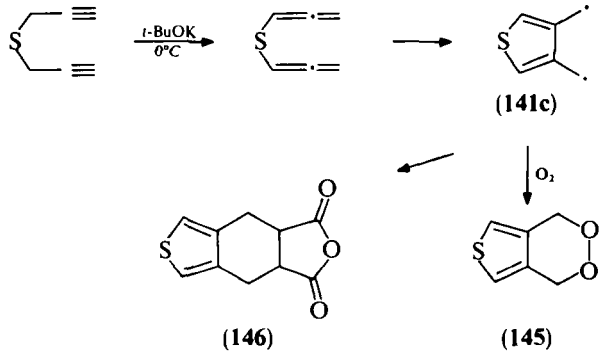
The base-induced general reaction of bispropargyl ethers (**140a**), amines (**140b**) and sulfides (**140c**) to dimers **142** of putative bismethylene heterocycle (**141**) was discovered by Garratt and Neoh[210]. Further studies in the sulfur and oxygen series were provided soon after by Braverman and coworkers[211] and by the Garratt group[212, 213]. When R = H or



a, X = O; **b**, X = NR'; **c**, X = S

Ph, the dimeric products **142** dominated, but in the cases where R = *t*-Bu, the cyclobutaheterocycle **143** was observed. Again, the bismethyleneheterocyclic biradical **141c** was invoked as an intermediate, supposedly being formed from the bis-allene **144c**, which was shown[211] to lead to dimer **142c** under the reaction conditions.

Attempts to trap the thiophene biradical **141c** with dimethyl maleate or fumarate were unsuccessful, but reaction in the presence of O_2 or maleic anhydride (M.A.) gave the peroxide **145** (in unspecified yield) or the adduct **145** (20% yield), respectively[212].

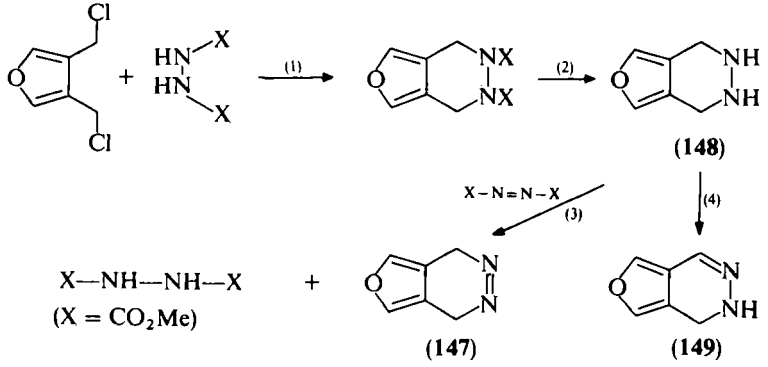


These reactions are plausibly formulated[212,213] as interceptions of the biradical **141c**. Kinetic evidence of a first-order rate-determining step in dimerization[213b] and in cycloadduct formation[213c] has been brought forward. The kinetic analysis[213c] uses known[214-220] criteria to determine that capture of biradical **141c** by olefins is much faster than return to bisallenyl sulfide.

A different approach to 3,4-bismethylenefuran and its thiophene analog **141a** and **141c** has been reported recently[213c,221a] in which the biradicals are generated from bicyclic azo compound precursors. The synthesis of the precursor is illustrated for the furanoid case.

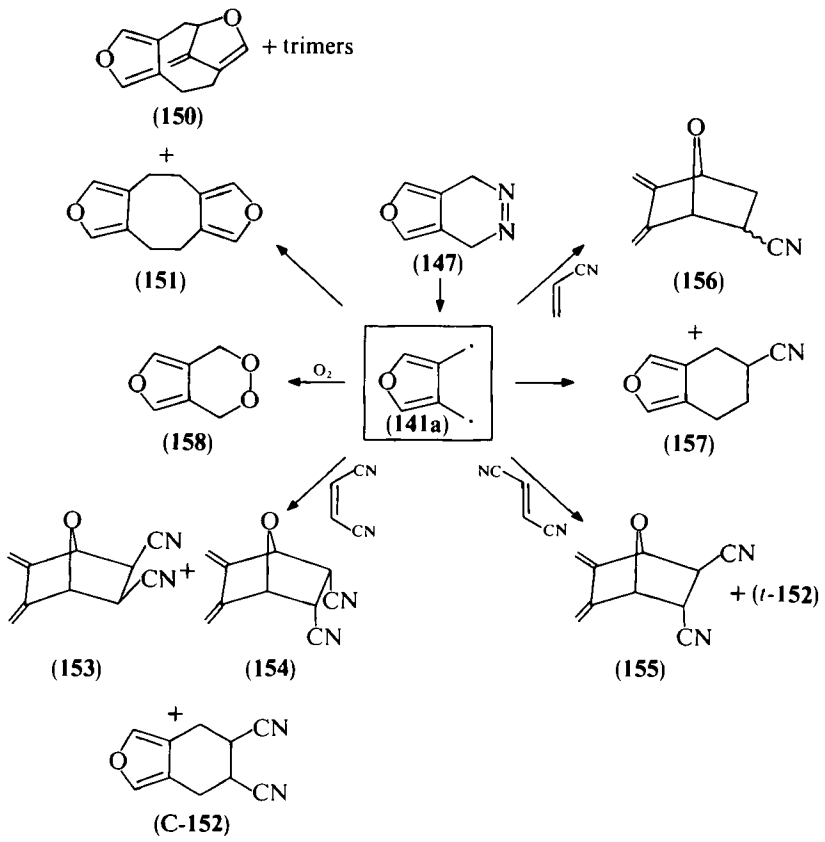
The oxidation of the hydrazine **148** with most reagents gives the hydrazone **149**, but dimethyl azodicarboxylate smoothly affords the desired diazene **147**.

The diazene **147** is stable in solution below 0°C. It decomposes thermally or photochemically in degassed solvent to give two dimers, **150** and **151**, and a group of trimers of unknown structure. Oxygen, however, efficiently suppresses dimer formation and traps the biradical **141a** as the cyclic peroxide **158** in good yield. Thermal



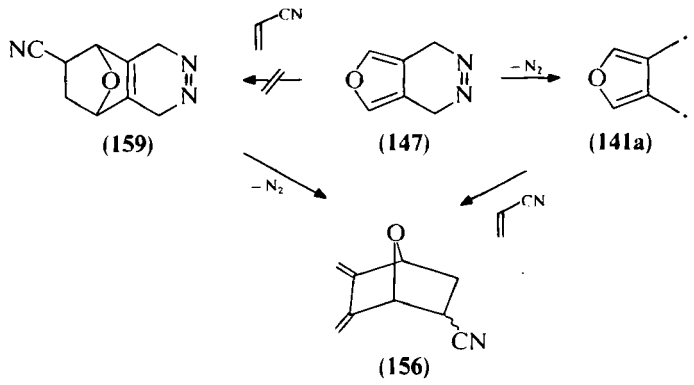
Methods: (1) NaH, DMSO; (2) KOH, H_2O; (3) dimethyl azodicarboxylate, $CDCl_3$, −10°C; (4) other oxidants (HgO, MnO_2, *t*-BuOCl; O_2).

decomposition of **147** in the presence of olefins gives mixtures of fused and bridged products. The cycloadditions are highly stereospecific: maleonitrile gives *cis* adducts *c*-**152**, **153** and **154**, whereas fumaronitrile gives *t*-**152** and **155**.



There is evidence that only one intermediate is interceptable in the olefin cycloaddition reactions. The product composition remains essentially unchanged at 60% *endo*-**156**, 22% *exo*-**156**, and 18% **157** over the range 0.01–15 M concentration of the trapping agent, acrylonitrile. Control kinetic experiments show that the mechanism of the cycloaddition is not an initial Diels–Alder reaction of the furan moiety of **147** followed by deazetation (**147** → **159** → **156**) but instead is a unimolecular decomposition of diazene **147** to a reactive intermediate followed by trapping of the latter (**147** → **141a** → **156**).

The biradical **141a** can be prepared in isolation media by photolysis of samples of diazene **147** in frozen solvents. Visually, these preparations are deep purple, and the optical absorption shows maxima at 338, 348 and 560 nm. The latter band is broad and intense, $E \geqslant 14\,000$. The same species is formed without delay during a 20 picosecond flash photolysis of solutions of **147**. The lifetime of the transient is about 3 microseconds in argon-purged media but is sharply curtained in the presence of O_2. Low temperature photolysis of **147** in a glassy medium of 2-methyltetrahydrofuran gives the intense purple color, but the sample shows no EPR spectrum in the range 12–80 K. In the absence of



obvious reasons why a triplet state of **141a** should not give an EPR spectrum, the interpretation that the ground state of **141a** is a singlet must be entertained as at least a plausible working hypothesis. This would be in accord with the theoretical predictions of Table 7.

Further evidence in favor of a singlet ground state for **141a** is provided by the observation of the cross-polarization magic angle spinning proton-decoupled ^{13}C-NMR spectrum of isotopically enriched material at 77 K[221b]. The resonance of CH_2-labeled **141a** appears as a narrow single absorption near 100 ppm. Even a small amount of triplet in equilibrium with the singlet would have caused the NMR absorption to be so broadened or shifted by the Fermi contact interaction as to have precluded a detectable signal in the normal ^{13}C region. Thawing or photobleaching the purple sample causes both the color and the ^{13}C resonance to disappear.

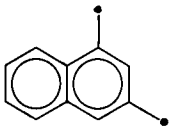
The identity of the 3,4-dimethylenethiophene intermediates from the bis-allenyl sulfide (**144c**) and diazene (**147**, S instead of O) starting materials has been demonstrated by a 'fingerprinting' technique in which olefinic trapping agents are allowed to compete for the biradical. The quantitative values of the relative reactivities of the olefins derived in this way are the same from either precursor[213c].

Biradical **141a** does not readily cyclize to the cyclobutane **139**, since the purple color persists in toluene glass up to 160 K. Moreover, the measured lifetime in fluid medium, as reported above, is 3 microseconds. This corresponds to a maximum value for the unimolecular cyclization rate, since no **139** is observed among the products. The activation barrier for cyclization therefore is at least $\Delta G\ddagger \geqslant 10$ kcal mol^{-1}. Among the factors contributing to the large barrier must be the strain energy of **139** and the necessity of twisting the two exocyclic methylene groups out of conjugation with the furan ring.

G. 1,8-Naphthoquinone Series

Of the ten possible bismethylenenaphthalenes, four (**160–162** and **50**) have aromatic non-Kekulé structures and hence may be considered to be relatives of the *m*-quinonoids. An oxy analog of **160**, *m*-naphthoquinomethane **92**, has been discussed in Section III.D. No derivatives of the types **161** or **162** have been reported, but the hydrocarbon 1,8-naphthoquinodimethane and a number of its tricyclic and heteroatom derivatives are well known, thanks largely to the important contributions from the laboratories of Michl, Pagni, Platz and Wirz. This work has been the subject of careful reviews[78,222], so that a brief examination of most references will suffice for the present purposes.

Pagni and coworkers[223] have studied the thermal isomerization of the dideuteriated hydrocarbon **163** to phenalene-d_2, **164**. The observed distribution of deuterium in the



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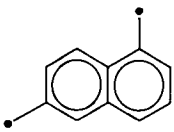

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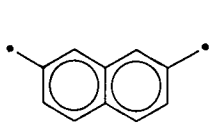

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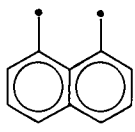
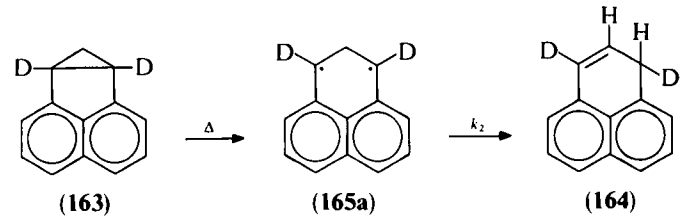
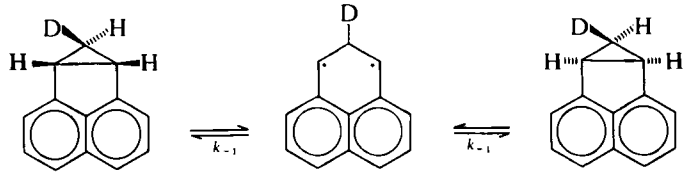


(48)

product is consistent with the intermediacy of the bridged 1,8-naphthoquinodimethane **165a**. In a faster but presumably related process studied by Roth and Enderer[224], the monodeuteriated analog **166** undergoes thermal epimerization. If the intermediate **165a–b** is invoked for the structural and stereochemical isomerizations, the ratio of rate constants for ring-closure vs. hydrogen shift is about 36 in the experimental temperature range

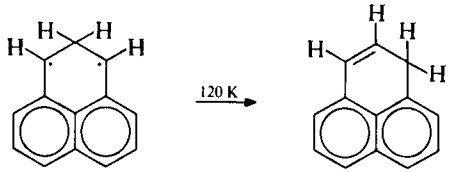


(163) (165a) (164)



(166) (165b)

(140–170°C)[223]. Pagni points out that this is to be contrasted with the behavior of biradical **165** in frozen matrices (at −140 to −154°C), which had been observed by Michl and coworkers[225] to give rearrangement product **164** (H instead of D) exclusively. Although



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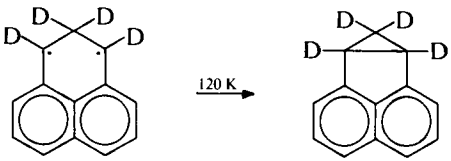


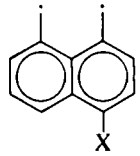
(165-d_4)

the difference in the results may be associated with a matrix effect[223], it is also possible that two different states of biradical **165** are reacting, the singlet at high temperature and the ground state triplet[226, 227] at low temperature. Michl and coworkers[227] recently have found a striking dependence of the products on the position of deuterium substitution:

The primary isotope effect on the hydrogen shift at the experimental temperatures apparently is large enough to retard the rate of formation of phenalene to the point where the ring-closure becomes the dominant reaction.

Michl and coworkers[227] also have partially photoreacted the two biradicals **165** and **165**-d_2 with linearly polarized light at two distinct visible wavelengths characterized by known mutually orthogonal electronic transition moment directions and have produced partially oriented samples. The infrared linear dichroism of these in stretched polyethylene is consistent only with a biradical of C_{2v} symmetry. The IR frequency of the α C–H stretching vibration is that expected for an sp^2 hybridized carbon, whereas that of the β C–H is at a strikingly low frequency, 111 cm^{-1}, shifted from its usual location.

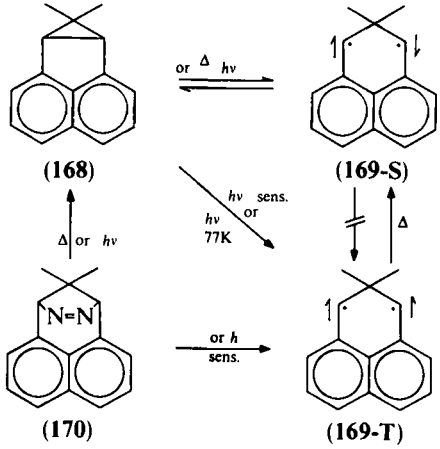
Platz and coworkers[228] have shown by EPR spectroscopy that the members of the series of 4-substituted-1,8-naphthoquinodimethanes **167** all have triplet ground states.



(**167**, X = H, Cl, Br, I, SPh, SO_2Ph)

Wirz has reviewed spectroscopic and kinetic investigations of conjugated biradicals, including 1,8-naphthoquinodimethanes[229], and he has published with Gisin[230] semi-empirical (PPP-SCF-CI) calculations and experimental observations of triplet–triplet optical absorptions.

Further work from the Wirz laboratory concerns the 2,2-dimethyl-1,3-perinaphthadiyl species **169**[231]. The biradicals can be formed by several pathways, as shown. The triplet

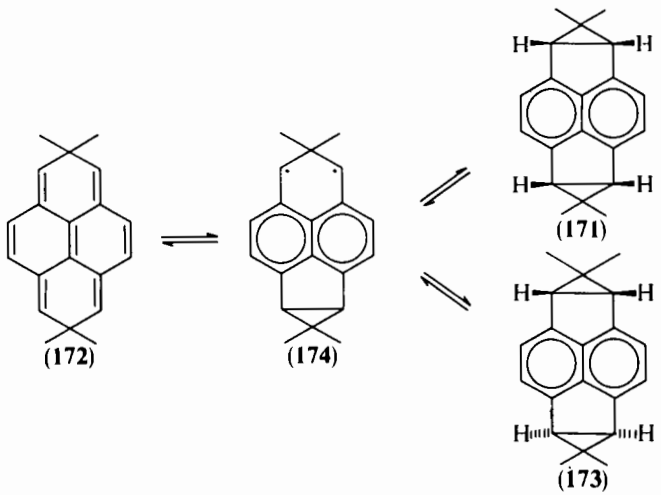


species **169-T** has been prepared by photolysis of the hydrocarbon **168** in EPA glass at 77 K and has been identified by optical and EPR spectroscopy. Curie law measurements suggest a triplet ground state.

The benzophenone triplet–triplet absorption (λ_{max} = 530 nm) is observed by nanosecond flash photolysis and is quenched by either hydrocarbon **168** or diazene **170** to form the spectrum characteristic of **169-T**. The unimolecular decay of **169-T** to the cyclization product can be followed in a viscous solvent, glycerol, in the temperature range −35 to 0°C. The activation parameters are log $A(s^{-1})$ = 8.4 and E_a = 7 kcal mol^{-1}. The low pre-exponential term is ascribed to the spin barrier. The triplet species can be trapped by O_2.

Using the known[224] rate of ring inversion for the parent compound **166** as a model, one may conclude that at 130°C during 40 hours, the dimethyl derivative would have passed through the singlet biradical **169-S** many times. Yet when the hydrocarbon **168** was heated in this way in the presence of 70 atm pressure of O_2, it was recovered unchanged[231]. Combined with the assumption that the exothermic spin-allowed reaction ^{1}(**169-S**) + $^3O_2$ → ^{3}(**169-T**) + $^1O_2$ would occur at a diffusion controlled rate, the absence of oxidation products led the authors[231] to conclude that an upper limit for the lifetime of **169-S** is 10^{-12} s.

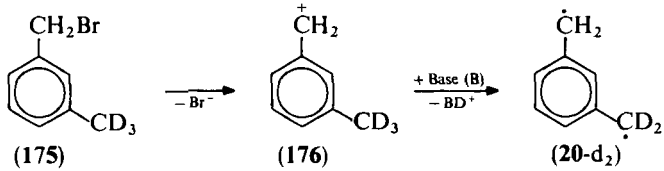
Reasoning that a hypothetical concerted 12-electron process **171** → **172** or **173** → **172** would be orbital symmetry forbidden and hence that a biradical **174** is a likely intermediate, Wirz and coworkers[232] have shown that stereoquilibration of the isomers **171** and **173** is at least two orders of magnitude faster than formation of the polyene **172** despite the fact that the latter is estimated to be 12 kcal mol^{-1} more stable than **171** or **173**. Ring-closure of biradical **174** therefore is much faster than opening of the second cyclopropane ring bond.



H. Conclusions and Prospects

The non-Kekulé structure of the *m*-quinonoids has stimulated the development of new theoretical insights, which in turn have led to the experimental investigation of entirely novel forms of matter. Patterns of reactivity, magnetic properties and spectroscopic characterization can be studied in detail for a number of these systems and provide uniquely penetrating tests of present day theoretical understanding of molecules that exist outside the realm of Kekulé's laws of valence. The future undoubtedly will bring more sophisticated studies of reaction dynamics by fast kinetic techniques and more precise characterization by low temperature spectroscopy, methods which are already in widespread use. Gas phase characterization in molecular beam experiments using the

newly developed techniques of mass-selected resonance enhanced multiphoton ionization spectroscopy combined with supersonic nozzle jet expansion may permit vibrational spectroscopy with unparalleled definition. It also seems likely that pulsed ion cyclotron resonance (ICR) spectroscopy can play an important role in gas phase studies of biradicals. One interesting application is the determination by Hehre and coworkers[233] of the heats of formation of the isomeric quinodimethanes by this technique: *para*, 50 kcal mol^{-1}; *ortho*, 53 kcal mol^{-1}; and *meta*, $\geqslant$ 76 kcal mol^{-1}. The basis of the experiment is outlined in the sequence of gas phase reactions **175** → **176** → **20**-d_2. The key value is the measurement of the proton affinity of the biradical (e.g. **20**) by ICR.



(175) **(176)** **(20-d_2)**

Beyond all this, the invention of new *m*-quinonoid and related non-Kekulé molecules and their application to synthesis is limited only by the imagination of the organic chemist.

IV. ACKNOWLEDGEMENTS

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CHAPTER 11

Quinones as synthones

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I. INTRODUCTION

In 1971 I cited 686 references to describe what had been accomplished in quinone addition and substitution chemistry in the 124 years since Wöhler's effort in that area. The best I have been able to do for the past 15 years is 796; boiled down from over 1100 obvious candidates!

New and exciting reactants and reactions have sprung up alongside familiar schemes. Young investigators are proving to be worthy successors of Smith and Fieser. Research groups which contributed to mid-twentieth century quinone chemistry have continued and expanded their interests. In general this field has grown in more fundamental ways than simply numbers.

The quinone chemistry treated here has played various roles, since both theoretical and applied contributions are abundant and significant. While the majority of the studies conducted involve quinones as intermediate goals, many make direct and important contributions to our understanding of these colorful compounds. In several instances the centrality of the quinonoid nucleus has demanded careful studies of its involvement. Sadly, there remains a notable deficiency of detailed mechanistic studies.

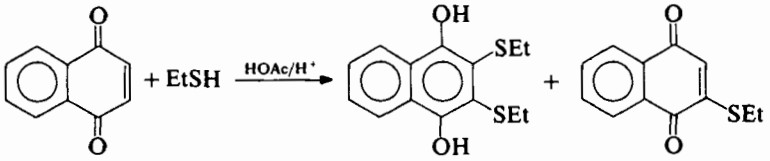
II. HETEROATOM ADDITION REACTIONS OF QUINONES

A. Sulfur Addition

1. Sulfides from thiols

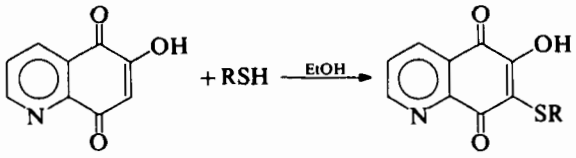
The nucleophilic addition of thiols to quinones continues to be of interest to chemists seeking more active drugs and searching for mechanistic detail in complex biochemical systems. There has also been a lively interest in the theoretical explanation of experimental observations. Perhaps the most detailed work in this area is happily understandable to the organic chemist[1]. Houk and his collaborators have applied their molecular orbital approach primarily to cycloaddition chemistry (see Section V.A.1) but they have provided a valuable overview of our severely limited quantitative data for nucleophilic additions. The past decade has also produced an expanded effort in the synthesis of sulfur heterocycles where quinone–sulfur interactions have proven to be of considerable utility.

The thioketal reported by Récsei[2] has been reinvestigated and shown to actually be a mixture of normal addition products (equation 1)[3].



(1)

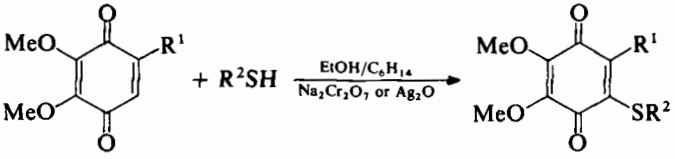
In a continuation of their search for antimetabolites of coenzyme Q, Folkers and coworkers prepared 7-alkylmercapto-6-hydroxy-5,8-quinolinequinones containing long-chain alkyl substituents (equation 2)[4]. The poor yields obtained (14–19%) contrast sharply



(2)

$R = n\text{-}C_{12}\text{–}C_{18}$

with their later work on analogous 2,3-dimethoxy-1,4-benzoquinone derivatives (equation 3)[5,6]. These studies demonstrate that optimum conditions for addition require collecting

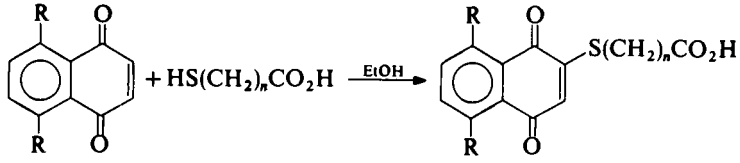


(3)

R^1 = H, Me; $R^2 = n\text{-}C_{12}\text{–}C_{18}$

the crude hydroquinone, reoxidizing and adding more thiol. Yields of 70–75% were obtained after three such cycles. With soluble products chromatography on silica gel provided acceptable yields.

The addition of ω-mercaptoalkanoic acids to 1,4-naphthoquinones gives fair yields (36–67%) of the corresponding 2-substituted products (equation 4)[7]. No evidence is

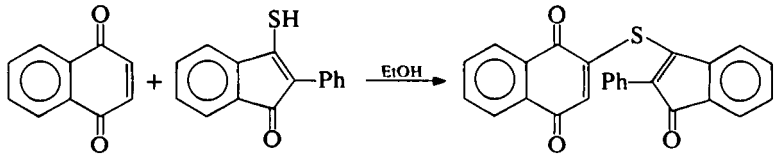


(4)

R = H, Me, OH, Cl n = 1–3

presented for products derived from 8-chlorojuglone. Alkyl and alkenyl sulfides were prepared but in poor yield.

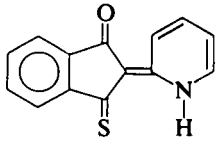
Unlike the carbon–carbon bond formation normally observed with 2-phenylindane-1,3-dione, its monothio analog (**1**) shows addition of the thioenol to quinones (equation 5)[8]. The product structure was assigned on the basis of an interesting nitrogen substitution



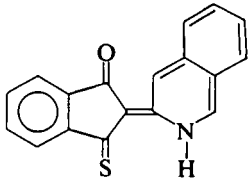
(5)

(**1**)

reaction. Buggle and Power have studied the apparently analogous compounds **2** and **3** and report that reaction occurs at carbon to form a bridgehead nitrogen heterocycle rather than at sulfur (see Section VII)[9].

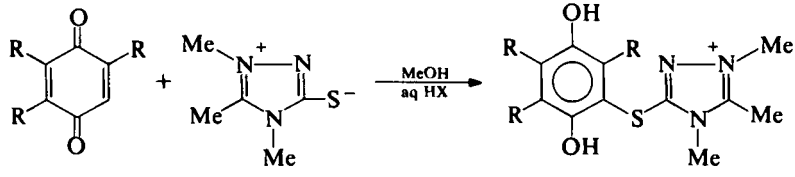


(**2**)



(**3**)

The addition of strongly acidic heterocycles like 1,4,5-trimethyl-1,2,4-triazolium-3-thiolate (**4**) to various quinones proceeds smoothly in aqueous acid (equation 6)[10]. Yields



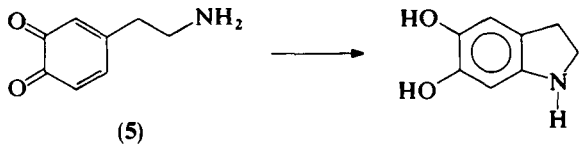
(6)

(**4**)

R = H, Me, Diels–Alder adducts X = TsO, CF_3CO_2, BF_4

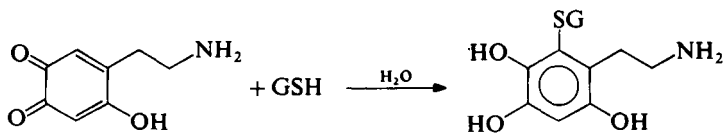
appear to depend rather strongly on the acid employed and divide into two distinct groups; 40–50% and 75–80%. This observation and some interesting structural effects should be followed up. The hydroquinone–sulfide products can be oxidized to the corresponding quinone in variable yields. The few unsymmetrically substituted quinones studied appear to react in a stereospecific fashion; for example, *o*-quinones give only the 4-substituted product, and 2-methoxy-1,4-benzoquinone gives a 78% yield of the 2,5-product.

The subject of possible addition reactions of protein thiol groups to nascent 1,2-benzoquinones has received a great deal of attention. Studies aimed at understanding the role of catecholamines in developing biochemical theories of mental illness have provided one of the major forces behind this work. Adams and his students have searched actively for information concerning the reactions which might be expected if 1,2-quinones are formed in brain tissue. They have measured the rates at which the model compounds 4-methyl- and 4-(2-aminoethyl)-1,2-benzoquinone (dopamine) react with external nucleophiles. Thiol groups like those present in cysteine and glutathione react three to four orders of magnitude faster than various amino acids lacking such a sulfur function. These addition reactions are also three orders of magnitude faster than the intramolecular cyclization of dopamine-1,2-benzoquinone (**5**, equation 7)[11].



(5) (7)

Evidence for such reactions with the quinone resulting from the oxidation of 6-hydroxydopamine was presented by Adams' group in 1975[12]. Later they reported the isolation and characterization of the sulfide product of this quinone with glutathione

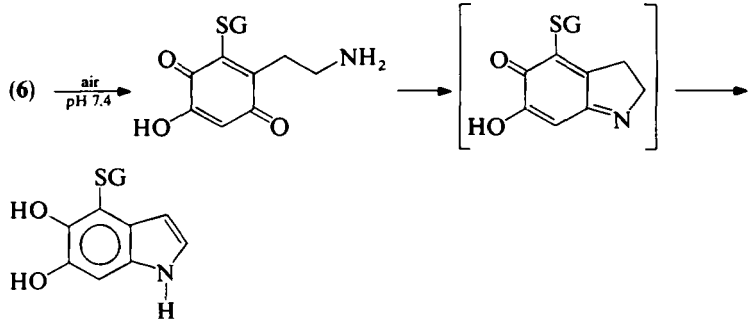


(8)

(**6**) ca. 70%

G = $HO_2CCH_2NHC(=O)CH_2NH(C=O)(CH_2)_2CH(NH_2)CO_2H$

(equation 8)[13]. It was also shown that further oxidation and cyclization can take place (equation 9). The same indole is formed when 6-hydroxydopamine is injected in rat brains.



(9)

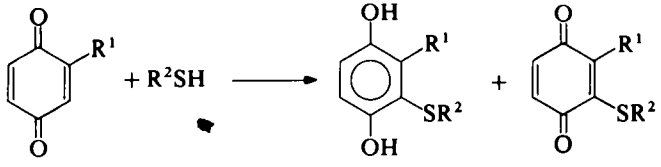
In a closely related study Vithayathil and Gupta report spectral evidence for the structure and chemistry of *o*-quinone–thiol adducts[14]. Unfortunately, much of the useful information is only found in Gupta's thesis from which this brief note is taken.

The addition chemistry of 3,5-di-*t*-butyl-1,2-benzoquinone and thiols has been suggested as a sensitive detection method in thin-layer chromatography[15]. Colored chelates are formed by spraying the catechols with iron(III) chloride solution. This procedure allows cysteine and reduced glutathione to be detected and differentiated at the 2 nanomole level and in the presence of a variety of other thiols.

Two sulfur-quinone studies deserve to be made more accessible. First, a polarographic investigation of the reactions of vitamin K with thiols confirmed the naphthohydroquinone intermediate in the absence of oxygen[16]. Admission of air changed the product to the quinone sulfide. Spectrophotometric and electrochemical measurements were used to confirm the mechanism with several different thiols. The reaction of cysteine gave more complicated polarograms suggesting that subsequent cyclization must be considered. These results contrast sharply with earlier reports on this system[17].

Second, some evidence concerning the relative reactivity of cyclic sulfides with quinones has been obtained[18]: 2-propyl or 2-methylthiophene > thiophene and 3-hexyl > 2-methyl > 2-methyl-4-pentyl > 4-pentylthiacyclohexane > thiacyclohexane. For the quinones studied the order was: *p*-benzoquinone > 2-(*N*-methylanilino)-*p*-benzoquinone > 5,8-quinolinedione.

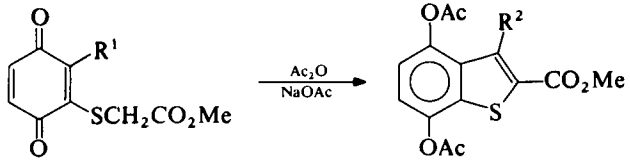
In their study of the addition of thiols to 1,4-benzoquinones bearing a strong electron-withdrawing group Fariña and Valderrama obtained excellent yields showing a high degree of stereospecificity (equation 10)[19]. Two examples were found in which the oxidized



(10)

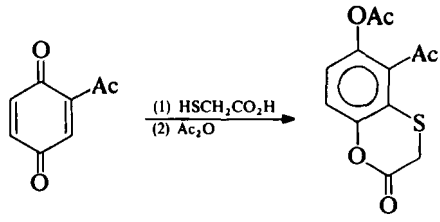
R^1 = OAc	R^2 =	%	%
	Et	81	100
	Bu	67	
	$PhCH_2$	74	
	MeO_2CCH_2	98	

product could be cyclized (equation 11). When thioglycolic acid was added to 2-acetyl-1,4-benzoquinone, cyclization occurred (equation 12) involving the quinonoid carbonyl in a fashion consistent with that observed by Snell and Weissberger[20].



(11)

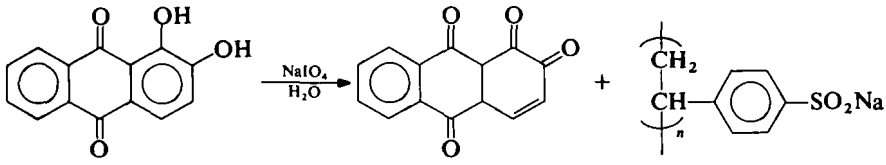
R^1 = Ac, CO_2Me R^2 = Me (92%), OMe (97%)



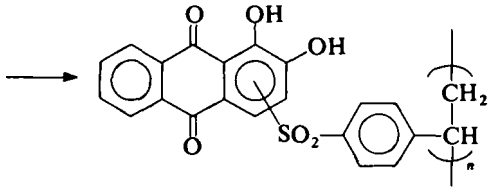
(12)

2. *Sulfones from sulfinic acids*

The extensive application of sulfinic acids and quinones in polymerization reactions makes their interactions important in detailed kinetic studies of such systems[21]. In other cases the sulfinic acid has proven to be an interesting reactant as a constituent of the polymer itself[22]. Included in this study is an example of the nascent quinone from alizarin (7; equation 13).



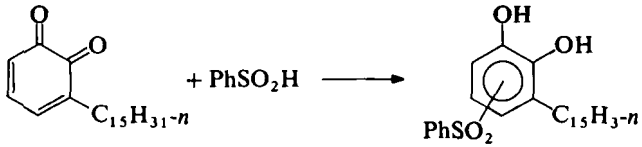
(7)



(13)

95 mole %

In their studies of the interactions of 3-pentadecylcatechol with proteins Castagnoli and coworkers found that benzenesulfinic acid is an inhibitor (equation 14)[23]. They obtained a



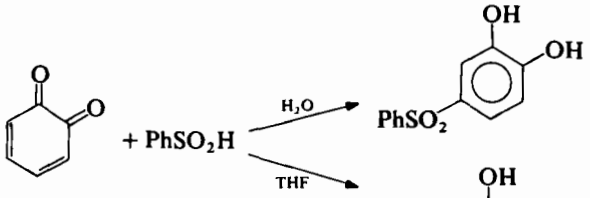
(14)

86%

single sulfone product from reaction with the corresponding quinone, but did not establish its structure.

The analytical application of benzenesulfinic acid as a trapping reagent for *o*-benzoquinones generated, or at least suspected, in enzymatic reactions has produced some

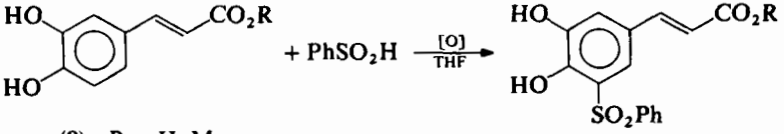
conflicting observations. These problem areas have been reviewed by Davies and Pierpoint[24]. Their results illustrate the great importance of solvent and suggest that the enzyme itself may influence the structural outcome. For example, with even the simplest structures a complete change of product can be observed (equations 15,16). Unfortunately,



(15)

(16)

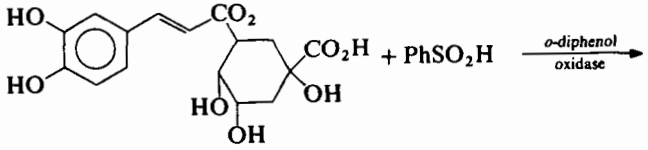
no yields are given. The more complicated caffeic acid (**8**) and its ester show the same regiospecificity in tetrahydrofuran (equation 17). Pierpoint has previously shown that the



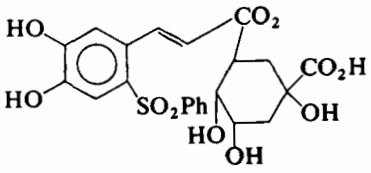
(17)

(**8**) R = H, Me

enzymatic oxidation of chlorogenic acid (**9**) leads to sulfinic acid addition in a different position (equation 18)[25]. The product structure (**10**) was demonstrated by Janes[26].



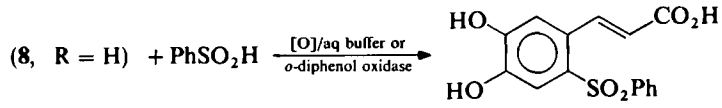
(**9**)



(18)

(**10**)

The oxidation of caffeic acid in the presence of benzenesulfinic acid in an aqueous buffer or with an enzyme produces **11**, the same sulfone as obtained from the hydrolysis of the chlorogenic acid product (**11**, equation 19).



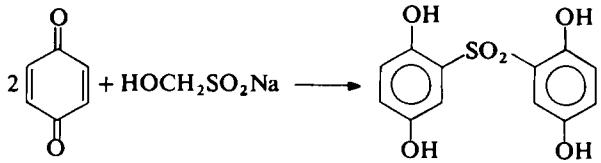
(19)

(11)

In related oxidation experiments with a different enzyme Stom and his colleagues obtained products which appear to differ from those just described, but their structures were not assigned[27, 28].

Benzenesulfinic acid itself is a suitable reagent for the photometric determination of quinones[29]. When coupled with an extraction procedure aqueous solutions can be measured satisfactorily in the 1–5 $\mu g\,ml^{-1}$ range.

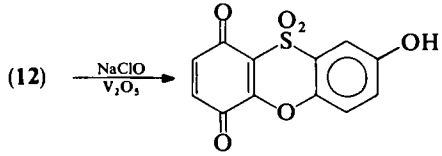
Finally, three unusual synthetic reports have been made. A method for the preparation of symmetrical sulfones involves the addition of hydroxymethanesulfinate to two molar equivalents of quinones (equation 20)[30]. The reaction also takes place with naphtho- and



(20)

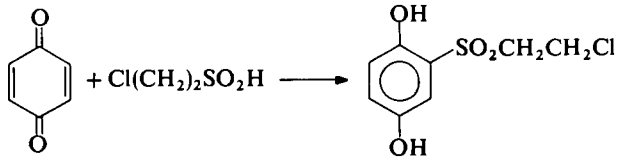
(12)

1,2-quinones. While the yields are modest (45–66 %) they provide entry to a useful series of heterocyclic compounds by oxidation of the initial adduct (equation 21).



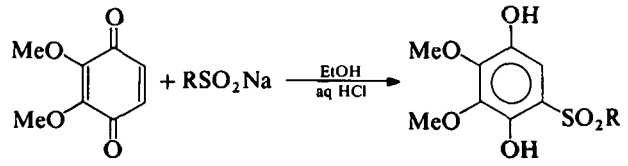
(21)

The addition of 2-chloroethanesulfinic acid to quinones provides a potential entry to vinyl quinones and redox polymers (equation 22)[31].



(22)

In the course of their studies reported above Folkers and his collaborators found high yields of sulfones from the addition of the rarely encountered alkyl sulfinic acids to quinones (equation 23)[6].



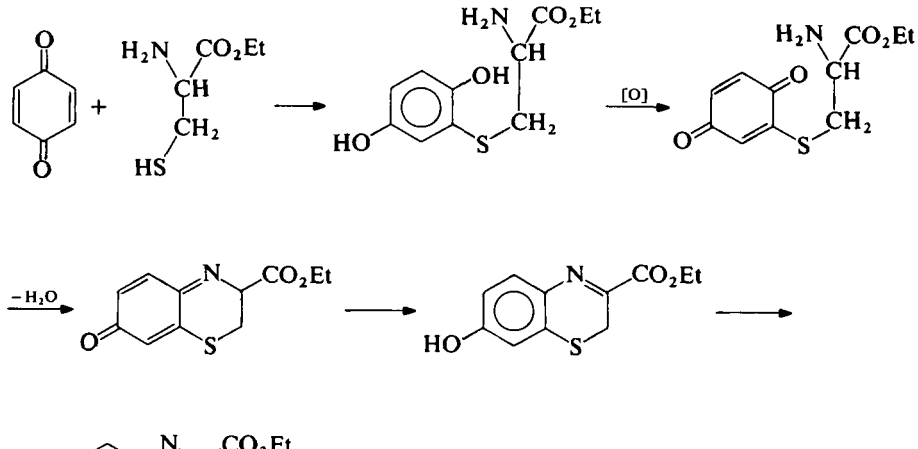
(23)

R = n-$C_{12}H_{25}$, n-$C_{18}H_{37}$ 90%, 78%

3. *Cyclization reactions*

An area of sulfur addition to quinones that has continued to show rapid growth during the past 15 years is that involving bidentate molecules and their subsequent cyclization. This vitality is entirely consistent with the great upsurge of interest in heterocyclic systems shown by organic chemists during this period.

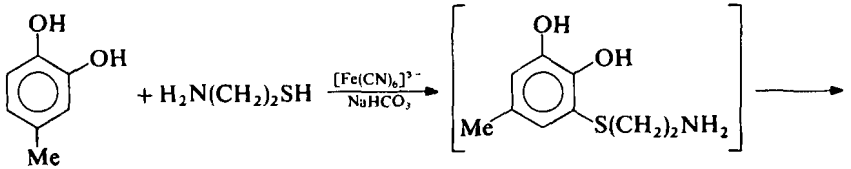
Interest in L-cysteine has continued with a reinvestigation of Kuhn's earlier studies[32, 33]. Prota and Ponsiglione found the product previously reported but the complexity of the reaction mixture caused them to discontinue that phase of their work[34]. With L-cysteine ethyl ester two substances, probably diastereoisomers, are formed. Elemental analysis and NMR spectra of the more soluble isomer are in agreement with a bi-benzothiazine structure (**13**) and consistent with the chemistry reported for the *o*-quinone series (equation 24).

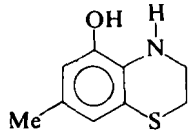


(24)

(13)

The same research group has demonstrated a useful synthetic application of a simpler model system (equation 25)[35]. Evidence for the predicted intermediate was obtained by carrying out the reaction under acidic conditions and treatment with acetic anhydride. The triacetate product after hydrolysis with dilute acid formed the dihydrobenzothiazine **14** in

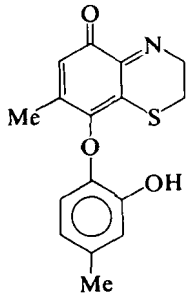




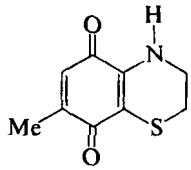
(14) 50%

(25)

78% yield. If the initial reaction is carried out with an excess of potassium ferricyanide present, two significant colored products (**15** and **16**) are formed. Their yields can be



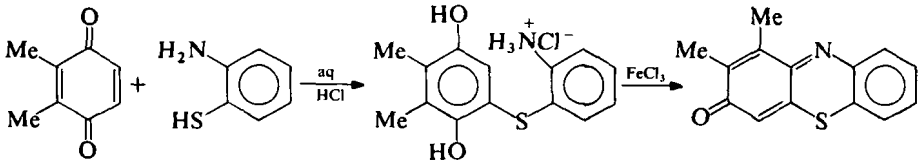
(15)



(16)

greatly increased (24 and 33% respectively) by oxidizing the initial product (**14**) in the presence of 4-methylcatechol.

Phenothiazones because of their utility in a wide variety of medical applications have stimulated extensive study of their synthesis. In general it has proven difficult to prepare these compounds by conventional methods, and recently Ueno and coworkers have investigated photochemical routes employing 1,2-dimethyl-3*H*-phenothiazin-3-one (**17**) as a substrate (equation 26)[36]. This chemistry was used as an alternative route to

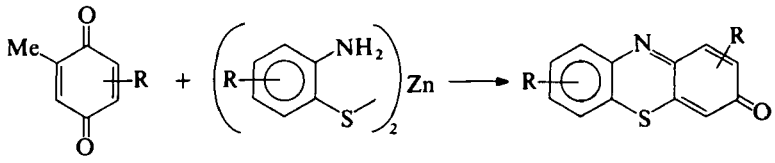


(17) 50%

(26)

substantiate their structural assignment of analogous photochemical products. Ueno has also reported similar chemistry with di- and trimethyl-1,4-benzoquinones[37].

One of the most widely used reagents for the direct preparation of the phenothiazones is the zinc salt of 2-aminobenzenethiols. Most often these reagents are used in substitution reactions (see Section VIII.A.3), but one example of addition chemistry exists. Terdic and Smarandache prepared a series of seven dimethyl-3*H*-phenothiazin-3-ones in generally low yields (equation 27)[38].

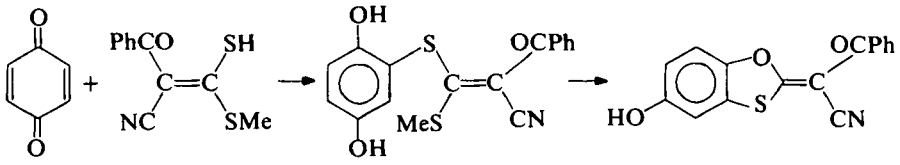


(27)

R = H, Me

Me_2	%	Me_2	%
1,2	52	2,4	17
1,4	15	2,6	3.8
1,6	1.3	2,8	19
1,8	13		

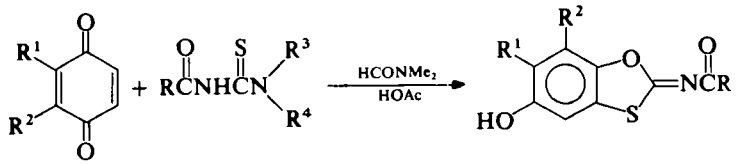
An interesting sulfur heterocyclic synthesis involves the initial addition of sulfur followed by an unusual oxygen displacement (equation 28)[39]. Unlike an earlier report of



82% 76% (28)

this reaction[40], involving the dithio enolate salt, the monothio ether prevents the formation of the dithio ring system. With 1,4-naphthoquinone the yield is 45% and the intermediate is not isolated.

The pioneering work on the addition of thioureas to quinones by Lau and his collaborators[41,42] has stimulated several studies which demonstrate important modifications, e.g., the addition of a wide variety of acylthioureas (equation 29)[43].

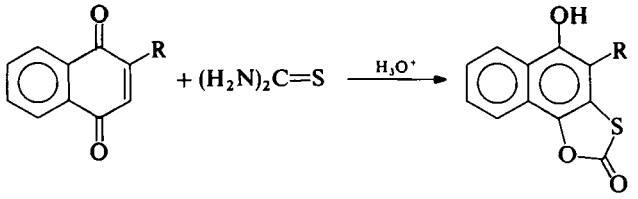


(29)

R^1, R^2 = H, carbocyclic
R = alkyl, aryl, heteroaryl, alkoxycarbonyl
R^3, R^4 = H, alkyl, aryl, N-ring

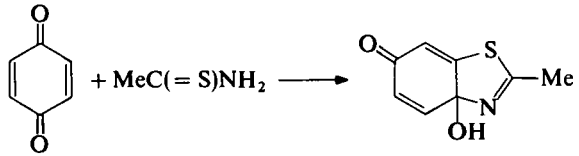
R = Ph, R^1 = R^2 = H 74%

Mann and his colleagues have expanded the earlier work to a series of monosubstituted 1,4-naphthoquinones (equation 30)[44]. The yields vary from modest to good (31–90%) over the range of electron-donating alkyl, alkoxy, and alkylthio substituents studied.



(30)

Horak and Manning have reported the addition of thioamides to 1,4-quinones and studied the simplest case of thioacetamide and 1,4-benzoquinone in greater detail (equation 31)[45]. The use of 2-methyl-1,4-benzoquinone produces an approximately

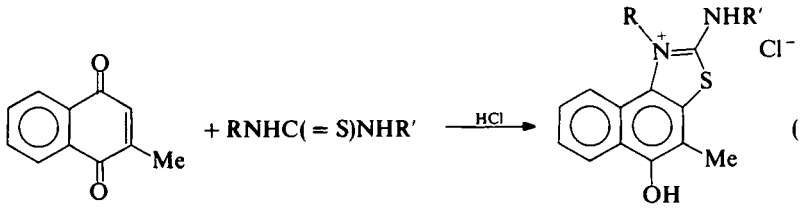


(31)

23% (35% by GC)

equimolar mixture of 2,4- and 2,5-dimethyl products (overall yield 26%). With thiobenzamide the 2-phenyl derivative is obtained in 51% yield. Possible explanations of the presence of several by-products is given. Significantly, more complicated quinones lead only to sulfur oxidation.

The use of *N*,*N*′-disubstituted thioureas with 2-methyl-1,4-naphthoquinone under the conditions developed by Lau gave fair yields of 1,N^2-disubstituted 2-amino-5-hydroxy-4-methylnaphtho[1,2-*d*]thiazolium salts (**18**, equation 32)[46]. Cyclic thioureas lead to the



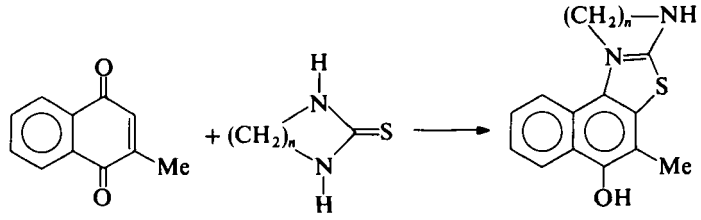
(32)

R = alkyl, allyl, aryl

(**18**)

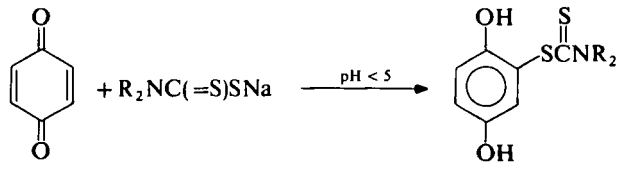
formation of tetracyclic naphthothiazolium compounds (equation 33). Interestingly, 1,4-naphthoquinone failed to give any identifiable product. The proposed mechanism which allows for a Michael attack on the quinonoid ring is consistent with this observation.

It is possible to add dithiocarbamic acids to 1,4-benzoquinone in good yield with rapid mixing of the aqueous/dimethylformamide and acetic acid solutions (equation 34)[47]. The initial addition products (**19**) can be converted to heterocyclic systems which vary depending on the solvent employed (equations 35, 36). The few examples given produced



(33)

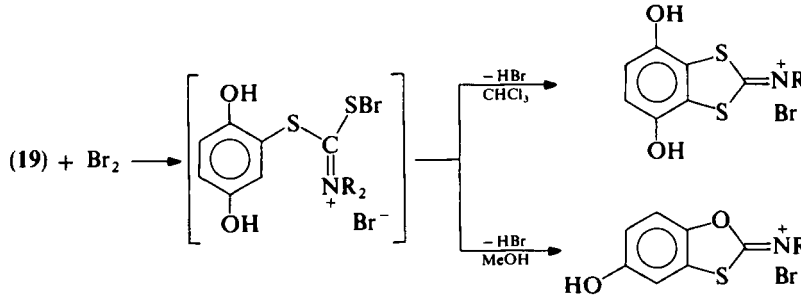
$n = 2, 3$ 56%, 27%



(34)

(19)

R = H, Me, Et, *i*-Pr, Bu, NH_2, cyclic 60–90%

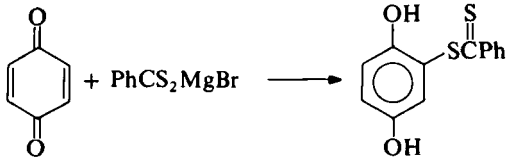


(35)

(36)

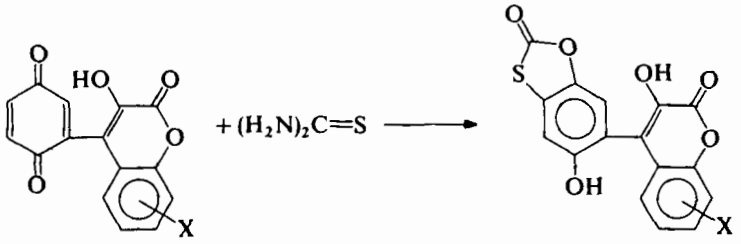
yields of 50–80%, but the structural influence varies in the two reactions. Finally, thiobenzoic acid adds to 1,4-benzoquinone in 95% yield under these conditions.

More recently the addition of a dithiobenzoic acid salt has been reported (equation 37)[48].



(37)

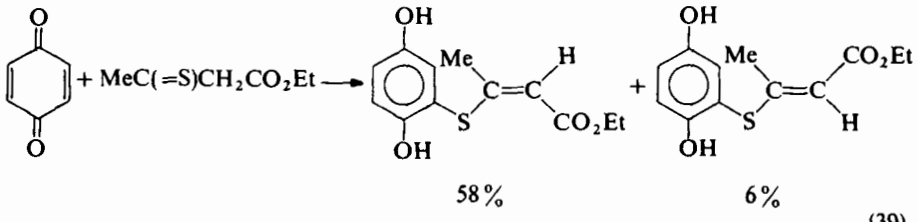
The condensation products from the reaction of 3-hydroxycoumarins and 1,4-benzoquinone (see Section VI) undergo thiourea addition reactions in approximately 75% yield (equation 38)[49].



(38)

X = H, 6-Cl and 6,8-Cl_2

In the addition of ethyl thioacetoacetate to 1,4-benzoquinone Campaigne and Abe found it possible to isolate and characterize all four combinations of geometric isomers and oxidation states (equation 39)[50]. The quinonoid form of each isomer was obtained as

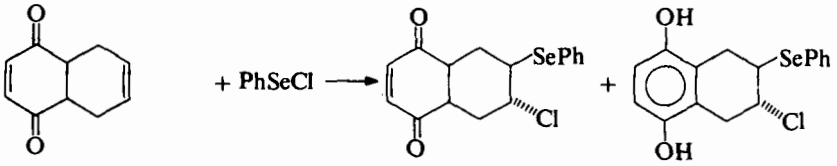


(39)

were the corresponding products of 1,4-naphthoquinone. In the latter case two separate addition experiments were carried out: one in refluxing alcohol and one completely below 40°C, including workup.

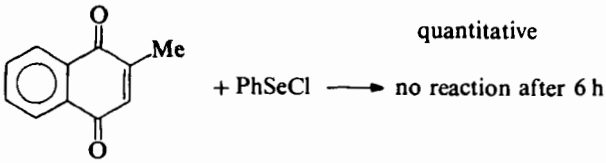
Two brief reports related to sulfur addition chemistry deserve mention. First, the formation of a polymeric quinonoid electrode from thiophenol and 1,4-benzoquinone offers strong evidence for the essential correctness of successive oxidation and addition as the preferred mechanistic pathway[51].

Second, adding phenylselenenyl chloride to alkenes produced excellent results except with the α,β-unsaturated carbonyl group where it failed completely (equations 40, 41)[52].



(40)

quantitative

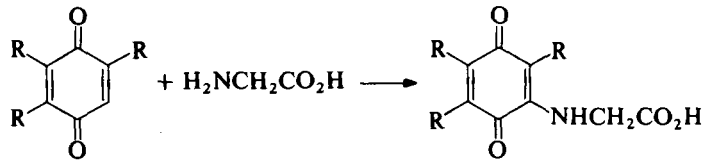


(41)

B. Nitrogen Addition

1. Kinetics and mechanisms

In contrast to the paucity of data for sulfur reactions kinetic studies of the addition of nitrogen nucleophiles to quinones continue to appear at a modest pace. Amonkar and Ghosh presented a brief, but systematic rate study of the addition of glycine to several 1,4-benzoquinones (equation 42)[53]. The reaction is first order in each reactant. The product(s)



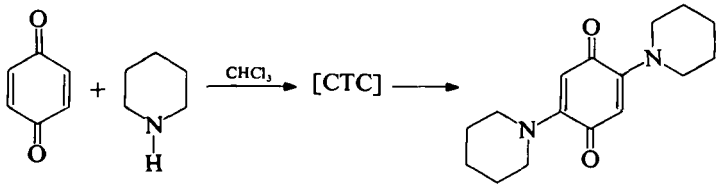
(42)

R = H, Me

were not reported, and it is difficult to see how the same rate law can be followed by both 1,4-benzoquinone and its trimethyl derivative. Earlier[54] studies on less highly substituted quinones show disubstitution and a second-order dependence on primary amines. Possibly the rate of formation of some common intermediate was being followed in what is clearly a rather complex system. The order of reactivity observed for the quinones is certainly not consistent with a simple nucleophilic addition reaction. The proposal that the reaction involves semiquinones is made and potentiometric studies are promised.

Much more recently Talati and his coworkers have published a study of the oxidation behavior of products obtained from the addition of aniline to 1,4-benzoquinone[55]. They claim high yields (80–85%) of a disubstituted product (surely the 2,5-dianilino). This product oxidizes readily and its oxidation capacity, after reduction with hydrogen iodide or sodium dithionite solution, increases by 60%. Thus, there is a substantial amount of hydroquinone product formed in the second aniline addition. Diamines form redox polymers; some with and some without cross-linking. Evidence for tautomeric quinone–anils is presented for the later examples.

Much of the kinetic and mechanistic study of quinone–amine reactions has centered on the formation of a charge transfer complex and its contribution to the addition reaction sequence. Muralikrishna and Krishnamurthy have made a careful investigation of the kinetics shown by the reaction of 1,4-benzoquinone and piperidine in chloroform (equation 43)[56]. The rate of appearance of the charge transfer complex, which is



(43)

excess

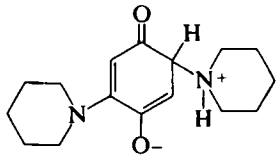
reasonably stable, and the rate of formation of product were both measured. The latter is several times greater than the rate of decomposition of the complex. On this basis another intermediate is postulated and the complete mechanism written as:

$$\text{quinone} + \text{piperidine} \overset{\text{fast}}{\rightleftharpoons} \text{charge transfer complex}$$

$$\text{charge transfer complex} + \text{piperidine} \overset{\text{fast}}{\longrightarrow} \text{intermediate}$$

$$\text{intermediate} \overset{\text{slow}}{\longrightarrow} \text{product}$$

These workers do not suggest a structure for the new intermediate, but on the basis of our general understanding of these reactions **20** seems reasonable. It should be noted that in



(20)

some instances there has been controversy concerning the evidence for charge transfer complex formation in the addition of anilines to quinones[57, 58].

Sasaki and his collaborators have used high-pressure kinetic methods to investigate the reaction between 1,4-benzoquinone and dibutylamine[59, 60]. In addition to chloroform they studied 1,2-dichloroethane and acetonitrile. There are differences among the solvents as reflected by all the activation parameters, but no detailed explanation could be offered on the basis of the present studies. Lowered activation energy coupled with increasing solvent dielectric constant suggests an electrostatic solvent–transition state interaction. The mystery lies in the failure of the activation volume to show a similar dependence.

Observations of greater interest in these studies concern the reaction's pressure dependence. Over several hours at one bar the rate is third order requiring two moles of amine for each quinone and only a monosubstituted product is obtained. With increased pressure a disubstitution product appears and it shows greater pressure sensitivity. The reaction sequence suggested involves a radical ion pair or a zwitterionic σ complex formed rapidly and reversibly. The following and rate-determining step is the abstraction of a proton by a second amine molecule.

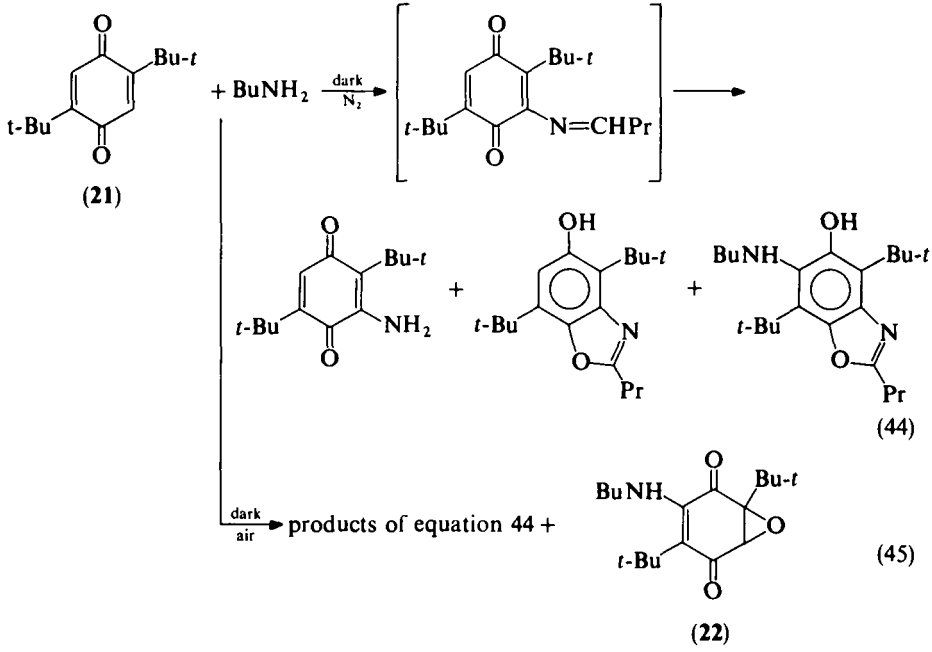
A relevant observation was made by examining the proton and ^{13}C spectra of 1,4-benzoquinone and various chlorinated derivatives in liquid ammonia[61]. Excellent evidence was obtained for reversible mono- and dicarbonyl addition of ammonia. The 1,4-benzoquinone adducts are stable for about 12 hours after which irreversible reaction occurs. The chlorinated quinones react more rapidly. While the chemistry in such a large excess of ammonia is undoubtedly different in some fashion, it may be worthwhile to investigate such intermediates with amines as the nucleophile.

Pelizzetti and his collaborators in conjunction with studies of the oxidation of catecholamines (see Section II.A.1) have presented data relevant to the intramolecular cyclization reaction (equation 7)[62]. Their evidence demonstrates the complexity of the system at higher pH and provides support for earlier structure–reactivity correlations.

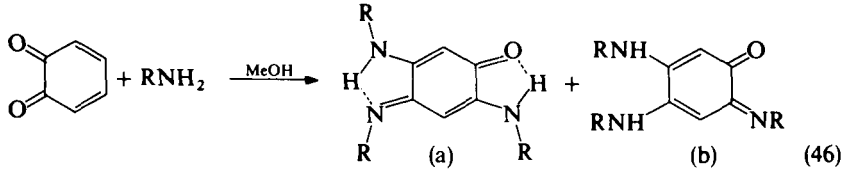
$$\text{adrenalin} \gg \text{L-dopa} > \text{dopamine}$$

Some product studies without kinetic data have advanced our knowledge of nitrogen addition to quinonoid systems. Baxter and Phillips have extended their earlier preliminary

work concerning 2,5-di-*t*-butyl-1,4-benzoquinone (**21**)[63] to include *n*-butylamine and *t*-butylamine[64]. In experiments with the former they found product yields identical to those of propylamine. Predictably, no dark reaction occurred with *t*-butylamine. No comment was made about the *n*-butylamine reaction intermediate and there is every reason to expect that the quinol analogous to that reported previously is involved. When this amine reacts with **21** in the dark and with air present, an epoxide (**22**) similar to that reported earlier is obtained (equations 44, 45).



It is often useful to examine 'simple' systems as models for molecules of greater complexity and interest, for example, the cyclization of nascent *o*-quinonoid compounds related to dopamine (see Section II.A.2). Davies and Frahn reported that the four simplest primary amines react with 1,2-benzoquinone by such complex pathways that thin-layer chromatography shows the presence of at least 50 products plus polymers in each case[65]. Still, it is instructive to examine the structure of the two products which could be isolated and purified (equation 46). The authors realize that these structures are tautomers and are surprised that the proton transfers are slow enough to allow their isolation. The chemical behavior of each isomeric pair as well as extensive spectral evidence strongly supports the proposed structures. A test of the suggestion that peptide bonds might react with oxidized polyphenols[66] was carried out, but no evidence could be found to support a reaction between 1,2-benzoquinone and *N*-methylacetamide.

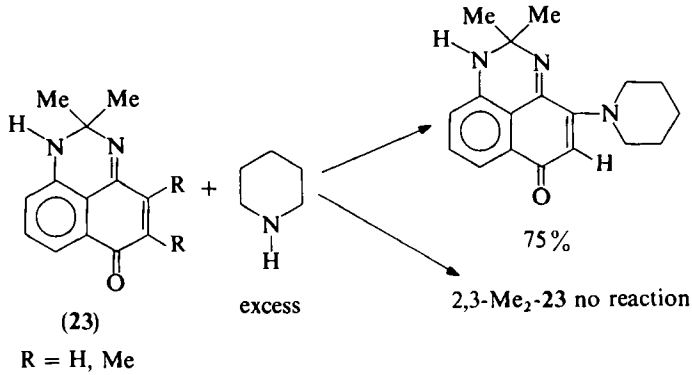


R	%a	%b
Me	8	11
Et	7	10
Pr	—	10
Bu	—	10

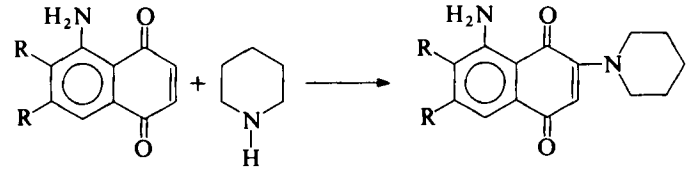
2. *Synthetic studies*

It is rather hard to distinguish a clear borderline between studies directed primarily toward mechanistic goals and those of a more preparatory nature. In fact the bulk of the research described as synthetic in this chapter is significant for its contribution to our understanding of chemical principles.

In a continuation of their studies of dihydroperimidione (**23**) Cameron and Samuel found that methylated 5-amino-1,4-naphthoquinones react with piperidine in a manner much like the heterocyclic quinone anil (equations 47, 48)[67]. For compound **23** lower rates

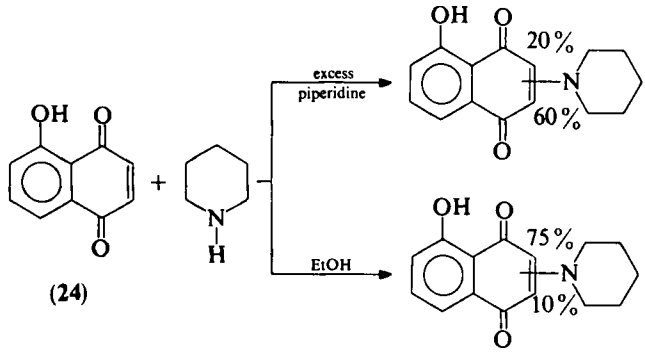


(47)



(48)

are observed and there is no evidence for side-chain amination in the 2,3-dimethyl derivative. These models were also compared with the important 5-hydroxy-1,4-naphthoquinone (juglone **24**) where a mixture in which the 2-piperidino addition product predominated was obtained (equation 49). If the solvent is changed from excess piperidine to ethanol, the isomeric distribution is just reversed (equation 50). The explanation offered for the change in reaction position in substrates **23** and **24** referred to the combination of greater electron-donating capacity of the amino group with its poorer intramolecular hydrogen bonding ability. The solvent effect with juglone was not investigated beyond

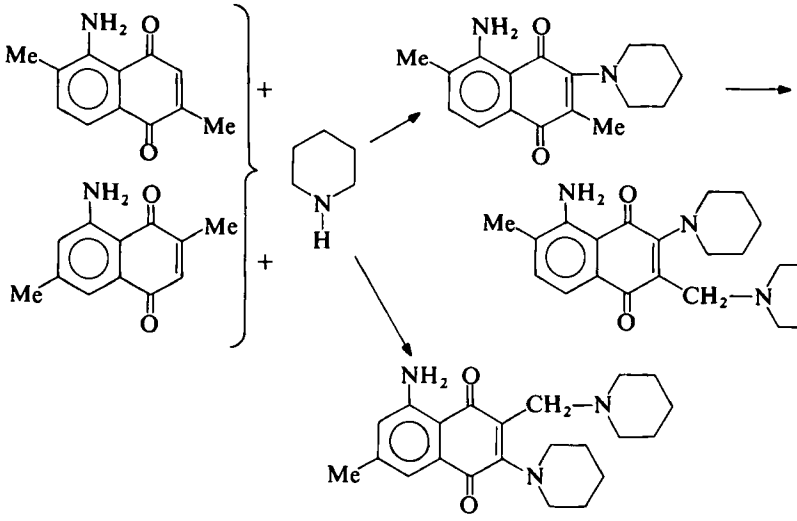


(49)

(50)

finding that it is not observed in the amino compounds. Surely this striking effect deserves attention other than merely stating that it might result from some combination of intramolecular hydrogen bonding, group polarity or ionization of the hydroxy group.

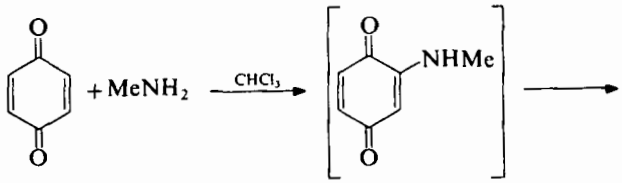
When 2,6- or 3,7-dimethyl-5-amino-1,4-naphthoquinone react with neat piperidine there is a strong preference for 3-substitution (equations 51, 52). There is no evidence of simple 2-piperidino addition for the 3,7-dimethyl substrate.

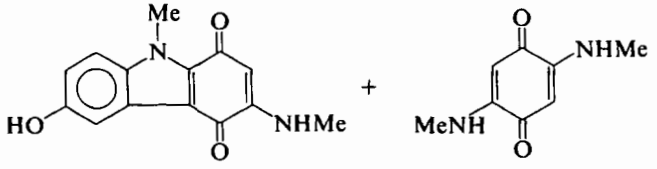


(51)

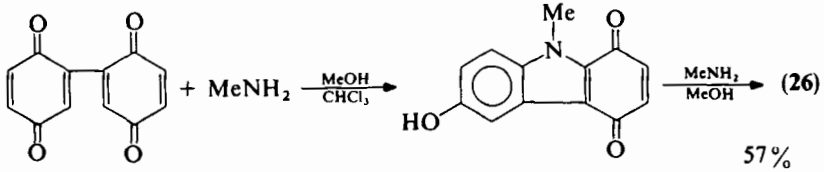
(52)

In a study of the addition of primary aliphatic amines to 1,4-benzoquinones Ott and his colleagues have discovered that the products are not as simple as was once thought and that solvent plays a significant role[68]. While in the addition of methylamine, 2-methylamino-1,4-benzoquinone is an intermediate and 2,5-bis(methylamino)-1,4-benzoquinone (**25**) is a product, the major product is 6-hydroxy-9-methyl-3-methylamino-1,4-carbazolquinone (**26**, equation 53). This result is consistent with the inability of Yamaoka and Nagakura to observe any spectra of 2-butylamino-1,4-benzoquinone in their detailed kinetic study of the butylamine system[69]. Chemical and spectral evidence combine to assure the correctness of the proposed structure. Furthermore, the carbazolquinone was prepared starting with 2,5,2',5'-biphenyldiquinone (**27**, equation 54).





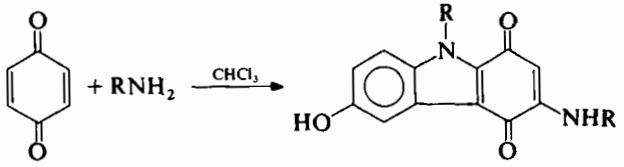
(26) 78% (25) 16% (53)



(27) 82% (54)

Several other solvents were examined and with both piperidine and dimethylformamide the product distribution was exactly reversed (19% **26**; 62% **25**). Finally, the use of ethanol at low temperature gave a 77% yield of the monoaddition product.

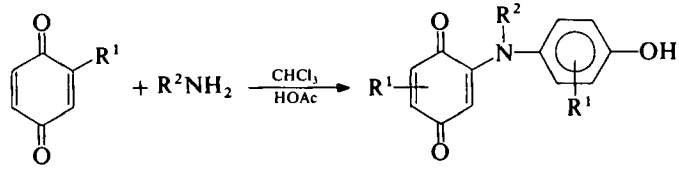
From a synthetic point of view Ott and his group have developed a generally useful pathway to the carbazolquinones (equation 55).



(55)

R	%	R	%	R	%
Et	47	Bu	19	$PhCH_2$	54
Pr	37	Hex	54	$HOCH_2CH_2$	43

In a subsequent publication Ott and his coworkers noted the presence of another unexpected product in these systems (equation 56)[70]. Lower yields of the two simple addition products were also found. The structures of the methylanilino phenols were supported by independent synthesis, and all product structures were consistent with various spectral studies. Changes in the acid component of the solvent did not effect the order of the products but did change their relative yield. These observations necessitate a



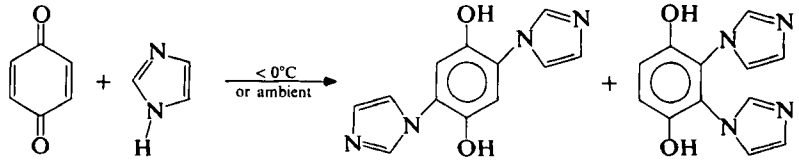
(56)

ca. 28%

R^1 = H, Me; R^2 = Me, Et, Pr, Bu

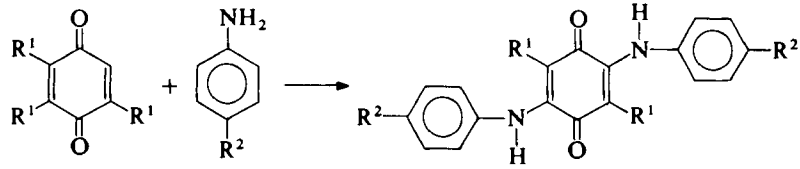
careful re-examination of the role of preliminary carbonyl–amine interactions and their influence on the nature of the isolated quinone addition product. One is reminded of the work in liquid ammonia discussed earlier[61].

The addition of imidazole to 1,4-benzoquinone produces both the expected 2,5- and the unexpected 2,3-diamino products (equation 57)[71]. The authors examined several solvents (acetone, methylene chloride and acetonitrile) but were unable to obtain information concerning the steps leading to the charge transfer complex. No yields were reported.



(57)

From a synthetic point of view the direct addition of anilines to quinones has continued to generate interest. Both ethanol and ethanol–acetic acid proved satisfactory for the addition of *p*-substituted anilines to 1,4-benzoquinone and its 2,5-dichloro derivative (equation 58)[72–74]. Many of the compounds prepared contained a sulfonamido group

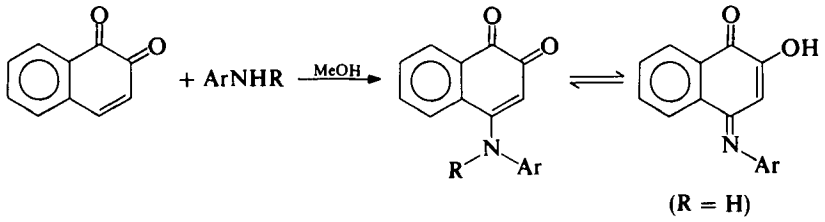


(58)

R^1 = H, Cl, Me, –CH=CHCH=CH–; R^2 = SO_2NHR^3 (R^3 = heterocyclic ring)

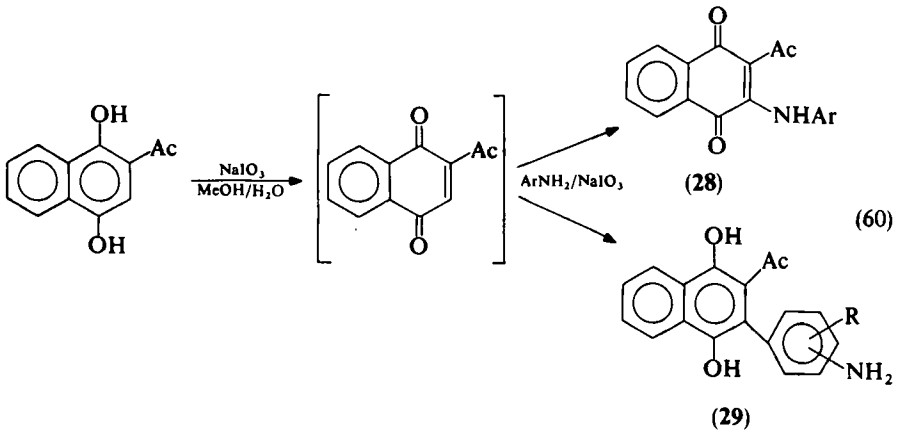
and a heterocyclic ring since these substituents often promote antitubercular or antimicrobial activity; 1,4-naphthoquinones were included for the same reason. The solvents selected produced uniformly high yields with the exception of reactions involving 2-methyl-1,4-naphthoquinone which were in the 20–50% range. A massive study by Clark (129 substituted 1,4-naphthoquinones) is especially valuable for the extensive set of truly comparable melting points for this important class of compounds[75].

In a study of the tautomerism of 4-(*N*-arylamino)-1,2-naphthoquinones Biggs and Tedder prepared their compounds by direct addition and included two examples of *N*-substituted anilines and hexylamine (equation 59)[76]. The yields in methanol vary widely and are not given in some cases, but most lie in the 40–70% range. The spectra of *N*-alkyl substituted cases are difficult to interpret, but the general pattern of 1,2-quinone structure in the solid or ethanol solution and 1,4-quinonoid structure in trifluoroacetic acid is clear.



Ar = 2,5-Cl_2, 2,5-$Me_2C_6H_3$, 4-An, 4-Br, 4-NH_2, 4-$NHCOMeC_6H_4$
R = H, Me, Et (59)

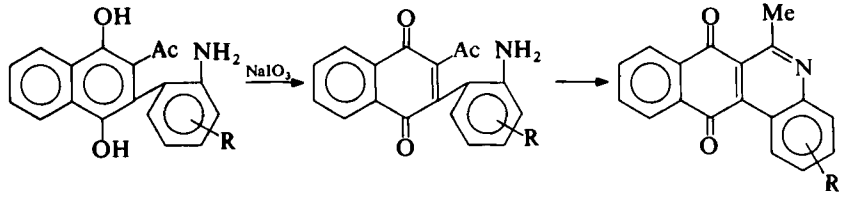
An interesting rearrangement leading to carbon–carbon bond formation is found in a nascent 1,4-naphthoquinone addition chemistry (equation 60)[77]. The product obtained is



(60)

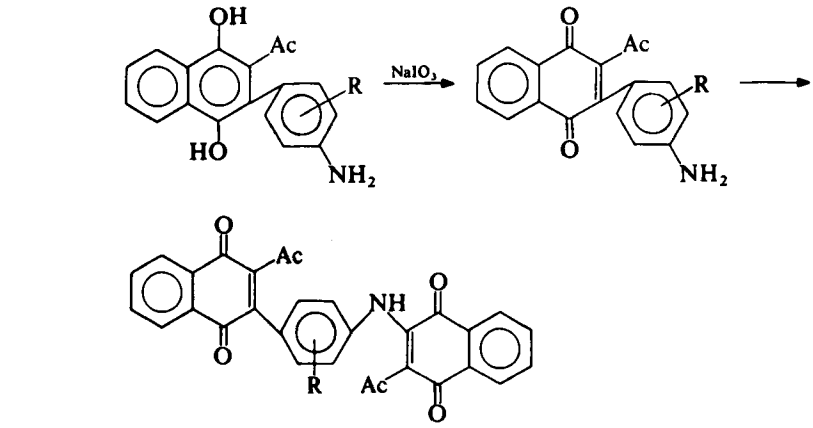
Ar = 2-, 3-, 4-Tol; 4-F, 4-Br, 3-Cl, 4-Cl, 4-CN, 4-$NO_2C_6H_4$; 2,5-$(MeO)_2C_6H_3$

determined by the structure of the aniline. With a 2-methoxy or 3-chloro group or any substituent in the 4-position the corresponding 2-arylamino product (**28**) is obtained in about 75% yield. The dialkyl, 2- or 3-methyl, 3-methoxy and 2,5-dimethoxy substituents give varying amounts of aminoarylation (**29**). These products were isolated after further oxidation and possess radically different structures depending on the orientation of the amino group (equations 61, 62). With strong electron-donating groups these products

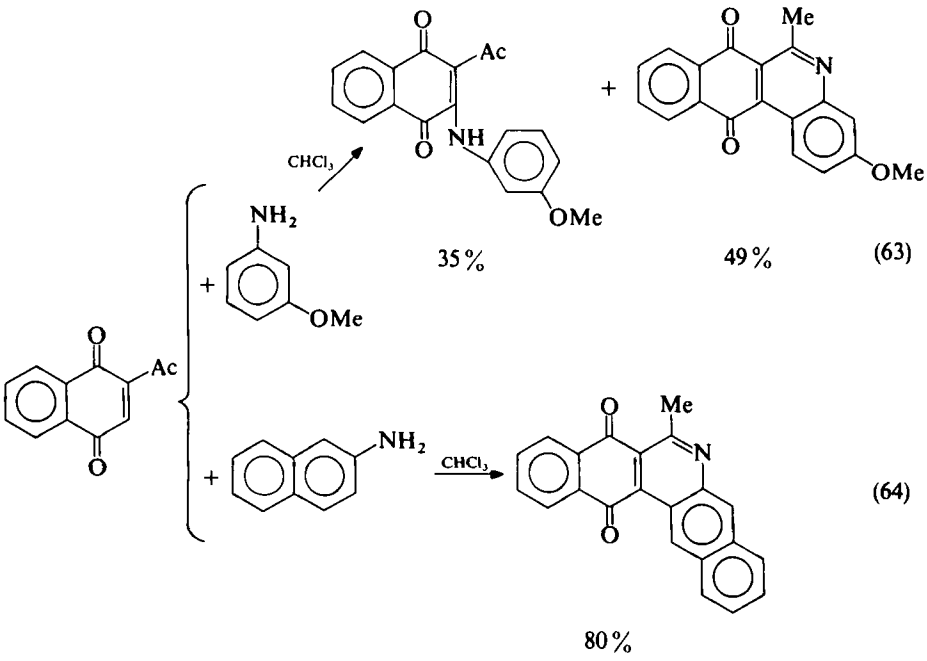


(61)

become important and in some cases are the only ones isolated. The reactions of the same anilines in chloroform and without added oxidant generally produce good yields of the direct amino addition. The 3-methoxyaniline and 2-aminonaphthalene are notable exceptions (equations 63, 64).



(62)

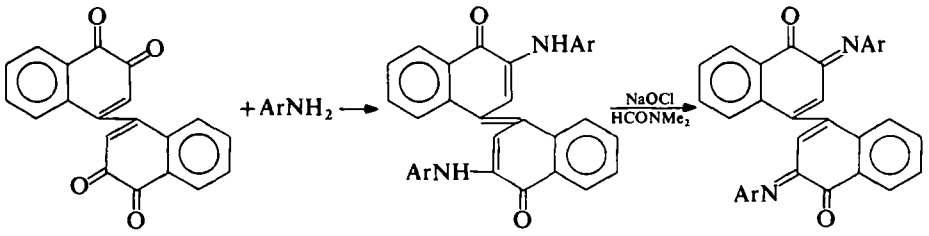


(63)

(64)

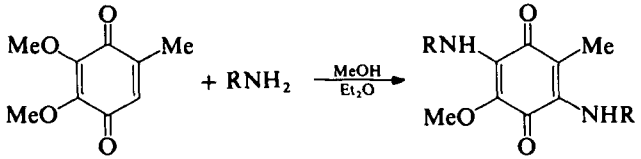
The addition of anilines to 1,2-quinones has been studied using the 4,4'-bi-(1,2-naphthoquinone) molecule[78]. For most substituents on aniline the expected addition product is obtained in good yield (equation 65). An exception is 2-pyridyl which gave only 27%. With phenyl and its methyl, methoxy and chloro derivatives oxidation to the quinone-anils is accomplished in generally good yields. The latter compounds were obtained directly with the halogenated anilines. No interpretation of these observations was presented.

Many studies involving the addition of nitrogen nucleophiles to quinones have been reported in connection with the search for dyestuffs, medicinals, etc. A few of these advance our understanding and raise questions of interest for further study. Folkers and his



Ar = Ph, 2,3,4-Tol, 2,4-An, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 2,4-ClC_6H_3, 2- and 3-pyridyl (65)

collaborators prepared a 12 new 2,5-bis(alkylamino)-1,4-benzoquinones using a combination of addition and substitution chemistry (equation 66)[79]. The yields, which do not

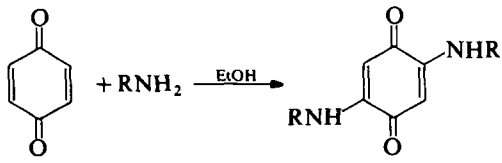


(66)

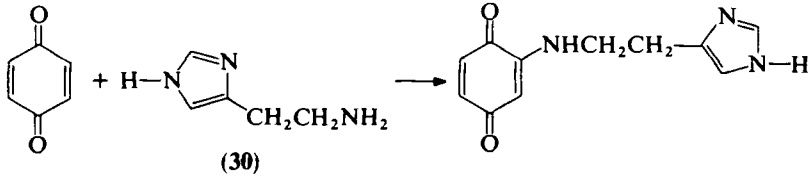
R = C_6 to C_{18} *n*-alkyl, C_5 to C_7 cycloalkyl, CH_2CH_2OH

appear to have been optimized, show a puzzling variation; six average 57% and four average 28%. Neither chain length nor reaction time appears to explain these observations. The reaction time was generally 16 hours, but was reduced to 3 without explanation in three instances. Ethanolamine produced only a 9% yield after 20 hours at room temperature.

Tindale applied standard methods of amine-quinone additions to certain biochemically interesting amines with significant results[80]. In ethanol solution at room temperature good, but unspecified, yields of 2,4-diamino addition products were obtained with the exception of histamine (**30**) which produced only the monoaddition product (equations 67, 68). Similar additions to 1,2-benzoquinones gave tar and many minor products. One



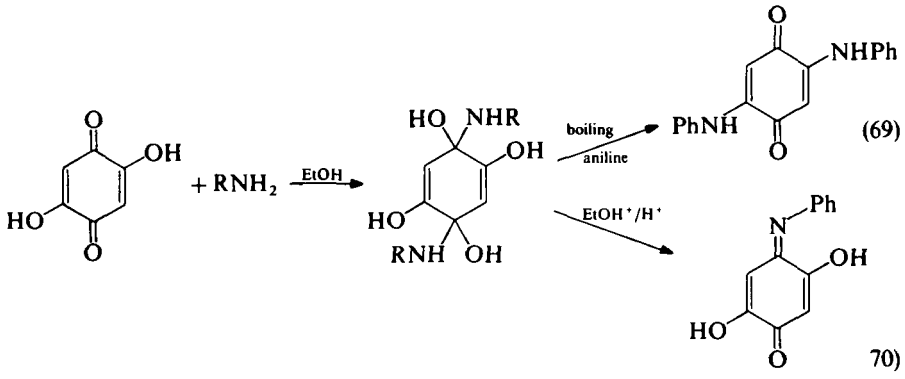
(67)



(**30**) (68)

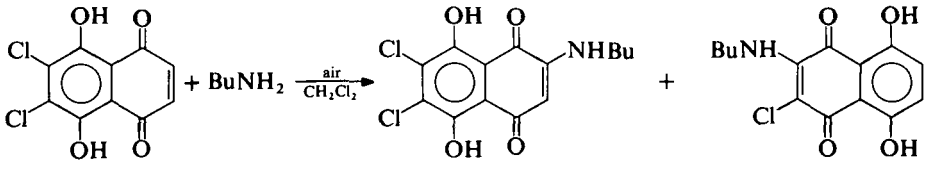
R = Ph, $PhCH_2CH_2$, 4-$HOC_6H_4CH_2CH_2$

product was isolated from the reaction with 2-phenylethylamine, but it was not characterized. With 2,5-dihydroxy-1,4-benzoquinone all four amines gave 1,2-carbonyl addition in contrast to the earlier report of unusual displacement of the hydroxyl groups[81]. However, in boiling aniline the net result of substitution is obtained, probably by an addition–elimination mechanism (equation 69). On long standing in ethanol, or upon the



addition of a trace of hydrochloric acid, the aniline monoimine is formed (equation 70). The other amines hydrolyzed, but did not form imines.

Naphthazarin has been of interest for some time both in the search for antibiotics and in the dye industry. A study of its 6,7-dichloro derivative (**31**) shows not only competition between addition and substitution, but also facile tautomerization (equation 71)[82].



(71)

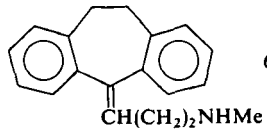
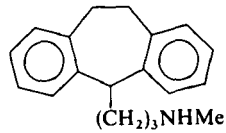
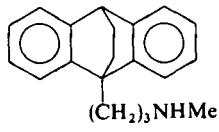
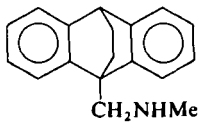
Ethanol gives the highest degree of selectivity with addition favored over substitution 76:1. This preference holds for the three other amines studied, but not for oxygen nucleophiles. Sodium methoxide gave a good yield of 2-methoxy-3-chloronaphthazarin while methanol or ethanol in the presence of triethylamine gave fair yields of both addition and substitution products analogous to those found with primary amines.

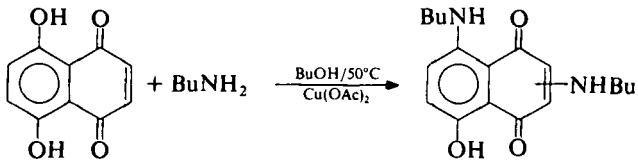
Kallmayer and Tappe have prepared a series of drugs related to desipramin through the addition of secondary amines containing polycyclic substituents to 1,4-benzoquinone (Table 1)[83]. The similar amounts of mono- and di-addition products in three cases is unlike most work in the field.

The results of Matsuoka and his colleagues[82] are especially surprising and promising in view of their earlier report on naphthazarin itself[84]. In ethanol solution excess butylamine gave a variety of butylamino addition and substitution products, all in very low yield. When the reaction was carried out in the presence of cupric acetate the product distribution, while still complex, changed markedly (equation 72). The structure of the product (**32**) was not determined, but it was discovered that the yield could be more than doubled (61%) using cupric chloride at ambient temperature. If the copper complex of naphthazarin is prepared and then allowed to react with butylamine, the yield of **32** also increases (41.8%) and potentially useful yields of a simpler array of by-products is obtained (equation 73).

Rapoport and Luly have shown that copper acetate promotes highly regioselective amination of unsymmetrical 1,4- and 1,2-benzoquinones (equation 74)[85]. Traces of the

TABLE 1. Distribution of 1,4-benzoquinone mono- and di-addition products from the synthesis of compounds related to the desipramin drugs[83]

Amine (R)	% Yield Monoadduct	Diadduct
	63	44
	55	41
	90	7
	17	19



(72)

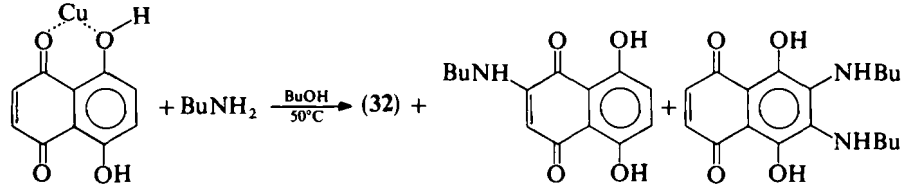
(32) 26.5%

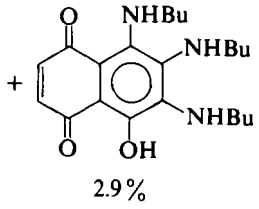
dipyrrolidine adduct and a demethylated analog resulting respectively from methoxy or methyl group displacement could be identified. In the absence of the copper salt the isomeric ratio became 2:1 showing the powerful effect of the complex formation.

The excellent regioselectivity found in the preceding model study was utilized by the same authors as the first step in a superb synthesis of 7-methoxymitosene (equation 75)[86]. As was expected from the more hindered and less nucleophilic proline methyl ester of 33 a product of higher isomeric purity was obtained; 96% with less than 1% of the demethylated product and no isomeric addition product. In the absence of the copper salt a major side product resulted from the displacement of the methoxy group.

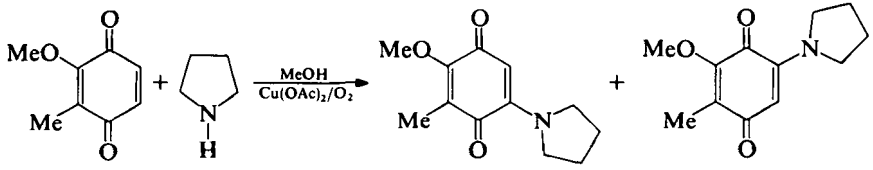
3. Cyclization reactions

The study of heterocyclic ring-forming reactions has become one of the most active areas of synthetic interest in recent years. In addition to his several studies already described Ott

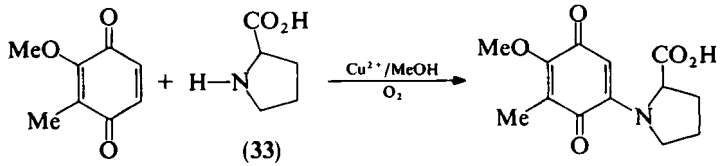




(73)

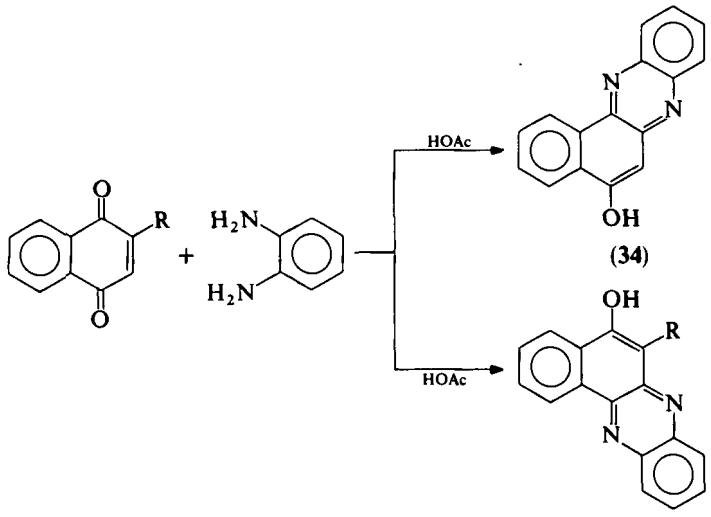


(74)



(75)

has looked at the chemistry of *o*-phenylenediamine and 2-substituted 1,4-naphthoquinones (equations 76, 77)[87]. While a great amount of detail of information concerning the intermediate steps of the reaction is presented, the essence of this study is that the quinone substituent controls the course of the addition and the structure of the product. Oxygen and nitrogen substituents are easily displaced, and acetic acid is the solvent of choice with yields in excess of 90% being common. The ratio of quinone to diamine seems to be important and 1:2 is preferred, but no clear pattern was found. Alcohol fails to be a useful solvent in all cases. Some rather puzzling observations emerge from the data; for example, while both the amino and the dimethylamino groups produce excellent yields of **34**, methylamino gives only very small amounts. All anilino substituents, except the 2-hydroxy case, are poor leaving groups; this system gave excellent yields for both itself and the *N*-methyl derivative. Unlike these nitrogen substituents the acetamido group and a 2:1 excess of quinone gave a nearly quantitative yield of the product resulting from reaction at the 3-carbon and 4-carbonyl (**35**). This drastic reversal of reactant ratio is typical of the second pathway and easily explained by the proposed mechanism which



(76)

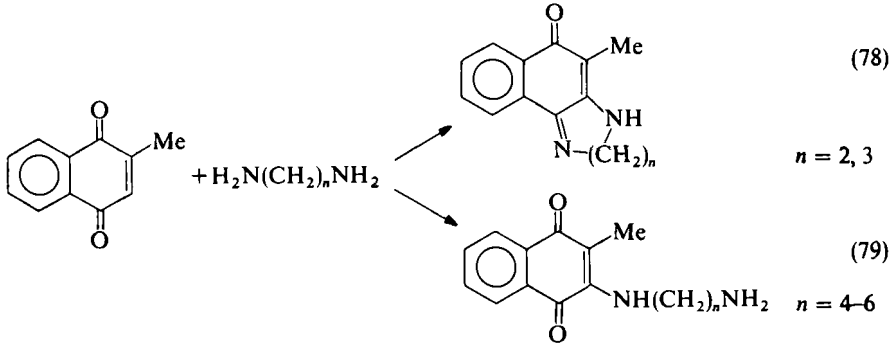
(34)

(77)

(35)

involves an additional oxidation step. Oxidized carbon or sulfur substituents are both successful in promoting this reaction direction; chloro groups somewhat less so. Alkyl and aryl, represented only by methyl and phenyl, also react in this fashion but give poor and fair yields respectively. For the acetyl group ethanol is an excellent solvent; water for the sulfonic acid.

The studies of Kallmayer and Seyfang complement those of Ott through an intensive examination of the addition of such aliphatic analogs as 1,2-ethylenediamine to naphthoquinones[88-91]. They have shown that 2-methyl-1,4-naphthoquinone reacts in the expected manner when either 2 or 3 methylene groups are present, but longer chains (4, 5, or 6) lead only to open chain products (equations 78, 79)[88]. In this particular study



(78)

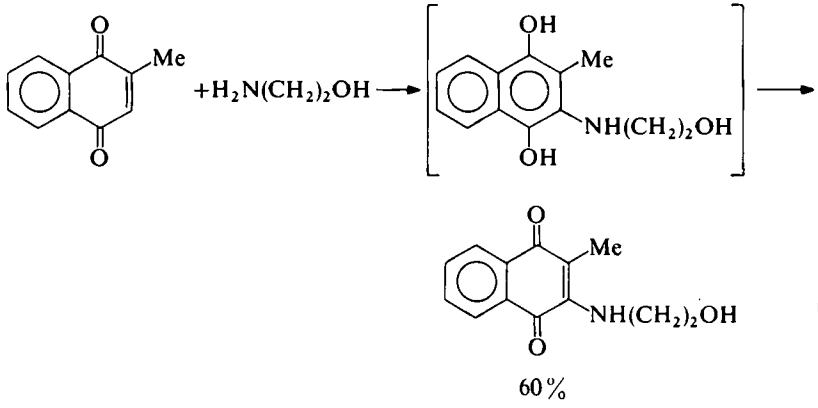
$n = 2, 3$

(79)

$n = 4$–6

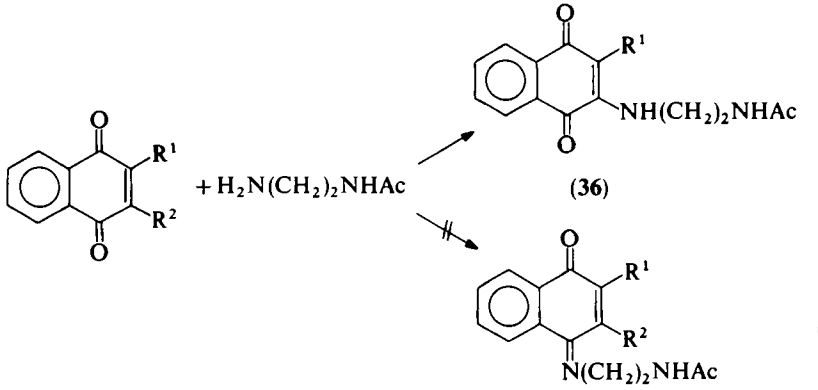
ethanolamine was examined and found to add in the usual fashion illustrating once again the great preference for nitrogen addition (equation 80).

An even closer analogy to Ott's work is found in the next paper in the series where the authors explore 1,4-naphthoquinones bearing a large range of 2- and/or 3-substituents[89]. No yields are given, but the cyclized products appear to be formed by substitution of one



(80)

amino group for the displaceable group. Using *N*-acetyl-1,2-ethylenediamine it was demonstrated (equations 81, 82) that the intermediate has the ring-addition structure (**36**) rather than that of an anil (**37**).

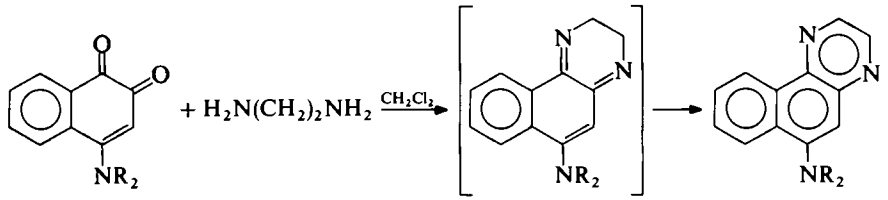


(81)

(82)

R^1 = H, alkyl, Ph, Br, MeO, AcO; R^2 = Me, Cl, Br (**37**)

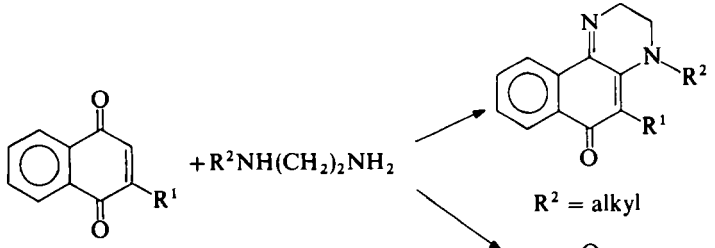
These workers have tried to prepare the 5-hydroxy derivative of some heterocyclic products[90]. While the efforts failed some unusual chemistry of cyclization did emerge (equation 83).



R = Et, $(CH_2)_5$ 38%, 49%

(83)

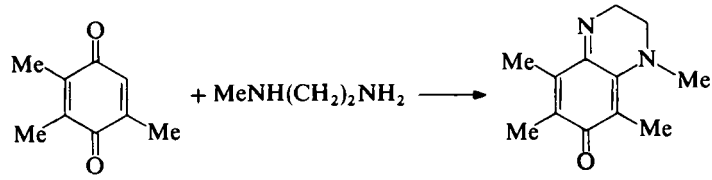
When *N*-alkyl or *N*-arylamino ethylenediamines are added to 2-bromo or 2-methyl-1,4-naphthoquinones the yields are low, but highly selective (equations 84, 85)[91]. The cyclized products are not produced by alkylation of the unsubstituted benzoquinoxalinones. The reaction also takes place with trimethyl-1,4-benzoquinone, again in low yield (equation 86).



(84)

(85)

R^1 = Br, Me; R^2 = Me, Et, Ph, 1-Naphthyl R^2 = aryl

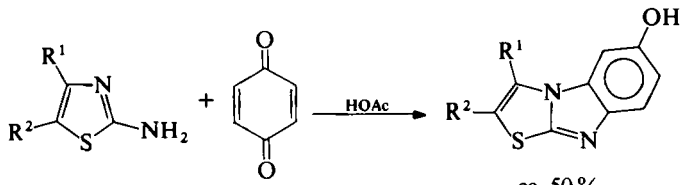


(86)

Saxena and Soni have conducted an interesting series of investigations involving the initial addition of 2-amino heterocycles to 1,4-benzoquinone followed by ring-closure, creating three series of multi-heterocyclic products (equations 87–89)[92–94].

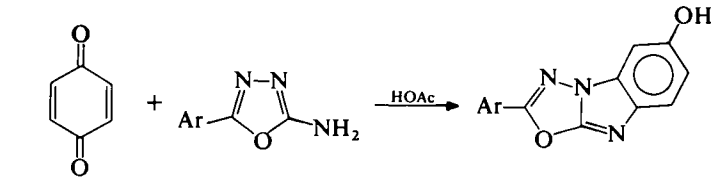
Chaaban and his collaborators have shown that the addition of 2-aminobenzoic acids followed by dehydration leads to acceptable yields of 2-halobenzo[*b*]acridine-6,11,12-triones (**38**, equation 90)[95].

The much studied competition between thiol and amino groups in their addition reactions with 1,2-quinones has produced an interesting example in the 1,4-benzoquinone series. In their model study of biosynthetic routes to a firefly luciferin McCapra and Razavi



(87)

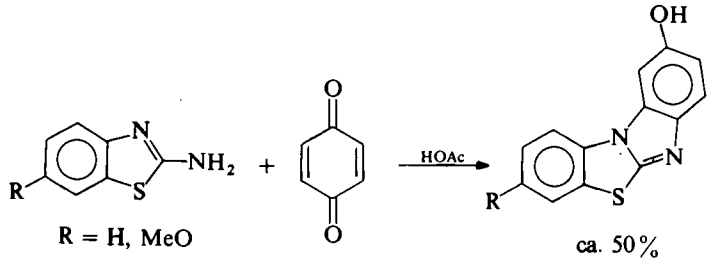
R^1 = H, Me, Ph, 4-Tol,
4-BrC_6H_4 4-HOC_6H_4, 2-thienyl,
2-naphthyl
R^2 = H, Me, Ph, CO_2Et



Ar = Ph, 4-Cl, 4-Me, or
4-FC_6H_4, 3,5-Br_2-2-HOC_6H_2

ca. 25%

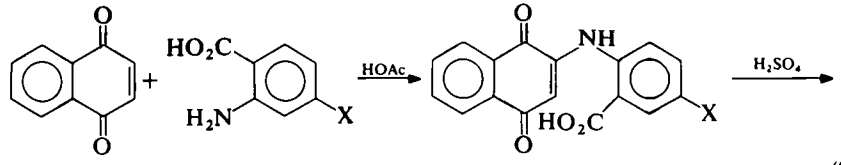
(88)



R = H, MeO

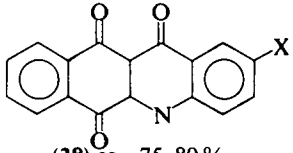
ca. 50%

(89)



X = H, Cl, Br, I

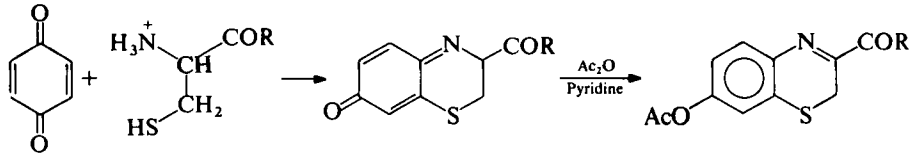
(90)



(38) ca. 75–80%

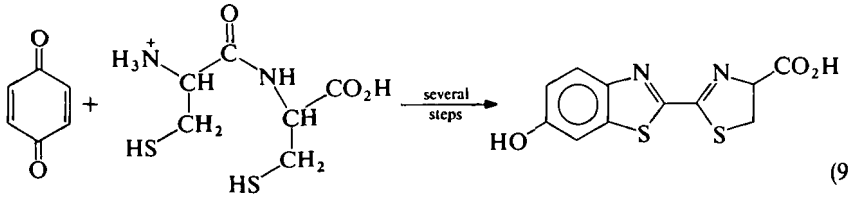
showed that under acidic conditions both groups add (equation 91)[96]. Under basic, aerobic conditions the amino heterocycle undergoes ring contraction; this chemistry was utilized with a more elaborate model (equation 92),

In an attempt to use 3,5-di-*t*-butyl-1,2-benzoquinone in the Strecker degradation of a sensitive α-amino acid Vander Zwan and coworkers found an interesting synthesis of



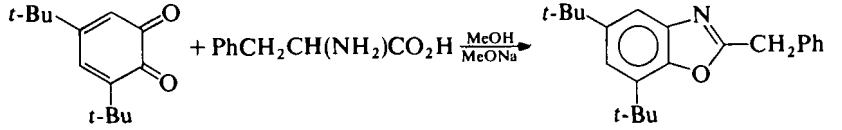
R = NH_2, OEt

(91)



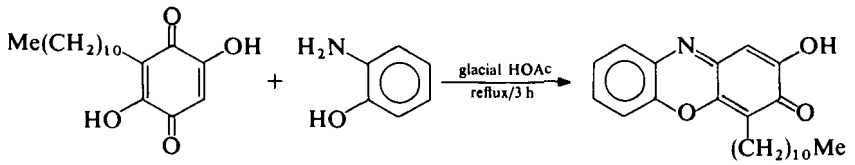
(92)

benzoxazoles (equation 93)[97]. While not many examples are given and the yield with phenylalanine is low, the method appears to be general for highly hindered *o*-quinones where ring-addition is restricted. The method is somewhat similar to Corey's preparation of benzoxazoles from this quinone and primary amines[98].



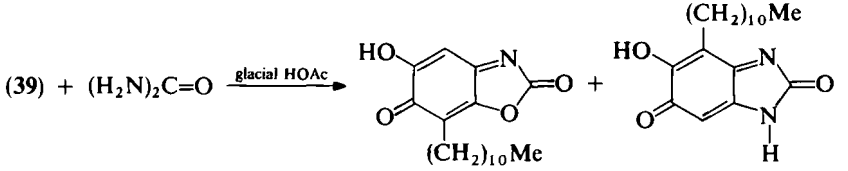
(93)

Interest in tautomeric quinonoid systems is potentially useful in the construction of heterocyclic rings, for example, treatment of the natural product embelin (**39**) with 2-aminophenol produced 2-hydroxy-4-*n*-undecyl-3(*H*)-phenoxazone (**40**, equation 94)[99].



(**39**) (**40**) (94)

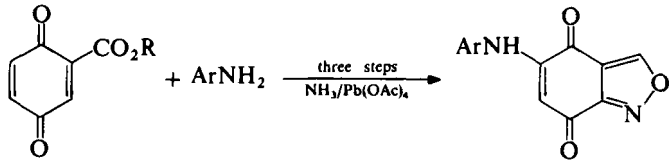
Rao and Nageshwar have also studied the reaction of embelin with *o*-phenylenediamines to produce phenazines[100]. Of greater interest is the later study in which Rao and a group of collaborators examined the reactions of embelin with urea (equation 95)[101]. With an



(95)

overall yield of 98% and useful quantities of both products this chemistry surely ought to be examined more fully.

Schäfer and coworkers have used 2,5-bisanilino-1,4-benzoquinones as the first intermediates in a synthesis of the labile and important isoxazolequinones (**41**, equation 96)[102]. A naphthoquinone analog was also prepared and the yields for all reactions are in the 70–80% range.



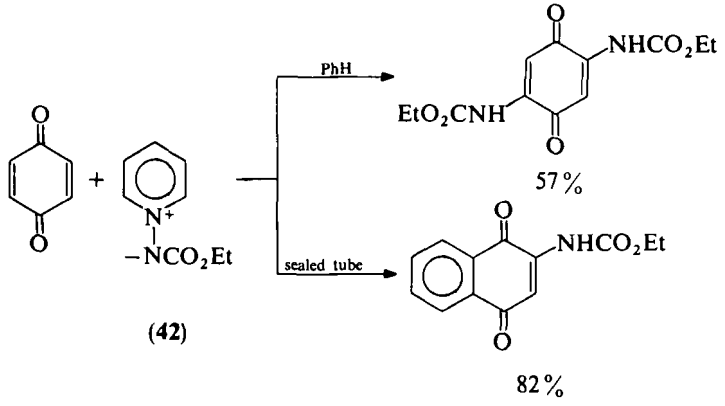
(96)

(41)

R = Me, Et; Ar = Ph, 4-Tol

4. *Brief notes*

The reaction of α,β-unsaturated carbonyl compounds with *N*-ethoxycarbonyliminopyridinium ylide (**42**) in the presence of silicic acid gives good yields of ethoxycarbonylamino derivatives including those of quinones (equations 97, 98)[103]. The structure of the benzoquinone product was demonstrated by synthesis of an identical material from 2,5-diamino-1,4-benzoquinone and ethyl chloroformate.

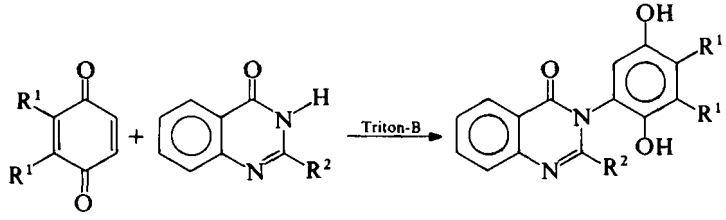


(97)

(98)

(42)

An example of the addition of a lactam to quinones presented by Seth and Khanna deserves special note (equation 99)[104]. The importance of adjacent substituents is also clear in their attempted syntheses of certain quinazolones.

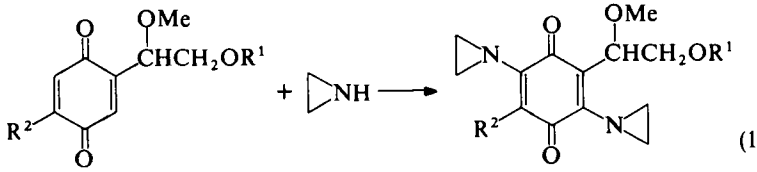


(99)

R^1 = H, −CH=CHCH=CH−; R^2 = SEt, $N(C_2H_4)_2O$, Me 60%, 55%, 0%, 0%

The extensive synthetic efforts directed toward quinones with aziridinyl substituents has usually involved nucleophilic substitution of a halogen, but Yoshimoto and his collaborators have used direct addition of ethylenimine in the synthesis of complex 1,4-

benzoquinones for structure–activity studies (equation 100)[105]. While the yields are hardly exciting this route does offer an alternative that may warrant further study.

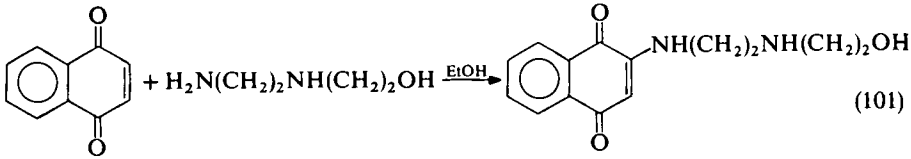


(100)

R^1 = H, $CONH_2$; R^2 = $CH(OMe)CH_2OR^1$ 15%, 29%

R^1 = 2,3,4,6-tetra-*o*-acetyl-β-D-glucosyl; R^2 = Me 7%

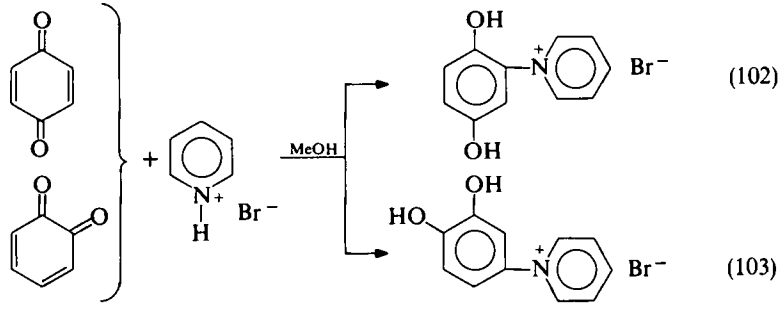
For a comparison of the antineoplastic activity of some aminoanthroquinones several naphthoquinone analogs have been prepared[106]. The point of interest lies in taking advantage of the much lower reactivity of a secondary amine or an alcohol to achieve specificity (equation 101). In a similar fashion 2-(dimethylamino)ethylamine added exclusively through the primary amino group (94%).



(101)

54%

An exception to this observation concerning tertiary amines is found with pyridine and other aromatic nitrogen heterocycles whose hydrobromides add readily to quinones (equations 102, 103)[107]. This reaction was actually discovered when it was found that



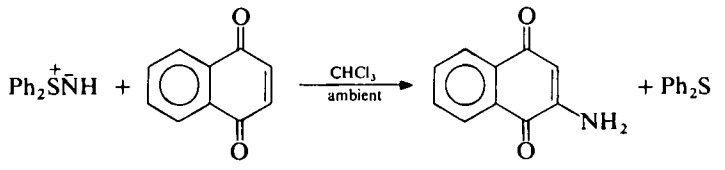
(102)

(103)

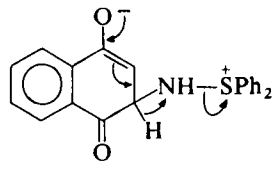
resorcinol fails to show evidence of nascent quinone formation under these reaction conditions. The yields are said to be about 60%.

A study of the nucleophilicity of arylsulfilimines included 1,4-naphthoquinone (equation 104)[108]. The proposed mechanism involves addition to the α, β-unsaturated ketone followed by a hydride shift and concomitant S–N bond cleavage (**43**).

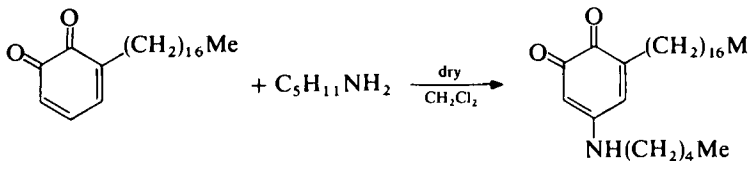
In connection with a study of the interactions of catechols found in poison oak and ivy Castagnoli and coworkers examined the reaction of a model nucleophile, pentylamine, with their model substrate, 3-heptadecyl-1,2-benzoquinone (equation 105)[23], and obtained 32% of a red solid whose spectra were consistent with the quinonoid structure **44**. They showed an impressive similarity between the extinction coefficient of **44** and the reaction



(104)



(43)



(105)

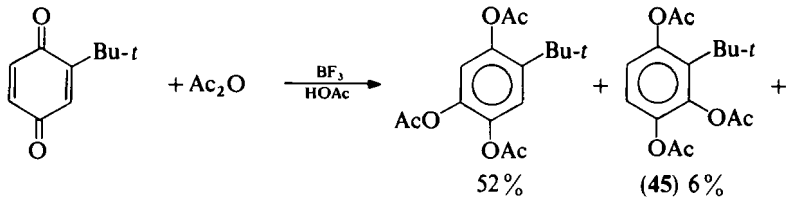
(44)

product obtained by incubation of an equimolar mixture of the original quinone with human serum albumin.

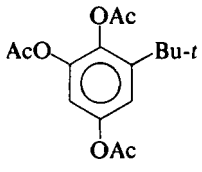
C. Thiele–Winter Acetoxylation

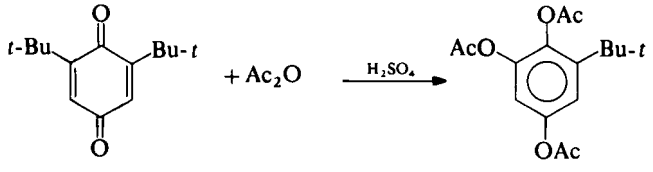
McOmie and Blatchly, two of the most notable workers in this field, have presented a detailed review of the synthetic and mechanistic aspects of the reaction in 1972[109]. The historical introduction is typical of the care they lavished on this study. Their recognition of Winter's importance and of the actual use of the reaction led them and me to favor the revised name over the traditional Thiele acetylation. Their subsequent primary publications also bear this new designation. In the first of that series to appear following the review they present a complete survey of the reactions of 1,2- and 1,4-benzoquinones containing one or two *t*-butyl groups (equations 106–108)[110]. Nearly all of the earlier work is repeated and discussed. In general the findings previously reported were confirmed, the structures more rigorously demonstrated and minor by-products discovered. Several points are significant in these experiments: (1) de-*t*-butylation does in fact occur, (2) small amounts of product from reaction adjacent to the *t*-butyl substituent are found, (3) no simple substitution product was found in the case of 2,6-di-*t*-butyl-1,4-benzoquinone and (4) in the simplest cases one product is obtained in a synthetically useful yield. It should be noted concerning yields cited above that these are all minimum figures which often, as in the 2-*t*-butyl case, involve hydrolysis and methylation prior to fractionation. The authors state, for example, that they do not regard the greater yield of the more highly hindered product **45** as significant for these reasons.

Similar results were obtained for most examples of methyl, bromo and hydroxyl-*t*-butyl-1,4-benzoquinones. An interesting exception is 2-hydroxy-5-*t*-butyl-1,4-benzoquinone

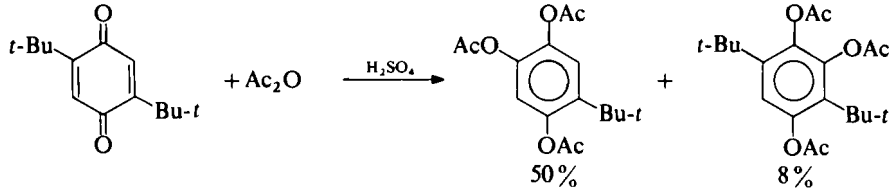


(106)



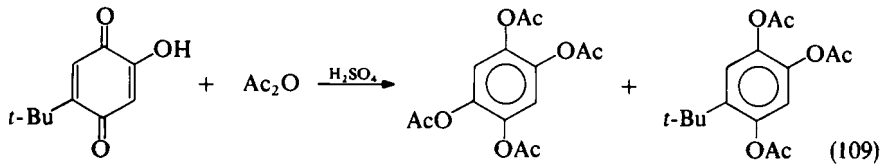


(107)



(108)

where Flaig and his coworkers had claimed, without reaction times or yields, both a de-*t*-butylation and a simple reductive esterification product (equation 109)[111]. In the present

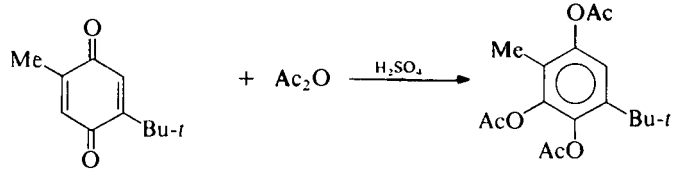


(109)

study[110] only the former could be identified and that in 5% yield. As would be expected neither group found any evidence for a Thiele–Winter product The importance of catalyst selection is shown in several examples, but is best exemplified by 2-bromo-5-*t*-butyl-1,4-benzoquinone where sulfuric acid produces low yields of purifiable products while the more modern boron trifluoride and perchloric acid gives only tars. There is a minor inconsistency in that the narrative describes the product, which was not completely characterized, as 1,3,4-triacetoxy-2-bromo-5-*t*-butyl-1,4-benzoquinone while the table gives 1,2,4-triacetoxy-5-bromo-1,4-benzoquinone. The latter, a de-*t*-butylation product would certainly have been noted in the text.

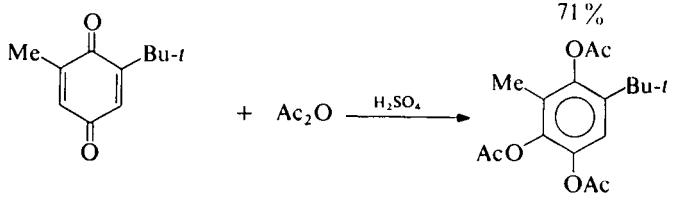
The reactions of 2-methyl-5-*t*-butyl- and 2-methyl-6-*t*-butyl-1,4-benzoquinones illustrate the critical importance of substituent position on the outcome of the

Thiele–Winter acetoxylation (equations 110, 111). While both reactions proceed normally there is a ten-fold difference in the production of the isomeric products that deserves more attention.



71%

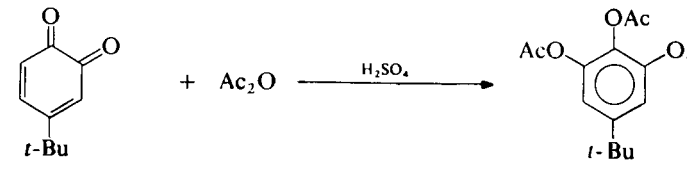
(110)



7.7%

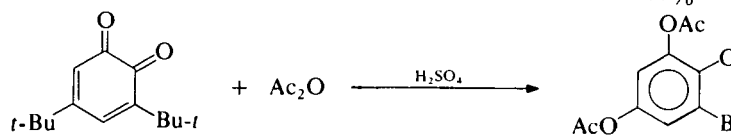
(111)

Studies of the alkyl-1,2-benzoquinones provide, with the exception of the 3-methyl-5-*t*-butyl case, markedly higher product yields for reasons that are not at all clear (equations 112–114)[110]. This low yield surprised the authors who reinvestigated an earlier report[112]



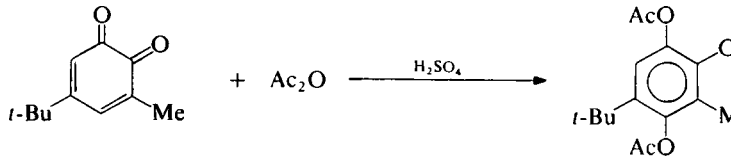
77%

(112)



64%

(113)

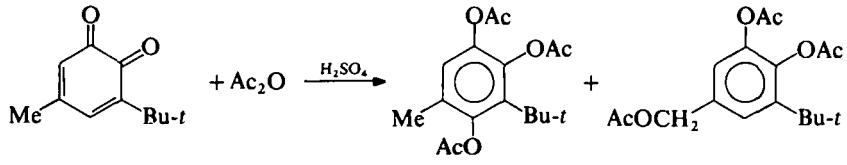


12%

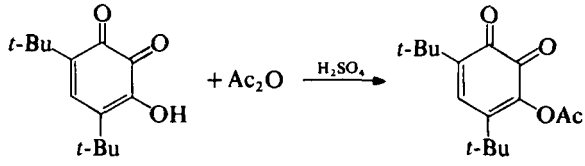
(114)

concerning 5-methyl-3-*t*-butyl-1,2-benzoquinone and found a new product (**46**) resulting from reaction by a *p*-quinone methide (equation 115)[110].

When an oxygen or halogen substituent are present very low yields or decomposition are the rule; the only exception is the non-Thiele–Winter esterification of 3-hydroxy-4,6-di-*t*-butyl-1,2-benzoquinone which isn't even reduced under these conditions (equation 116).

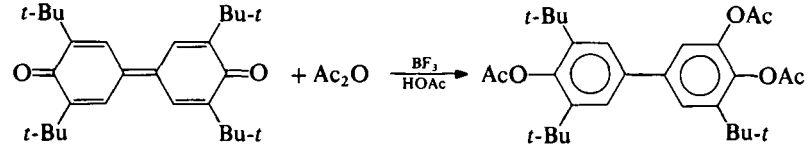


(115)



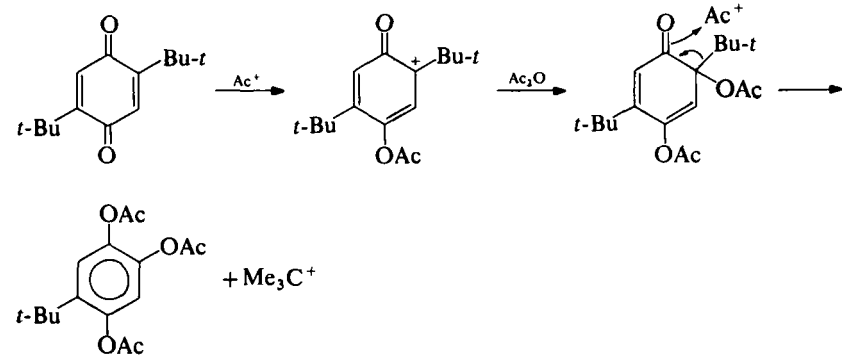
(116)

Several more complex quinonoid systems were examined and shown to exhibit interesting chemistry. For example, 3,3', 5,5'-tetra-*t*-butyldiphenylquinone gave a nearly quantitative yield of the 1,8-addition product involving an alkyl group displacement (**47**, equation 117).

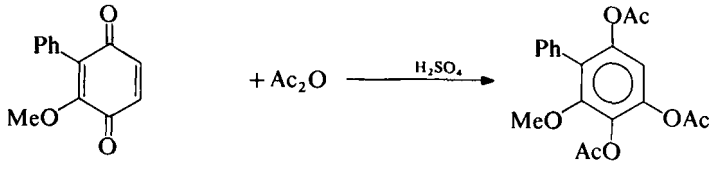


(117)

Since *t*-butyl is the only alkyl group known to be displaced in these reactions a carbonium ion mechanism seems reasonable.

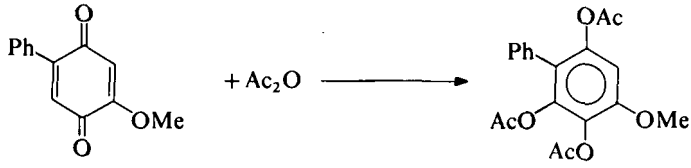


In their continuing studies of the synthetic utility and mechanistic detail of Thiele–Winter acetoxylations Blatchly and McOmie have examined the products of phenyl and 4-substituted phenyl 1,4-benzoquinones in which there is also a hydroxy, halo, or methoxy group present (equations 118–120)[113]. The corresponding hydroxy quinones

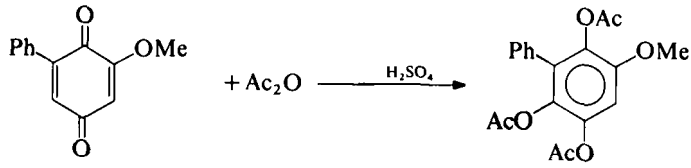


54%

(118)



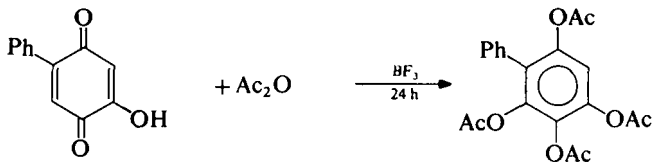
(119)



(120)

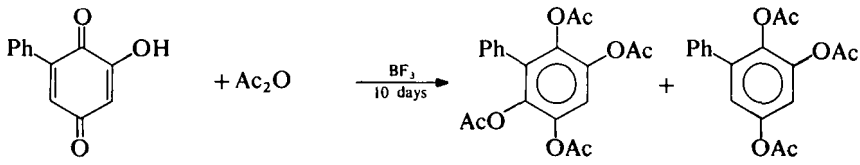
ca. 2%

are much less reactive and give comparable or better yields (equations 121, 122). In the first example the intermediate had been reported by Fieser[114].



56%

(121)

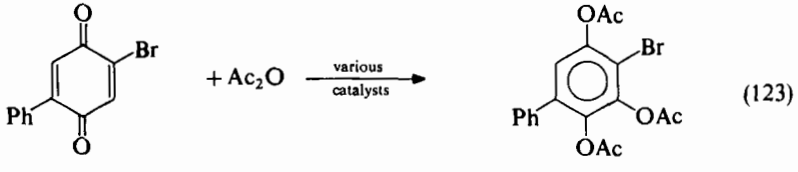


30% 6% (122)

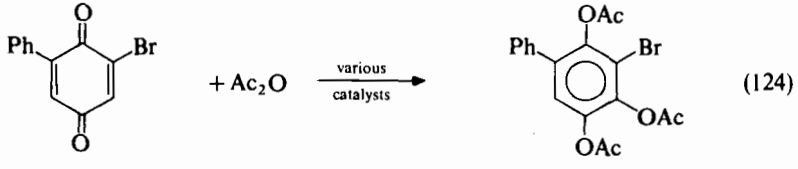
The knowledge that strong electron-withdrawing groups, e.g. cyano, direct to the adjacent position (often incorrectly referred to as *ortho*) prompted an investigation of 2-(4-nitrophenyl)-1,4-benzoquinone. The results of this study extend the concurrent work of Wilgus and Gates[115] and confirm their conclusion that such *p*-substituents have a very small influence. While the question of the resonance effect of the 4'-nitro group does seem resolved there are other, perhaps minor, questions not answered. Thus, the yields of the 4'-nitro of bromo products are high (82% and 86% respectively) while the same can hardly be said for those bearing 4'-hydroxy or acetoxy groups (48% and 45% respectively). It is true that the authors point out[113] that the differences in yield are related to the relative

solubility in ethanol since all values were reported after two recrystallizations. What is more bothersome is the implication that only one isomeric product is found even in the high yield cases. Wilgus and Gates reported significant amounts of more than one isomer in the three 2-aryl substituted examples studied including all three isomers for 4'-nitro-1,4-benzoquinone[115]. Surely, the stated purpose of this paper, to propose an improved mechanism for this important reaction, demands a careful consideration of such electronic influences.

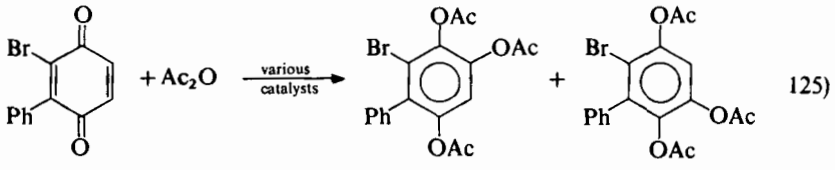
In the final paper of this mini-series McOmie and his collaborators examine the influence of bromo and phenyl groups on the orientation and reactivity of 1,4-benzoquinones under Thiele–Winter conditions[116]. This group of compounds proved to be a most interesting selection since two of them yield a specific orientation (equations 123, 124), one, a mixture of isomers (equation 125), and two, reduction only (equations 126, 127). The product mixture from 2-bromo-3-phenyl-1,4-benzoquinone was found to be



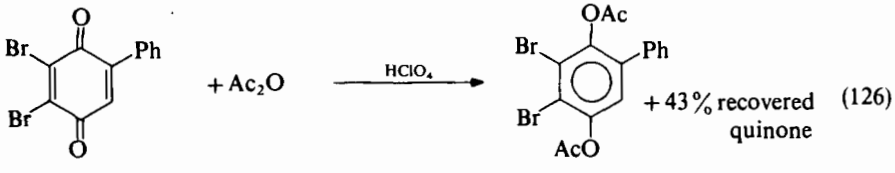
(123)



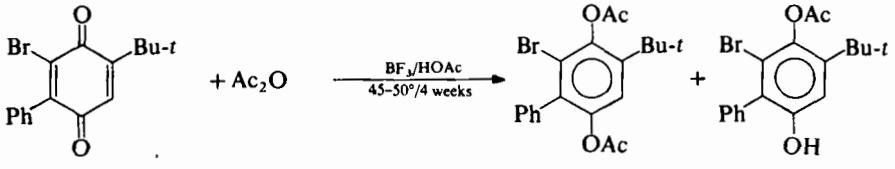
(124)



125)



(126)



(127)

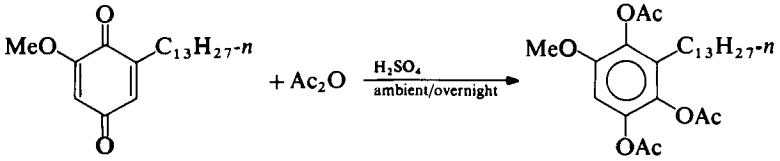
approximately 40:60, but the major component was not determined. The structure of the 3,4,6-triacetate was demonstrated by hydrolysis, methylation, debromination and comparison with an authentic sample. The comparison of catalysts presented in Table 2 is consistent with earlier work in showing no significant effect. It is hardly surprising that these two greatly hindered substrates do not undergo the reductive addition reactions.

TABLE 2. Effect of catalyst on the yield of Thiele–Winter acetoxylation product (equations 123, 124)[116]

	% Yield with		
Substituents	BF_3	H_2SO_4	$HClO_4$
2-Br-3-Ph	69	84	82
2-Br-5-Ph	77	80	76
2-Br-6-Ph	62	73	65

These studies taken together present a fairly complete picture of what can be expected from Thiele–Winter reactions in a wide variety of steric and electronic situations. They fail to reach the detailed mechanistic description one might desire for this important transformation. Kinetic studies are clearly needed to supplement the product and reactivity information available. There also remains completely untouched the rather fundamental question of the relationship between this clearly electrophilic reaction and the normally encountered nucleophilic reductive addition reactions of the quinones.

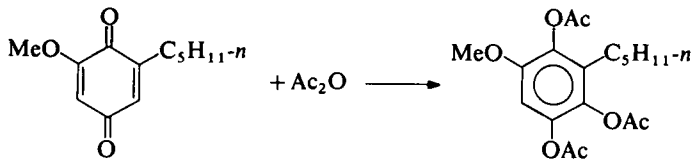
Several applications of Thiele–Winter chemistry have appeared in the recent literature. Interest in the role of resorcinols in certain groups of natural products prompted the study of the relationship of one such compound to quinonoid compounds[117]. During this study 2-methoxy-6-tridecyl-1,4-benzoquinone was treated with acetic anhydride and sulfuric acid (equation 128). The single product obtained illustrates once again just how reluctant



(128)

0.36g 0.36 g crude gum

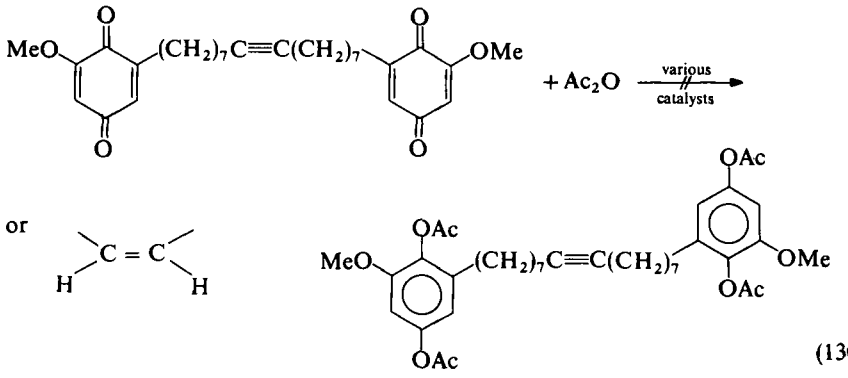
this reaction is to place the acetoxy group adjacent to a methoxy substituent. Nearly identical chemistry was reported by Marini-Bettolo and coworkers (equation 129)[118].



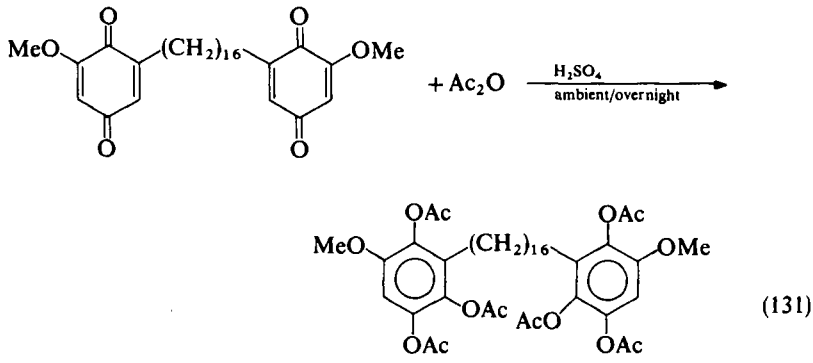
(129)

The information gained from these experiments failed to provide the desired route for the proposed total synthesis because both an acetylenic and an alkenyl bond were attacked by acetic anhydride in preference to the quinonoid structures under all of the usual

conditions (equation 130). Two completely reduced analogs were used successfully (equation 131)[117].

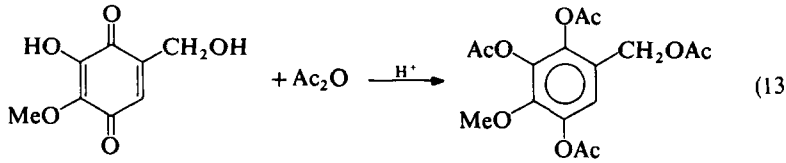


(130)



(131)

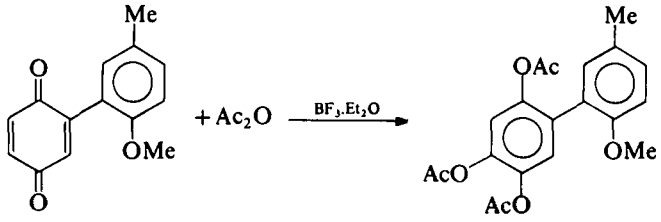
An interesting case involving Thiele–Winter acetoxylation conditions produced reductive acetylation (equation 132)[119] reminiscent of Fieser's work with 2-hydroxy-5-phenyl-1,4-benzoquinone[114].



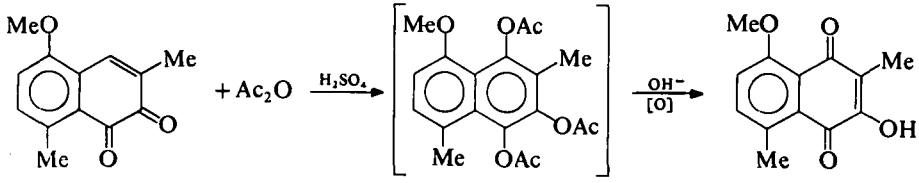
(132)

Noteworthy are two reports demonstrating that an *o*-methoxy group in an attached or fused ring does not have the fatal effect observed by both Gates[115] and McOmie[113] for the 4'-methoxyphenyl group. For example, as one step in a study of arylated quinones Cameron and his collaborators carried out an acetoxylation in which the reaction site is *para* to an aryl substituent (equation 133)[120]. The crude acetylated mixture was reacted with dimethyl sulfate in methanol and the corresponding tetramethyl ether isolated.

The conversion of a 1,2-naphthoquinone to the corresponding 2-hydroxy-1,4-naphthoquinone was accomplished in overall 56% yield (equation 134)[121].

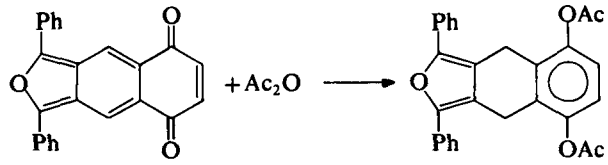


(133)



(134)

In their studies of quinones derived from *m*-diols in the naphtho [2,3-*c*]furan series Villessot and Lepage found that compound **48** undergoes reductive acetylation across the *m*-carbon atoms (equation 135)[122].



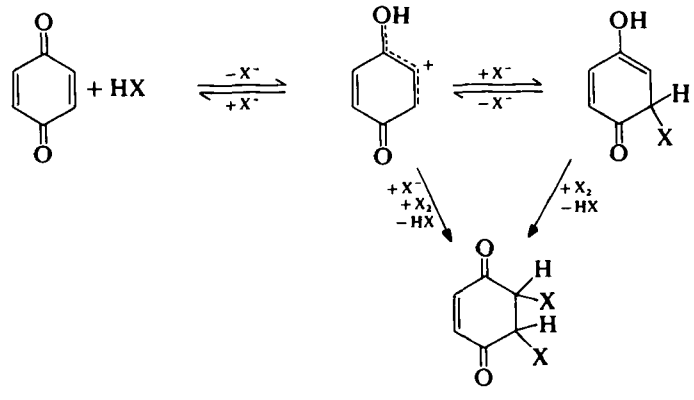
(135)

(48)

D. Addition of Inorganic Substances

1. Halogens and hydrogen halides

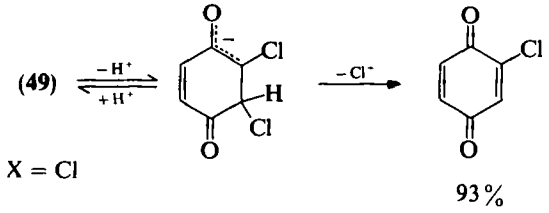
The haloquinones have played an increasingly important role in several areas (see especially Section V.A.2) and the reactions leading to such substrates have been examined in detail. Unlike most areas of Michael addition to quinones we have a rather detailed mechanistic picture for chlorine, bromine and bromochloride addition in acetic acid[123]. In elaborate product study de la Mare and his collaborators found the ratio of bromochloride/dibromide ratio to vary widely depending on the relative availability of bromine and chlorine. The only serious competing reaction is the addition of hydrogen halide, a very effective catalyst. No evidence of dichloro or acetoxy products could be obtained. Earlier reports of the kinetically controlled formation of the *trans*-dihalogeno-enedione were confirmed as well as extended to the mixed halogen. The proposed mechanism (equation 136) requires the first halogen to be attached nucleophilically while the second reacts electrophilically. The evidence does not require the involvement of a 1,2-adduct. The results obtained with 1,4-naphthoquinone show a similar pattern although competition from hydrogen halide addition appears to be less important. The authors point out that in synthetic applications there is no need to add the hydrohalic acid since its effect is very powerful and enough of it is supplied by other trace reactions.



(136)

(49)

The ethanolysis kinetics of hydrogen halide elimination from the dihalide (**49**) show a reaction approaching an *E*1cB mechanism (equation 137). Thus, the loss of a proton to solvent becomes the dominant feature and accounts for the relative rates of loss of HCl and HBr.

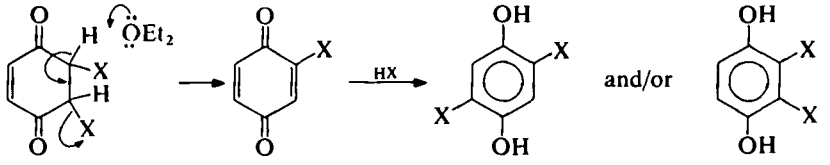


(137)

X = Cl

93%

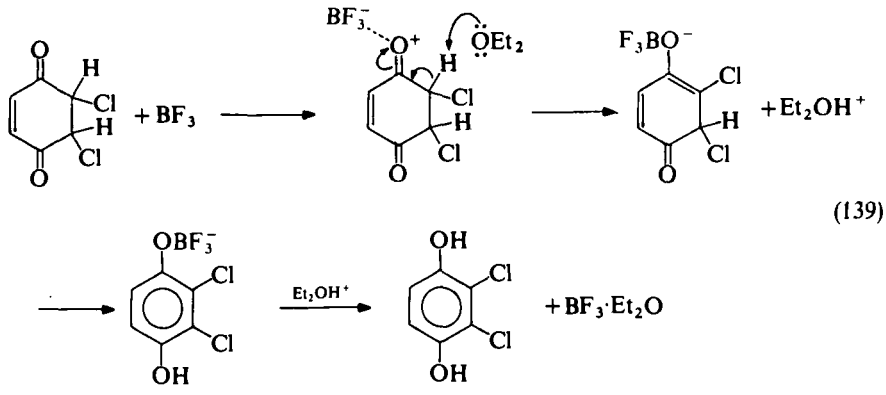
In connection with the mechanistic study just discussed the fine earlier work of Norris and Sternhell should be read[124]. For five 5,6-dihalocyclohex-2-ene-1,4-diones they found that all except 2,3-dichloro react by elimination–addition (equation 138). For that example a true keto–enol isomerization exists (equation 139).



(138)

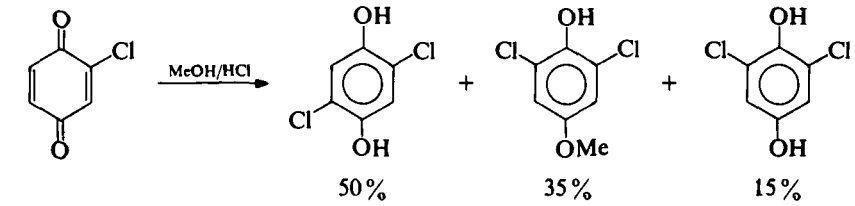
An earlier examination of the addition of hydrogen chloride to 1,4-benzoquinone and its 2-chloro derivative by Chaillet and his coworkers shows both an interesting involvement of solvent (methanol) and the utility of theoretical calculations[125]. In this solvent the normal addition product represents only a minor constituent (equation 140). Methanol also enters in a significant fashion the reaction with 2-chloro-1,4-benzoquinone (equation 141).

Consideration of the following array of potential intermediates (equation 142) and the application of Hückel, Hückel ω and Wheland polarization energy methods allowed good interpretations of the experimental results. Similar results were obtained for the 2-chloro

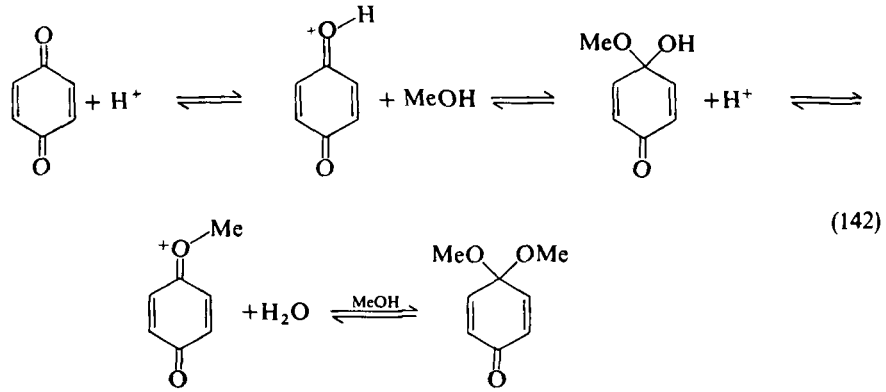


(139)

(140)



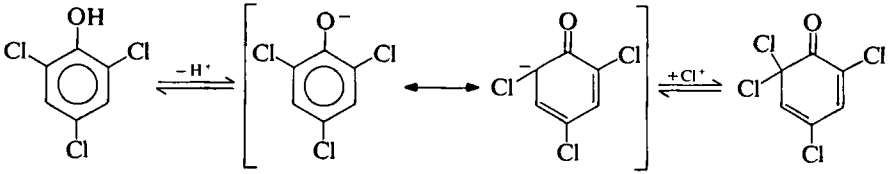
(141)



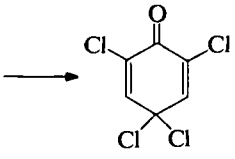
(142)

derivative, and a later report describes an analogous study of 1,4-benzoquinone monooximes[126].

Some rather surprising evidence concerning the more highly chlorinated 1,4-benzoquinones came to light in a study of the hydrolysis of 2,4,4,6-tetrachloro-2,5-cyclohexadienone (**50**) which results from the further chlorination of 2,4,6-trichlorophenol (**51**; equation 143)[127]. In the absence of chloride **50** reacts with water or dilute sulfuric acid to



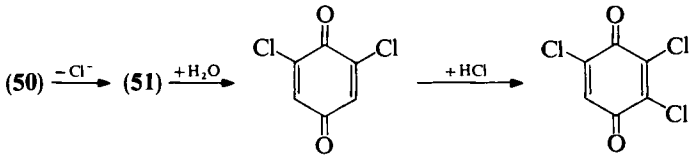
(**51**)



(143)

(**50**)

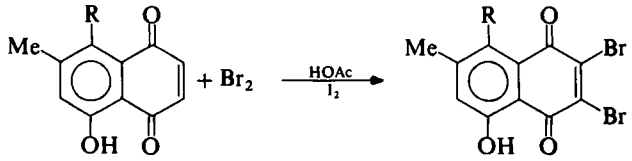
give a complicated mixture, but in hydrochloric acid significant amounts of **51** along with chlorinated quinones and hydroquinones can be identified (equation 144). The inter-



(144)

mediates **51** and 2,6-dichloro-1,4-benzoquinone occur only at short reaction times and the concentration of 2,3,5-trichloro-1,4-benzoquinone remains fairly constant.

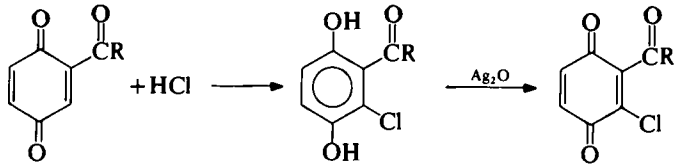
Several useful synthetic methods involving halogen have appeared in the literature. Laatsch has used halogenation–dehalogenation as an effective blocking and directing procedure in the synthesis of the natural product stypandron (equation 145)[128].



(145)

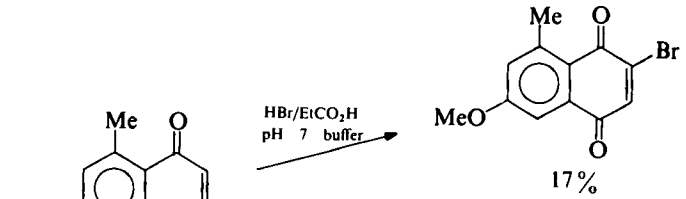
R = H,Cl, Br

Fariña and Valderrama have provided additional examples of the strong directive influence of electron-withdrawing substituents on nucleophilic addition to quinones (equation 146)[129]. The excellent yields and high regioselectivity of both additions along with the possibility of reoxidation to quinones should be of synthetic use.

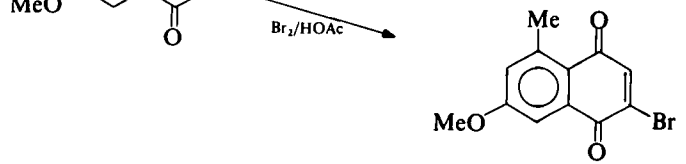


(146)

Cameron and his colleagues have applied bromination imaginatively in the synthesis of naturally occurring anthraquinones (equations 147, 148)[130]. The 3-bromo isomer was

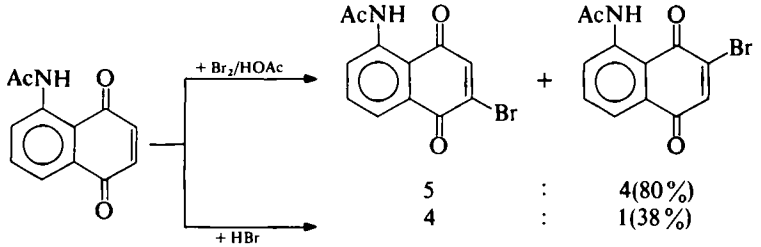


(147)



(148)

easily prepared, but in low yield, by hydrobromination and oxidation. Compounds with such groups present are of significance in directing subsequent cycloaddition chemistry (see Section V.A.2). This same group has studied these complimentary routes and confirmed that benzenoid substituents with strong electronic influence provide routes to the isomeric products[131]. Of greater importance is the observation that weaker groups, while not as discriminating, can still lead to synthetically useful methods (equations 149, 150). The 5-methyl substituent behaved differently and easily gave 60% 2-bromo product

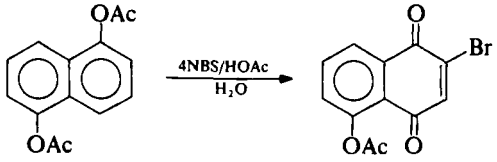


(149)

(150)

from bromination while hydrobromination produced only 15% of an inseparable 1:1 mixture of 2- and 3-bromo products.

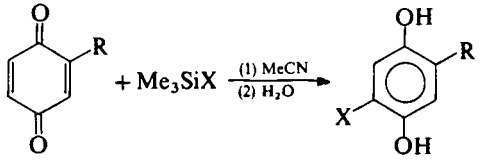
Other approaches to the synthesis of brominated naphthoquinones have been reported[132] and recently Jung and Hagenah have given evidence that the brominated naphthol **52** and the tribromonaphthalen-1-one **53** are both intermediates (equation 151)[133].



(151)

(52) (53)

A promising synthetic method for chloro- and bromo-1,4-benzoquinones has been suggested (equation 152)[134]. The yields with the limited range of substituents studied are



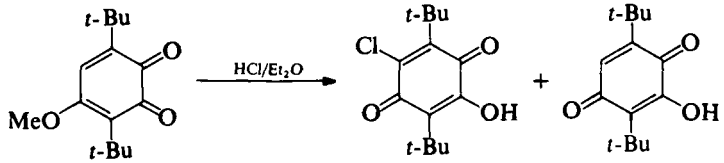
(152)

R = H, Me, Cl, OMe

good to excellent and the reaction can be applied to nascent 1,2-benzoquinones. A further modification involves treatment of the unhydrolyzed product with hexamethyldisilazane to form the disilyl ether. The authors rightly point out that this work should be studied in greater detail.

The synthesis of chloranil in nearly quantitative yield has been achieved by treating 1,4-benzoquinone with antimony(V) chloride[135]. Both 2,5- and 2,6-dichloro-1,4-benzoquinones are intermediates in the reaction.

In the specific instance of 3,6-di-*t*-butyl-1,2-benzoquinone there is, probably because of the serious steric hindrance of the carbonyl groups, a tendency towards reduction rather than acid addition. However, it has been found that in the equally special case of the 4-methoxy derivative of this quinone (54), hydrolysis of the methoxy group and addition of hydrogen chloride are the principal reactions (equation 153)[136].

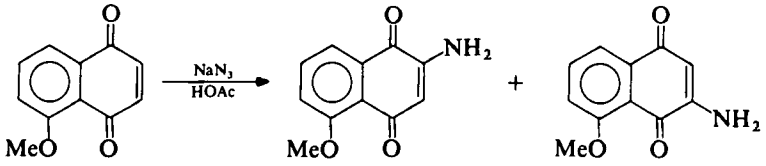


(153)

(54) 52% 36%

2. *Azides*

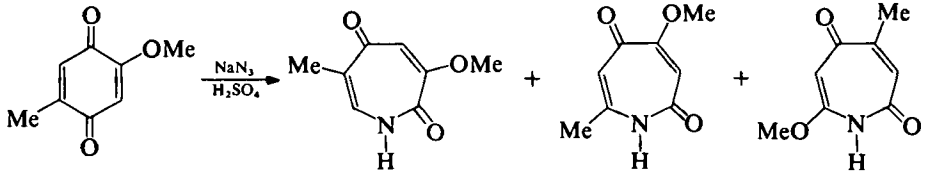
The need of a 3-aminojuglone derivative led Parker and Sworin to repeat earlier work by Thomson and his colleagues[137] concerning the regioselective addition of hydrazoic acid to



(154)

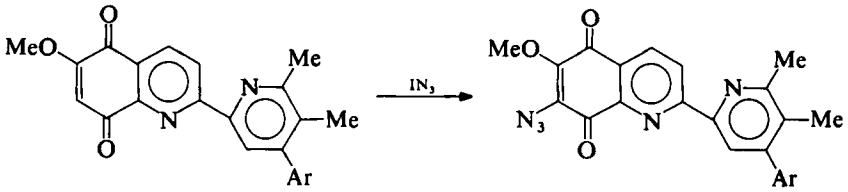
the 5-methyl ether (equation 154)[138]. They were able to show that both products are formed and that the 3-amino isomer predominates. The structures were established by unambiguous synthesis and detailed spectral evidence. Juglone and its acetate were also examined. The former compound gave only the 3-amino product (27%) and the latter a 4:1 preference for the same orientation. A very useful discussion of the confused history of these reactions is presented.

Rees and his collaborators found three of the four possible ring expansion products from the Schmidt reaction of 2-methoxy-5-methyl-1,4-benzoquinone and sodium azide (equation 155)[139]. All three compounds were isolated and studied, but only **55** showed appreciable aromatic character, i.e. can be considered an azatropolone.



(155)

Kende and Naegely have used iodine azide generated from iodine chloride and sodium azide to overcome a synthetic difficulty in the next to the last step of their model synthesis related to streptonigrin (equation 156)[140].



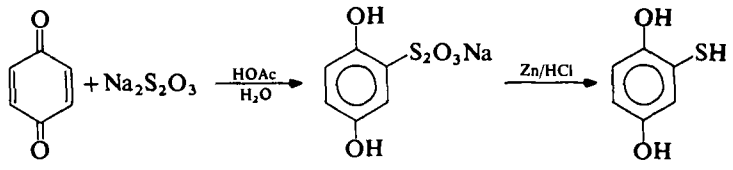
(156)

3. *Inorganic sulfur*

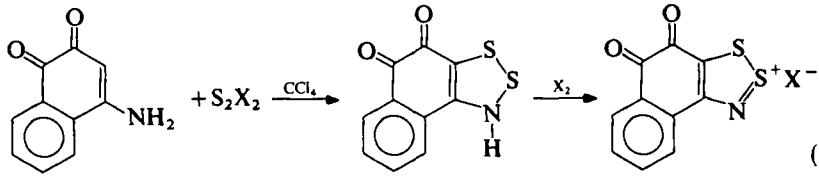
Nichols and Shulgin have used the method developed by Alcolay[141] as a starting point for the synthesis of some sulfur analogs of psychotomimetic amines (equation 157)[142].

An unusual heterocyclic system has been synthesized by the addition of S_2X_2 to the enamine bond in 4-amino-1,2-quinones (equation 158)[143].

Arai and his collaborators have carried out a series of mechanistic studies of the reactions between quinones and sodium sulfite[144-147] and sodium thiosulfate[148-150]. It is clear that, depending on the oxidation–reduction potentials of the quinone, either redox



(157)



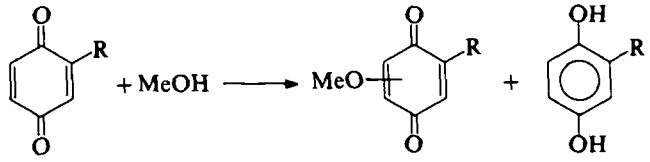
(158)

or addition chemistry is observed. Unfortunately these efforts are available only in Japanese at this time.

E. Oxygen Addition

1. The alkoxyquinones

The frequency with which quinones, or substances directly related to quinones, bearing oxygen functions occur in natural products has created surprisingly little interest in the study of alcohol addition. An exception to this sad picture is the useful investigation by Singh and Turner in which they examined methanol addition with and without Lewis acid catalysts (equation 159)[151]. Various 2-alkyl groups made very little difference in the



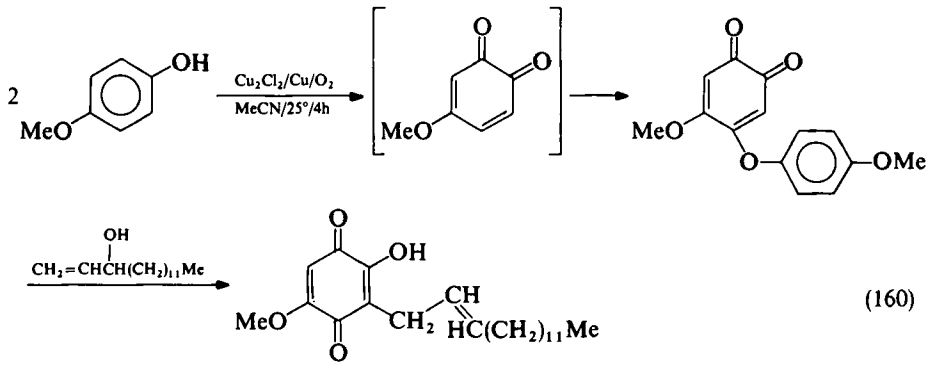
(159)

R = Me, Et, *s*-Bu, *t*-Bu, Bz

product distribution in the absence of catalyst. Similar results were obtained for the zinc chloride catalyzed reaction except for the two bulkiest substituents where only the 2,6-isomer was found. Under both conditions 1,4-benzoquinone gave the 2,5-dimethoxy product. In ethanol 2-methyl-1,4-benzoquinone showed essentially the same behavior as in methanol. Finally, 2-benzoyl-1,4-benzoquinone reacts with methanol under both experimental conditions to produce only the 3-methoxy product. Similar results have been reported by Fariña and Valderrama in their studies of the acetyl, methoxycarbonyl and cyano groups[129]. They also were able to add phenol and 4-methoxyphenol to 2-acetyl-1,4-benzoquinone in the presence of pyridine, but 4-nitrophenol failed to react. An earlier report by these investigators showed the best conditions for addition to be equimolar reactants in dry benzene[152].

A recent application of phenol addition to a nascent 1,2-benzoquinone provides an important intermediate in the alkylation of quinones (see Section IV.E)[153]. Displacement

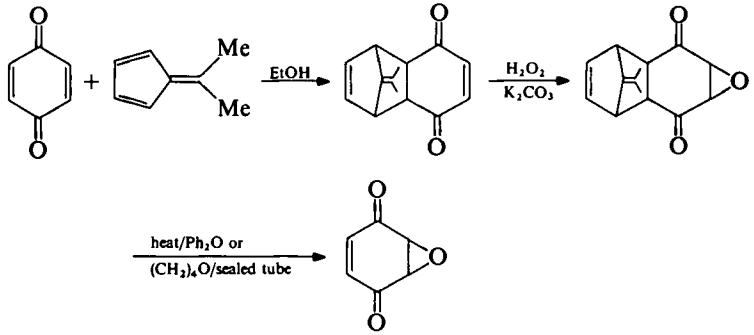
of the aryl ether by an allylic alcohol followed by a Claisen–Cope rearrangement allows the transformation of 1,2- to 1,4-quinones (equation 160).



(160)

2. *Epoxidation of quinones*

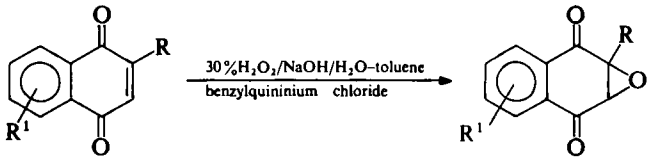
The preparation of most simple epoxy-1,4-benzoquinones is complicated and produces low yields, but Ichihara and his coworkers have developed a system based on retro-Diels–Alder chemistry which has demonstrated great versatility (equation 161)[154]. The



(161)

diene of choice is dimethylfulvene which releases the epoxide under milder conditions than cyclopentadiene; the mixture of *endo* and *exo* adducts are epoxidized without separation. Only three substituents are reported and while the yields for 1,4-benzoquinone and the 2-methyl derivative are near quantitative, 2-hydroxymethyl-1,4-benzoquinone gave at best 43 %. An earlier preliminary report of this chemistry indicated that the sealed tube method with lower boiling solvents gave improved results[155].

Pluim and Wynberg have made a detailed study of the synthesis of optically active epoxy-1,4-naphthoquinones (equation 162)[156]. With a variety of alkyl and a few aryl



(162)

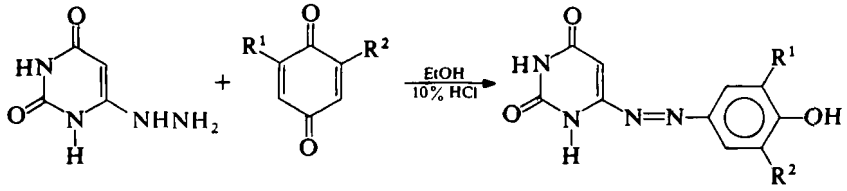
R = H, alkyl, c-C_6H_{11}, Ph, Bz, $CH_2CH = CMe_2$
R^1 = H, 5-, 6-, 7-Me, 5-MeO

substituents they used a phase-transfer oxidation method to obtain good yields of epoxides with a substantial excess of one enantiomer. Both the yield and the enantiomeric excess are excellent in certain cases; for example, 2-phenyl-1,4-naphthoquinone was converted to its epoxides in 92% yield with a 45% excess of one enantiomer. Some discussion of the effect of substituent and the absolute configuration of the products is presented.

III. CHEMISTRY AT THE QUINONE CARBONYL

A. Nitrogen Addition

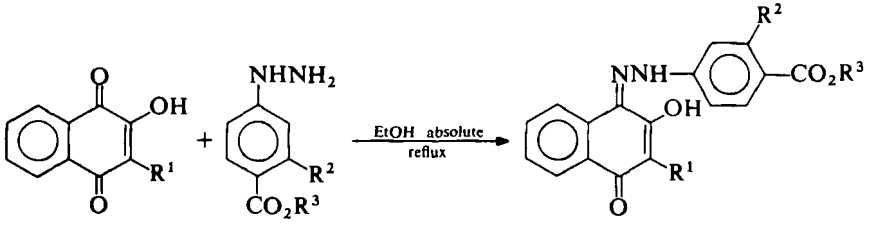
To a large extent the recent chemistry of quinonoid carbonyl groups has dealt with the preparation of non-quinonoid products, thus, a great many opportunities exist for profitable study. For example, Wright and Brown prepared several arylhydrazinouracils starting with 6-hydrazinouracil and 1,4-benzoquinones (equation 163)[157]. The yields from



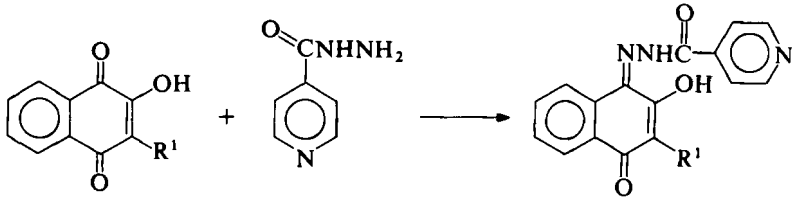
R^1,R^2 = H, Me, Cl, Br (163)

unsymmetrically substituted quinones were approximately 60% and isomerically pure. By implication the more soluble isomer was not isolated.

Roushdi and Habib have shown that a wide variety of 2-hydroxy-1,4-naphthoquinones form hydrazines at the 1-carbonyl in good to excellent yields (equation 164)[158]. A similar reaction occurs with isoniazide (**56**, equation 165).

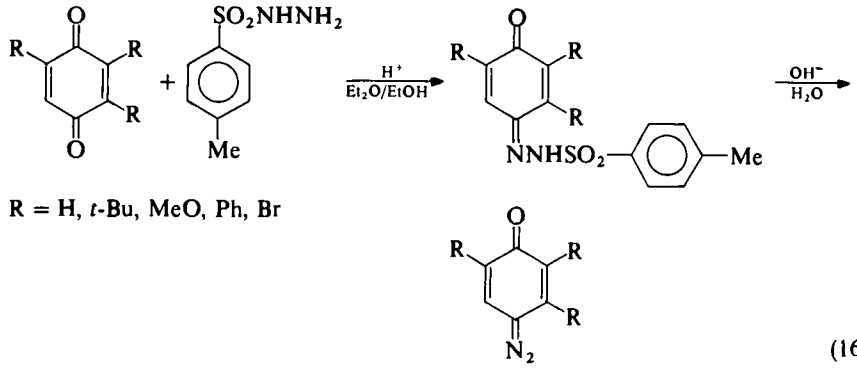


R^1 = alkyl, CO_2Et, R^2 = H, OH, R^3 = H, Et 59–94% (164)



(56) (165)

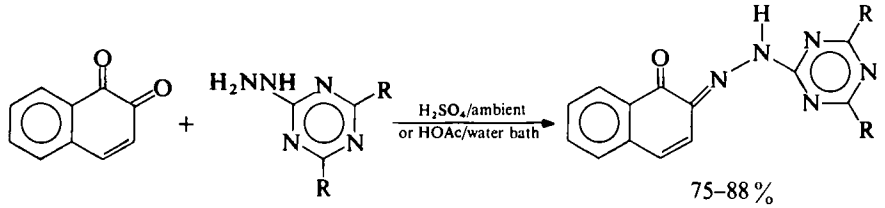
Several phenyl-substituted 1,4-benzoquinones have been converted to the azo derivative through reaction with *p*-toluenesulfonhydrazide followed with aqueous potassium hydroxide (equation 166)[159]. The yields are good (ca. 85%) except for the trisubstituted



R = H, *t*-Bu, MeO, Ph, Br (166)

cases in which two phenyl groups are present (30%). The intermediate hydrazones were not isolated, but could have been if necessary. Boron trifluoride etherate is also satisfactory as a catalyst with dry tetrahydrofuran as solvent.

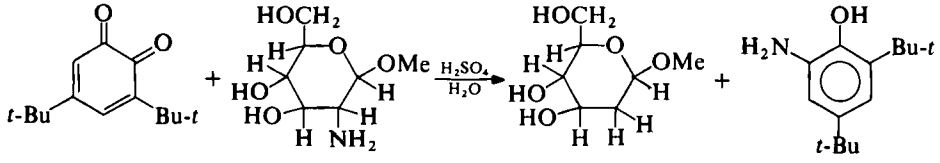
Synthetic dyes derived from 1,2-naphthoquinone have been prepared by reaction with substituted hydrazino-*s*-triazines (equation 167)[160]. The NMR spectra indicate the



R = NHAc, NMe_2, OMe, $N(CH_2)_5$, $N(C_2H_4)_2O$, NHPh (167)

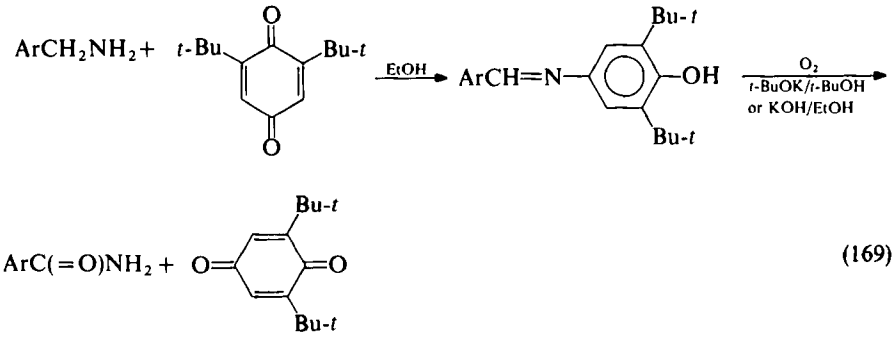
hydrazone form shown, but the mass spectra indicate conversion to azonaphthols under electron bombardment. The reaction at the 2-carbonyl is consistent with these spectra.

The method devised by Corey and Achiwa[98] has been applied to the oxidative deamination of aminoglucosides (equation 168)[161]. Yields of 30–35% are typical.



(168)

An analogous method involving a hindered 1,4-benzoquinone provides an attractive route for the conversion of a methylamino group into an amide (equation 169)[162]. The intermediate imine is found in yields of 40–80%. The yield of amide varies greatly. The base obviously plays an important role, but from the small number of examples studied there is

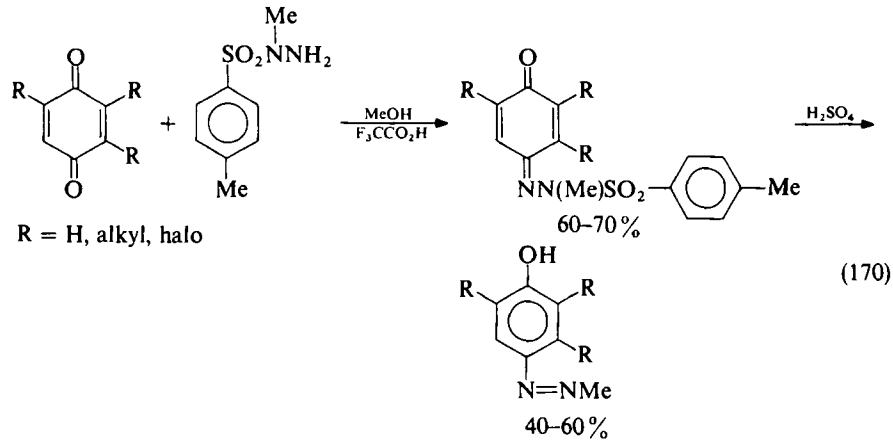


(169)

Ar = Ph, 4-Tol, 4-An, 4-ClC_6H_4, 3-pyridyl, 2-furyl

no clear pattern. With the proper selection of conditions good yields (60–85%) can be obtained.

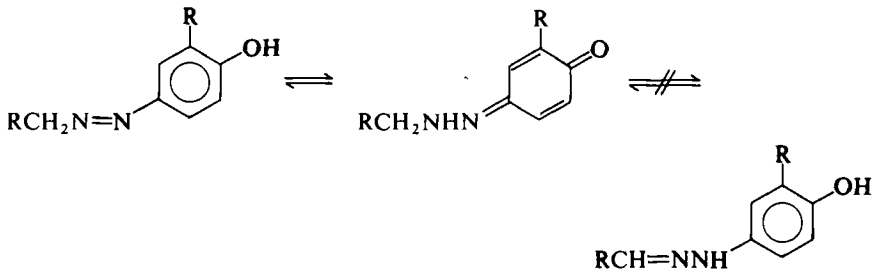
Another application of the tosylhydrazones is found in a convenient synthesis of 1-(4-hydroxyphenyl)-2-methyldiazenes (equation 170)[163]. In addition to the synthetic work,



R = H, alkyl, halo

(170)

investigation of tautomerism in these compounds shows the presence of certain forms and the absence of others (equation 171). The same chemistry takes place with 2-methyl-1,4-naphthoquinone.



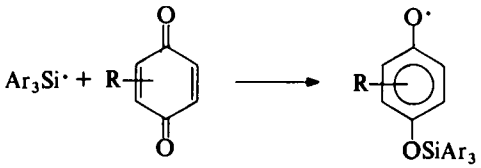
(171)

B. Silyl and Organolithium Additions

Neumann and Neumann have reported in great detail their studies of the reduction of quinones with bis(trimethylsilyl)mercury and confirmed the radical mechanism of this efficient process[164]. Similar results were obtained by Adeleke and Wan for chemically generated triarylsilyl radicals[165]. The mechanism proposed is supported by other published observations (equation 172). With 2,6-di-*t*-butyl-1,4-benzoquinone the ESR

$$(t\text{-Bu})_2O_2 \xrightarrow[PhH]{h\nu} 2\ t\text{-BuO}^{\cdot}$$

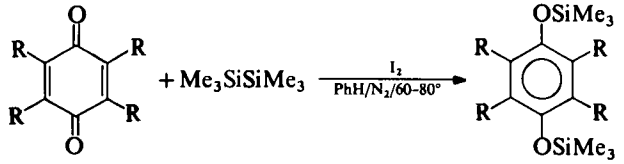
$$t\text{-BuO}^{\cdot} + Ar_3SiH \longrightarrow t\text{-BuOH} + Ar_3Si^{\cdot}$$



(172)

spectra of both isomeric radicals were observed unlike the 2,6-dimethyl case. It appeared to the authors that such substituted quinones are excellent spin traps for silyl radicals.

The application of reductive silylation in synthesis as a protective method is attractive for quinonoid systems (equation 173)[166]. The very high yields (85–100%) are coupled with

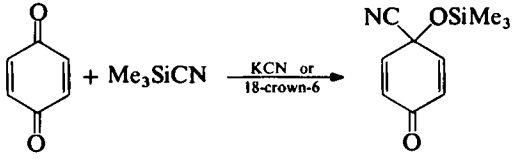


(173)

R = H, Me, Cl, —CH=CHCH=CH—

mild conditions and reasonable reaction times. An alternative approach to these protected quinones has been suggested, but only two examples are given and the yields are somewhat lower[167].

A particularly exciting variant of the silylation theme has been advanced by Evans and his colleagues in the addition of trimethylsilyl cyanide (57, equation 174)[168]. Their work

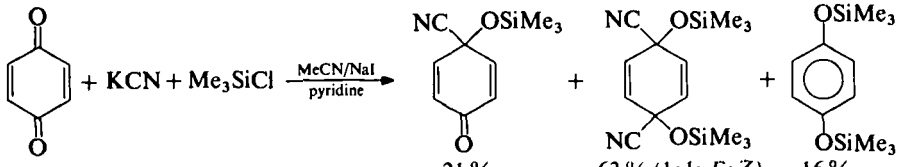


(57) 80%

(174)

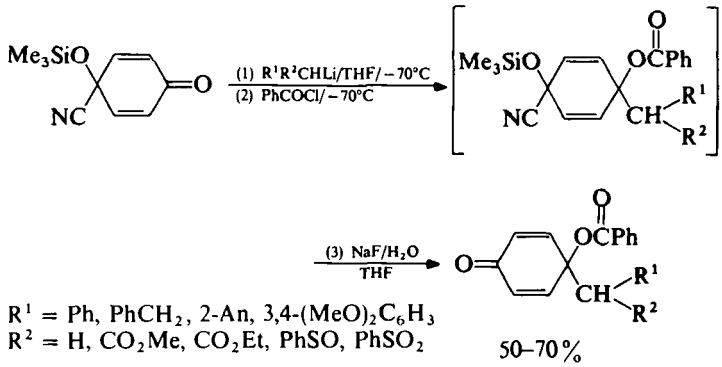
shows that only the quinones show selectivity towards catalysts, i.e. are inert towards Lewis acids. These studies have been reported in greater detail and applied to additional quinonoid substrates[169–171].

Some disadvantages of the use of cyanide might be overcome by its generation *in situ* and such a scheme has been developed (equation 175)[172]. Unfortunately, the one reaction with a quinone produced a mixture of products, but more work was promised.



(175)

Cyanosilylation followed by addition of organolithium reagents to the second carbonyl, and finally esterification is an efficient method of synthesis for *p*-quinol benzoates (equation 176)[173]. The reaction is carried out at low temperatures to avoid a facile



(176)

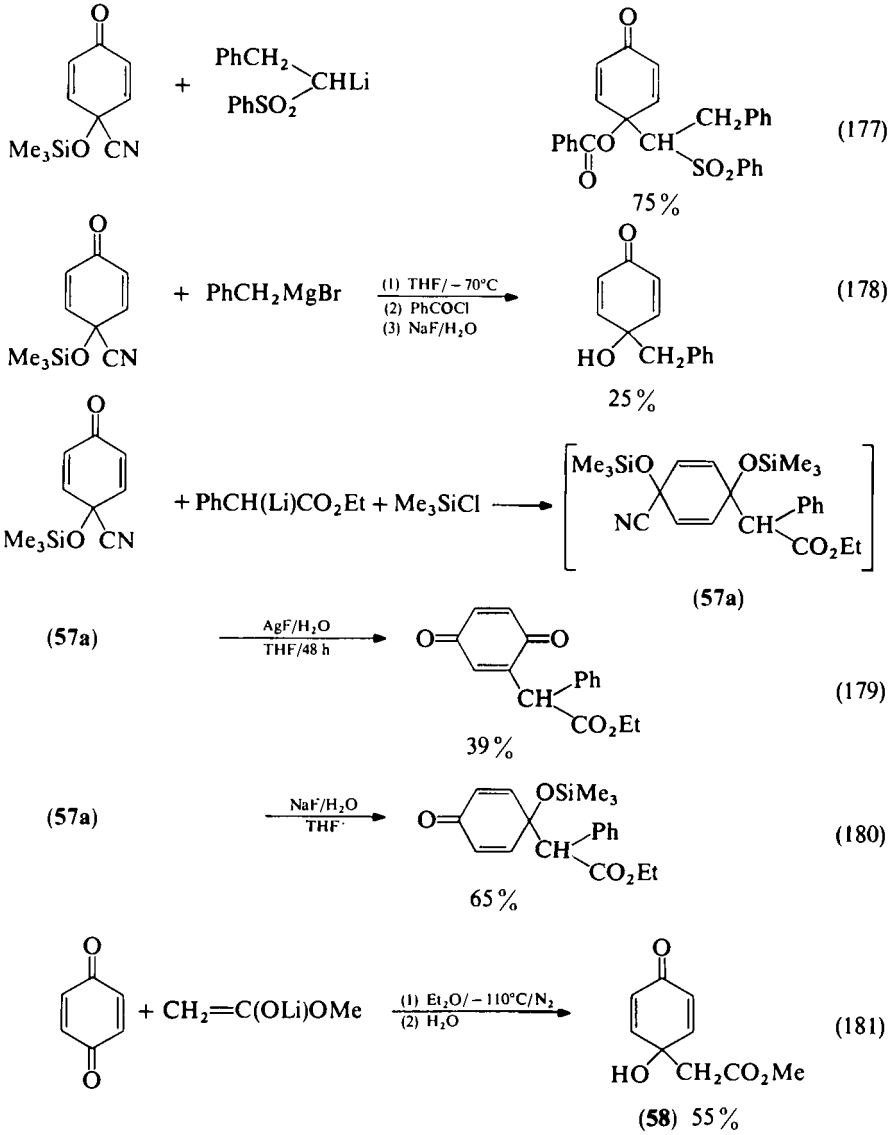
dienone–phenol rearrangement. With phenyl and sulfoxyphenyl substituents the two diastereomers are readily separated. Several related reagents were explored in a preliminary fashion and give evidence of a versatile synthetic method (equations 177–180).

In the past ten years great progress has been made on the 1,2-addition of carbanions, mostly organolithium compounds, to quinones. Such reactions are often highly selective with above average yields; an example is the direct synthesis of jacaranone (**58**, equation 181)[174].

Moore and his students made the earliest report of this method when they developed a clever synthesis of 2,5-disubstituted 1,4-benzoquinones (equation 182)[175]. The yields are very reasonable and the potential for the development of new synthetic pathways is considerable.

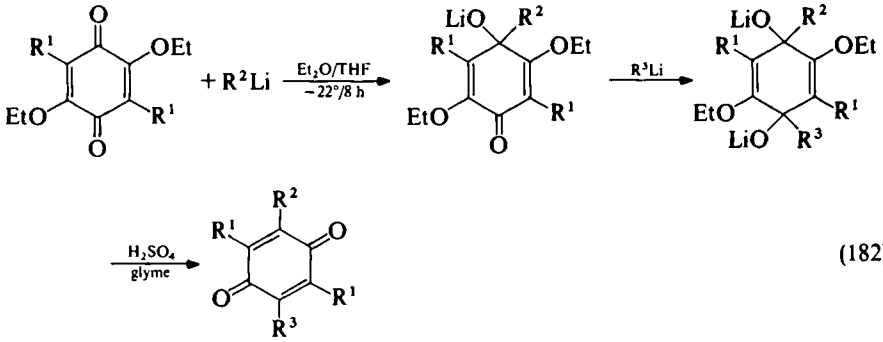
Fischer and Henderson showed that in 1,2-additions (equation 183)[176], the solvent plays an important role in directing the reaction to mono- or di-addition and that the major product in the latter case has *cis* stereochemistry. The yields are excellent although the selectivity of **59/60** is not very great. In a later paper the authors demonstrated that a variety of alkyl lithium compounds add to quinones in satisfactory yield[177].

Liotta and coworkers examined the problem of poor regioselectivity in unsymmetrical quinones[178]. They made the argument that the site of attack should be dependent on the size of the carbanion including its degree of solvation. The test they devised involved the methyl carbanion in two different systems; one sterically, the other electronically controlled (equations 184, 185). With a few limitations involving very bulky carbanions, similar results were demonstrated for several combinations of quinones and carbanions.



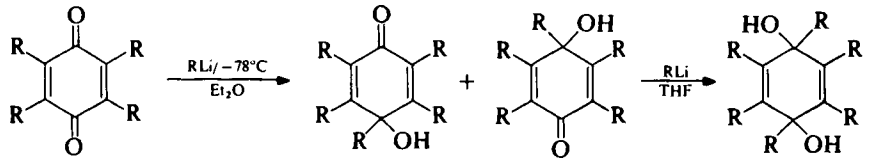
Moore and his coworkers continued their original study cited above and determined that for the synthesis of unsymmetrical quinones the first substituent introduced must be alkynyl[179]. This requirement is not much of a limitation when one considers the possibilities inherent in the carbon–carbon triple bond. Additional groups studied include 4-methoxyphenyl, phenylalkynyl and 3-hydroxypropylalkynyl. Yields in the 45–65% range were realized for either symmetrical or unsymmetrical quinones.

The utility of such an approach to 2,5-disubstituted-1,4-benzoquinones was illustrated in the synthesis of a ring system containing important elements of mitomycin (**61**, equation



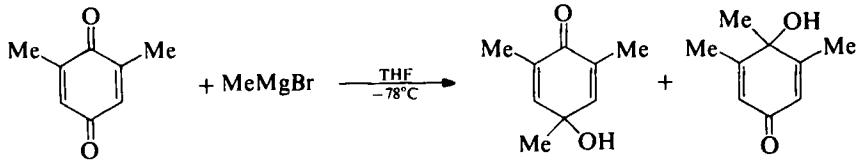
50–65%

R^1 = H, Cl; R^2 = R^3 = Me, Ph, $PhCH_2OCH_2C{\equiv}C$ (182)

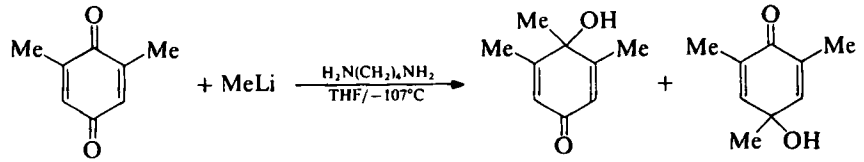


(59) (60)

R = Me, Bu, *t*-Bu, Ph (183)



62% 10% (184)

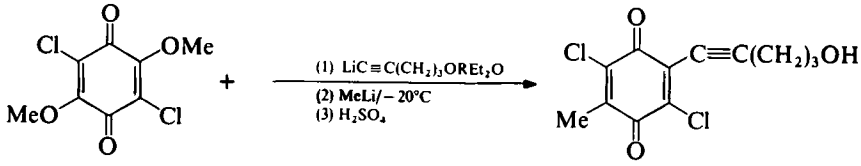


87% 9% (185)

186). Some aspects of the stereoselectivity shown are certainly worthy of further investigation along with more extensive application of the overall strategy.

A useful variant of these methods involves 1,2-benzoquinone (equation 187)[180]. The importance of the 2-oxygen-5-hydrocarbon pattern in naturally occurring quinones and its potential in drug synthesis is widely recognized.

One especially promising method for the introduction of an α,β-unsaturated nitrile substituent failed completely with 1,4-benzoquinone (equation 188)[181]. It certainly deserves additional attention.



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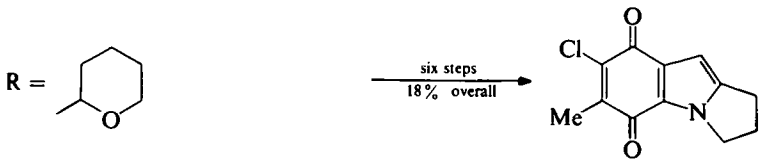
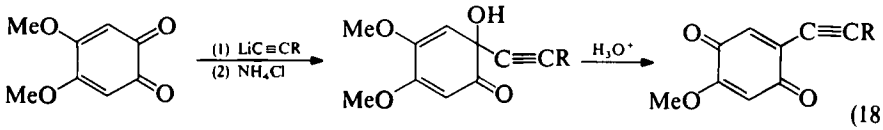


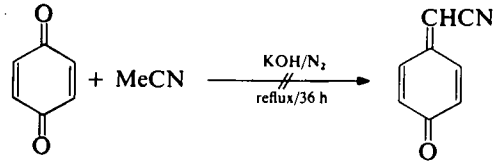
(61)



(62) 70–95% 85–95%

(187)

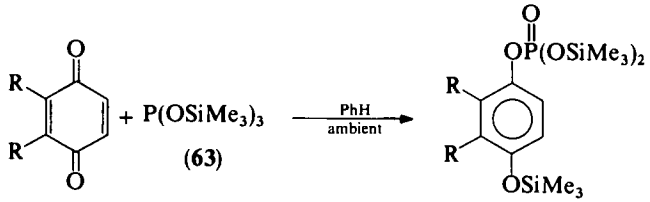
R = Bu, Ph, CO_2Et, $MeC{=}CH_2$, $(CH_2)_4C{\equiv}CH$, OMe, CH_2NEt_2



(188)

C. Ramirez and Wittig Phosphorous Chemistry

An important modification of the pioneering work by Ramirez and his students involves the reductive addition of tris(trimethylsilyl) phosphite (**63**) to 1,4-benzo- and naphthoquinones (equation 189)[182]. The combination of high yields and ease of hydrolysis of the silylated ether suggests further study.

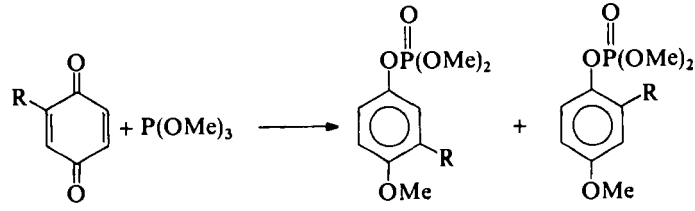


86%, 92%

(189)

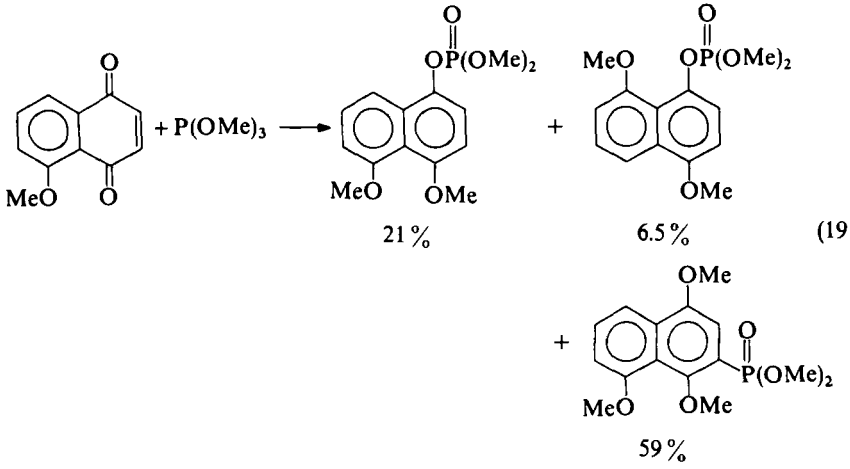
R = H, —CH=CHCH=CH—

Duthaler and his coworkers examined the reaction of ten monosubstituted 1,4-benzoquinones with trimethyl phosphites (equation 190)[183]. Control of regioselectivity is



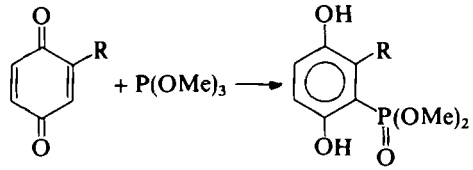
(64) (65) (190)

determined by the expected variables; for example, bulky groups such as *t*-butyl and trimethylsilyl give good yields of the 3-substituted product **64**, while the electron-donating methoxy group directed largely to the 2-substituted product (**65**). Solvent also plays an important role in controlling the product distribution with the non-polar benzene giving the best selectivity. With juglone methyl ether and in cases involving strong electron-withdrawing groups modest yields of ring phosphorylation are observed (equations 191, 192). This new understanding was put to use in a critical intermediate step directed toward



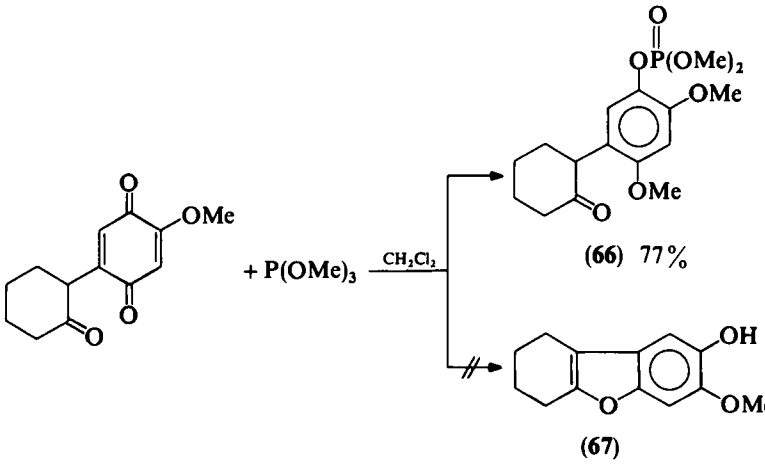
21% 6.5% (191)

59%



R = COPh, CO_2Me 43%, 48% (192)

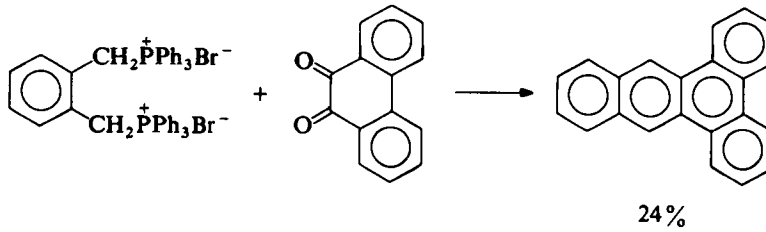
the synthesis of the antibiotic Lysolipin I. The appropriate quinone formed the desired product (**66**) without any detectable amount of its regioisomer or the tetrahydrodibenzofuran (**67**; equations 193, 194).



(193)

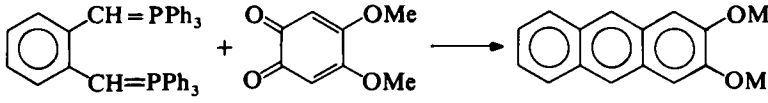
(194)

The extensive interest in synthesis of polycyclic aromatic compounds has made the bis-Wittig reaction attractive in spite of low yields and difficult reaction conditions. Minsky and Rabinovitz have shown that under phase-transfer catalysis conditions the phosphonium salt acts both as reagent and catalyst (equation 195)[184]. The yields are not



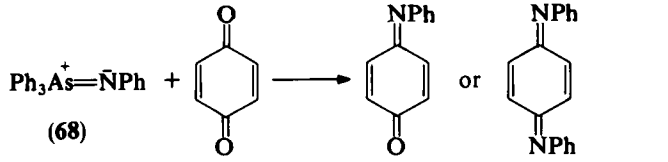
(195)

unreasonable when compared with methods far more demanding in terms of maintaining an inert atmosphere and anhydrous conditions. The chief limitation is with quinones sensitive to aqueous base. A complementary procedure under non-basic conditions extends the synthetic application of this chemistry to these more delicate substrates (equation 196)[185].



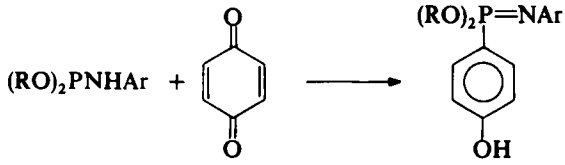
(196)

Frøyen has examined the reactions of triphenylarsine phenylimine (**68**) with quinones and found chemistry similar to the Wittig reaction resulting in the production of mono- or diimines (equation 197)[186]. The differences in reactivity between these two reagents are discussed; unfortunately no yields are given.



(197)

A very active Russian research group led by Pudovik has made important contributions in the study of phosphinous amides with quinones (equation 198)[187]. They obtained



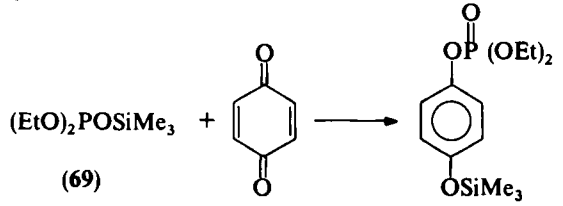
(198)

R = Et, Pr, Bu
Ar = Ph, 4-An, 4-Tol, Naphthyl

74–90%

excellent yields of esters as opposed to carbon–phosphorous bond formation. These intermediates undergo thermal rearrangement to the analogous 4-ethers. In a later publication the occurrence of one-electron transfer and the formation of radical ions was demonstrated by ESR studies[188].

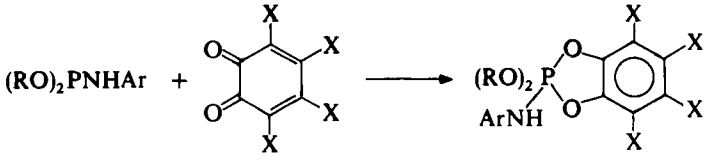
The addition of diethyl trimethylsilyl phosphite (**69**) to 1,4-benzoquinone produces an 81% yield of the phosphate ester containing the 4-trimethylsilyl ether group (equation 199)[189].



(199)

(69)

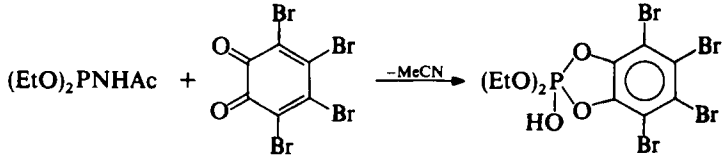
Finally, the reaction of these versatile reagents with the halo-*o*-quinones generally results in the formation of the phosphorous heterocyclic system 2,2-dihydro-1,3,2-benzodioxaphosphole (**70**; equation 200)[190]. If the starting material contains an acetamido



(200)

(70) 70–75%

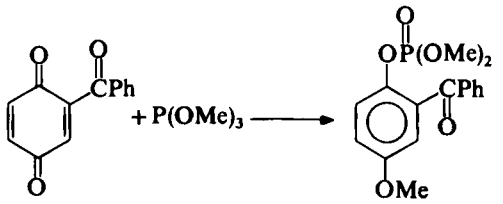
group the initial adduct loses acetonitrile to form an intermediate which is slowly transformed to a hydroxyphosphate (**71**; equation 201).



(201)

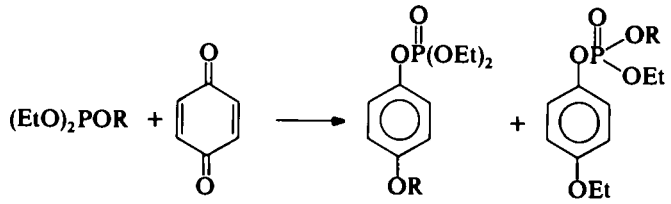
(71)

Arbuzov and his colleagues studied the reductive addition of trimethyl phosphite to 1,4-benzoquinones bearing strong electron-withdrawing groups (equation 202) and found the more highly hindered arylphosphate ester formed; no yields are given[191].



(202)

Mixed phosphite esters generally give good yields of the ether corresponding to the more stable carbonium ion (equation 203)[192]. For example, with the ethyl and propyl cations the



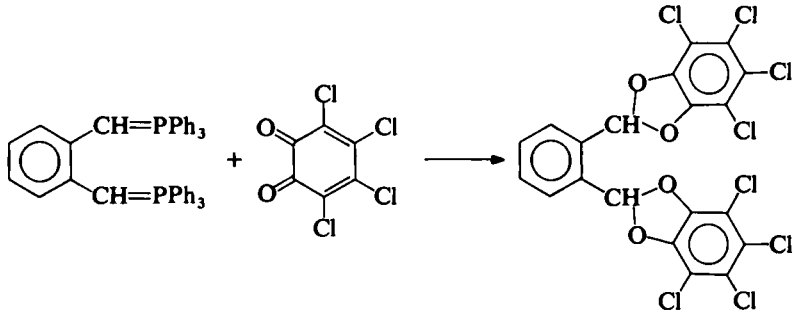
(203)

R = Pr, Allyl, Bz, *t*-Bu

product ratio is 3:1; not too unlike the 2:1 ratio of the alkyl groups. When the alkyl group other than ethyl would be expected to form a much more stable cation the *para*-ether formed from it is generally formed in good yield. An exception is the *t*-butyl case where a significant quantity of 2-methylpropene is also formed.

D. Brief Notes

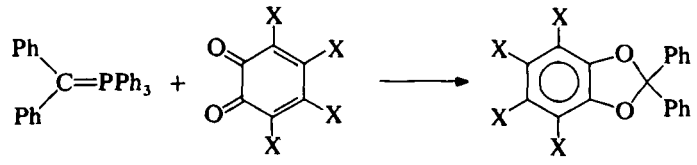
During the course of a study of the bis-Wittig reaction described earlier[185] Nicolaides and Litinas were surprised to find that reaction between the ylide and *o*-chloranil produced the bisbenzodioxole (72, equation 204). This has also been reported for both *o*-chloranil



(204)

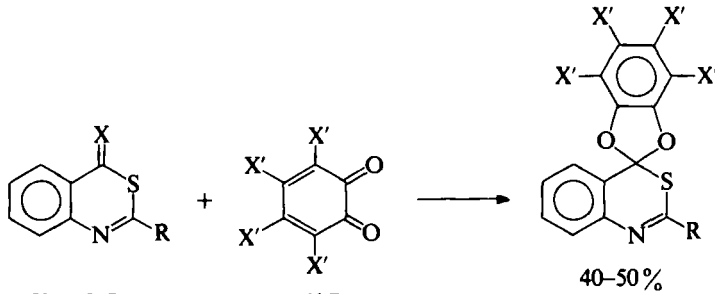
(72)

and *o*-bromanil in reactions with several mono-triphenylphosphoranes (equation 205)[193]. The authors note the similarity between these reactions and that of diazomethane with 1,2-quinones.

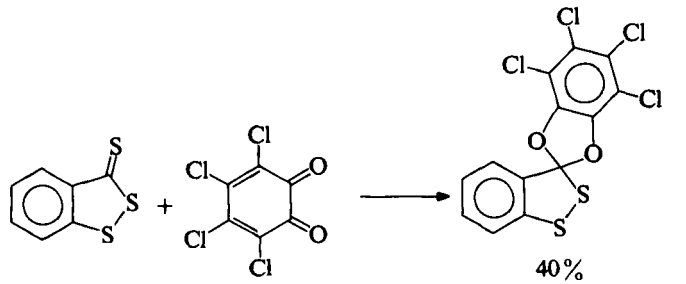


X = Cl, Br 92%, 95% (205)

A new class of spiranes has been prepared by Latif and his colleagues using heterocyclic thiones and halogenated 1,2-benzoquinones (equations 206, 207)[194, 195]. The yield is not as



X = O,S X′ = Cl,Br 40–50% (206)



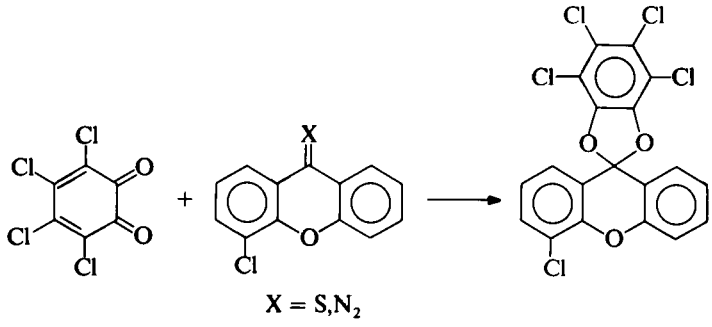
(73) 40% (207)

high in the case of 3*H*-1,2-benzodithiole-3-thione (73), but all products are only obtainable by this route and show promising chemical attributes beyond the range of this review.

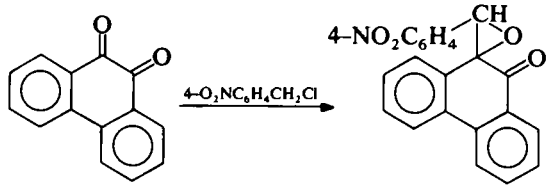
More recently Zeid and colleagues have provided experimental evidence of the similarity between the reactions of *o*-chloranil with a thione and diazoalkanes (equation 208)[196]. The range of chemistry displayed by the spiro products was also usefully expanded.

Awad and his coworkers have studied the Darzens reaction of quinones and shown that while both phenanthrenequinone and chrysenequinone react with 4-nitrobenzyl chloride they give rather different chemical outcomes (equations 209, 210)[197, 198].

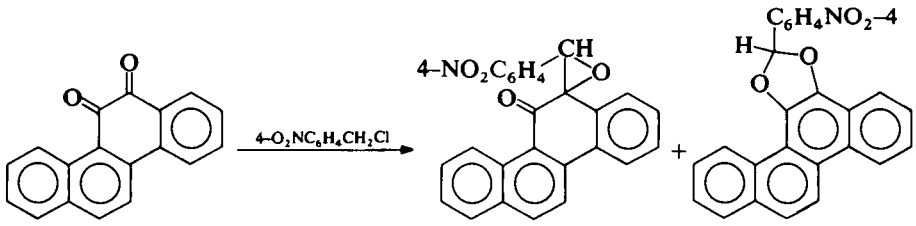
In an effort to prepare fluorine-substituted quinodimethanes bis(trifluoromethyl)ketene was added to 1,4-benzoquinone (equation 211)[199]. The initial product undergoes the dienone–phenol rearrangement and adds a second mole of the ketene to produce the observed γ-lactone in 60% yield. Attempted reactions with chloranil, fluoranil and anthraquinone which could be expected not to rearrange failed even at high temperatures.



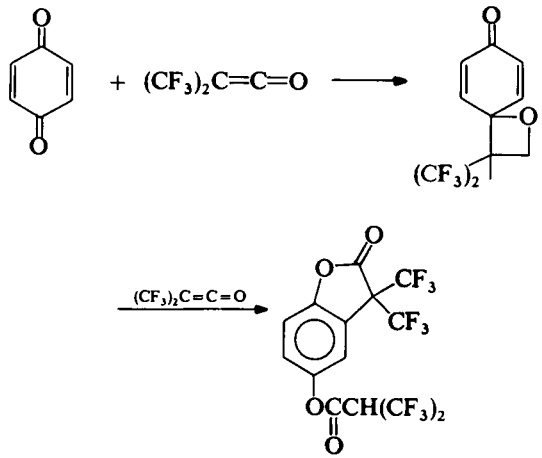
(208)



(209)

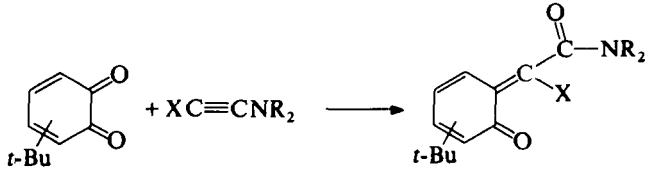


(210)



(211)

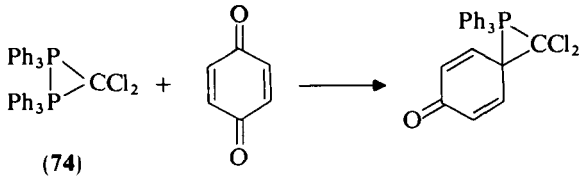
A more successful effort to prepare mono-carbon analogs of quinones is found in the work of Verboom and Bos who added *t*-butyl-1,2-benzoquinones to acetylenes in good yield (equation 212)[200].



(212)

X = Ph, SMe; R = Et, *i*-Pr, pyrrolyl

The addition of a cyclic diphosphirane (**74**) to quinones gives low yields of the intriguing cyclic phosphirane derivatives (**75**; equation 213)[201].



(213)

(74) (75)

IV. THE ALKYLATION OF QUINONES

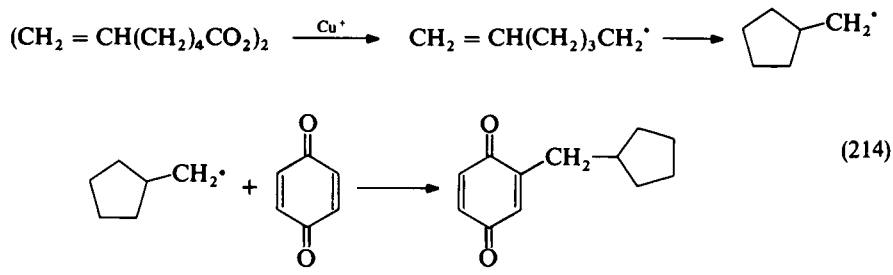
A. Mechanism of Radical Additions

The need to attach hydrocarbon chains to quinones for the synthesis of natural products continues to stimulate activity in the study of radical alkylations. In a detailed review of radical substitution reactions Dou and his collaborators included a useful table of relative reactivities for quinones with methyl radicals (Table 3)[202].

TABLE 3. Reactivity of various quinones toward methyl radicals at 65 °C[202,203]

Quinone	Relative rates
1,4-Benzoquinone	15 200
2-Methyl-1,4-benzoquinone	10 400
2,5-Dimethyl-1,4-benzoquinone	6500
Duroquinone	790
2-Methoxy-1,4-benzoquinone	8000
2-Chloro-1,4-benzoquinone	27 000
2,5-Dichloro-1,4-benzoquinone	39 200
2,6-Dichloro-1,4-benzoquinone	38 400
Chloranil	300
1,4-Naphthoquinone	3400
2-Methyl-1,4-naphthoquinone	4100
2,7-Dimethyl-1,4-naphthoquinone	4100
2,3-Dimethyl-1,4-naphthoquinone	550
2,3-Dichloro-1,4-naphthoquinone	90
2-*t*-Butylanthraquinone	90

Citterio has been especially active, along with his colleagues in the determination of rates of addition of alkyl radicals to 1,4-benzoquinone[204]. They have demonstrated the importance of nucleophilic polar effects on these reactions using the cyclopentylmethyl radical formed from the 5-hexenyl radical (equation 214). The very high rate observed

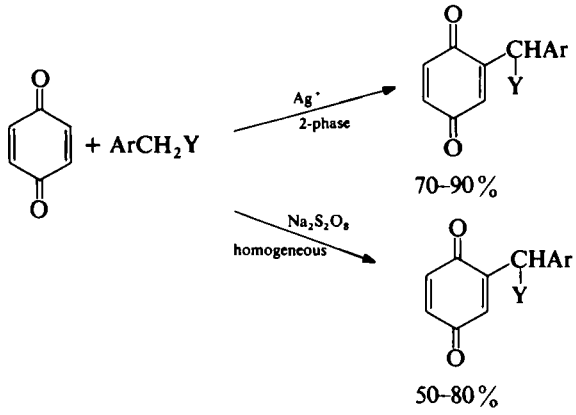


(214)

(9×10^6 M^{-1} s^{-1} at 40°C) is not found with electrophilic radicals of the amino or oxygen types. These observations are further supported by the increased reactivity of quinones bearing electron-withdrawing substituents. Several examples are given which extend the synthetic utility of the method.

More evidence for the importance of polar effects in quinone–radical reactions is found in a detailed comparison with several conjugated alkenes[205]. Discussion of the probable contribution by a charge transfer interaction is phrased in terms of recent orbital theory calculations.

The synthetic utility of radical benzylation of quinones has been significantly increased by Citterio who showed that either homogeneous or two-phase reaction conditions can be employed (equations 215, 216)[206]. With 2,5-dimethyl-1,4-benzoquinone and 1,4-naph-



(215)

(216)

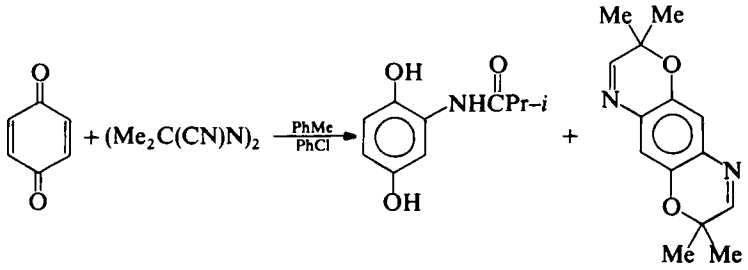
Ar = Ph, 2-Tol, 4-Tol, 4-An, 4-*i*-PrC_6H_4
Y = H, Me, OH, Ac

thoquinone the results are not as promising because of lower yields and less discrimination between mono- and dibenzylation; no unsymmetrical quinones were studied.

The competition between alkyl and aryl radicals has been studied by Citterio[626] and Asmus[627]; these data will be discussed in connection with the arylation of quinones (see Section VI).

A detailed kinetic study of the *n*-decane–dicyclohexylperoxydicarbonate system, which produces *s*-decyl radicals, has been made[207]. The inclusion of di-*t*-butyl and diphenyl quinones makes this treatment an important complement to earlier studies. The rate constants and inhibition coefficients determined are in agreement with analogous studies of simpler systems and account for the widespread use of these quinones as inhibitors in radical polymerizations.

Finally, the extensive use of azobisisobutyronitrile and 1,4-benzoquinones for initiation and inhibition of polymerization reactions has continued to create interest in their interactions[208]. Both non-polar (toluene or chlorobenzene) and polar (acetonitrile) solvents were employed and the nature of the products changed dramatically. The former systems produced simple crystalline products after work-up (equation 217) while the latter



(217)

gave only quinonoid resins. In both cases there was no evidence of a nitrile or ether in the products and only hydroquinone–nitrogen bonds could be detected. This evidence requires that the 2-cyano-2-isopropyl radicals react in the dimethylketenimine form (76,

$$Me_2\dot{C}CN \longleftrightarrow Me_2C{=}C{=}N^{\cdot} \qquad (218)$$

(76)

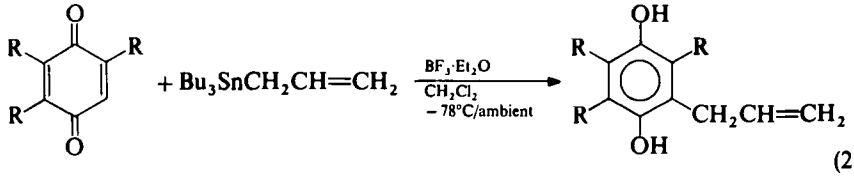
equation 218). It also casts serious doubt on the earlier reports of hydroquinone mono- and diethers from this reaction[209].

B. Alkylation with Organotin, Nickel, or Silicon Reagents

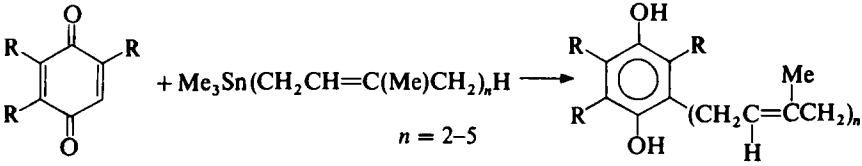
In their efforts to synthesize members of the vitamin K and coenzyme Q families, the group of Maruyama, Naruta and Uno, have made a major contribution. The basic chemistry involves alkylation with trialkylallyl or polyprenylstannanes in the presence of a Lewis acid (equations 219, 220)[210,211]. Good to excellent yields of product are isolated; however, no unsymmetrical quinones were reported. Boron trifluoride etherate is clearly superior to the other Lewis acids examined and starting the reaction at low temperature is also important.

Naruta[210] has provided compelling evidence that the initial product involves 1,2-carbonyl addition (equation 221) followed by a dienone–phenol rearrangement. He also examined the regioselectivity of unsymmetrical allylic groups and found that steric effects in either the quinone or the allylic reagent lead to a marked preference for α-addition (equation 222).

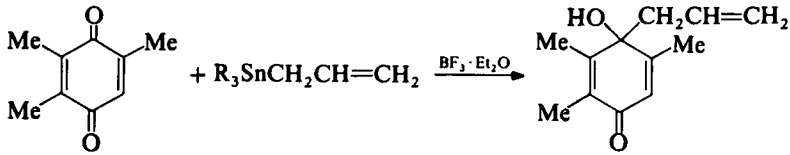
This chemistry has been extended to the synthesis of 4-allyl-1,2-naphthoquinones where the regioselectivity depends on the nature of the quinone 3-substituent (equations 223, 224)[212]. Unlike the 1,4-quinones these substrates show either preliminary 1,2-addition or direct 1,4-addition to the enone (77, equation 225). Both electronic and steric factors are significant in determining the preferred course of the reaction.



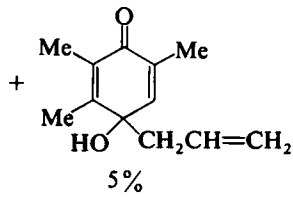
(219)

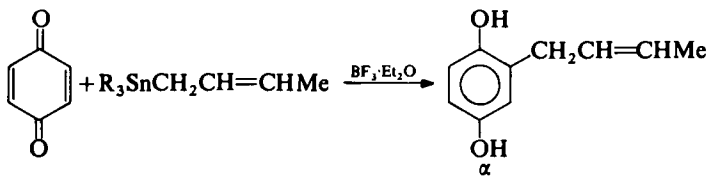


R = H, Me, —CH=CHCH=CH—, MeO (220)

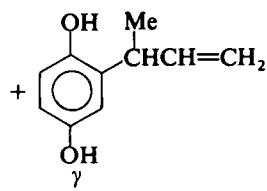


(221)

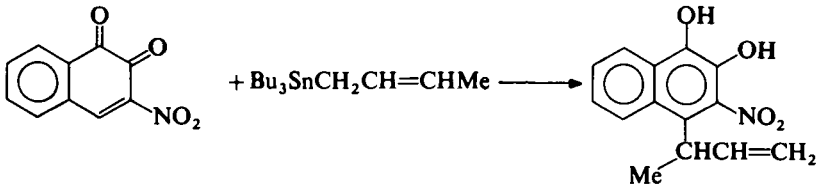




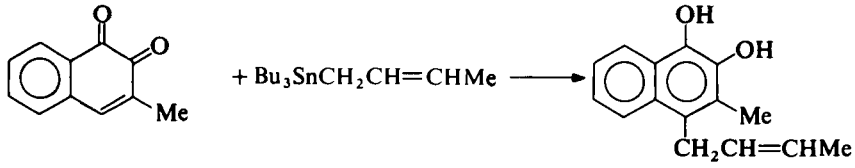
(222)



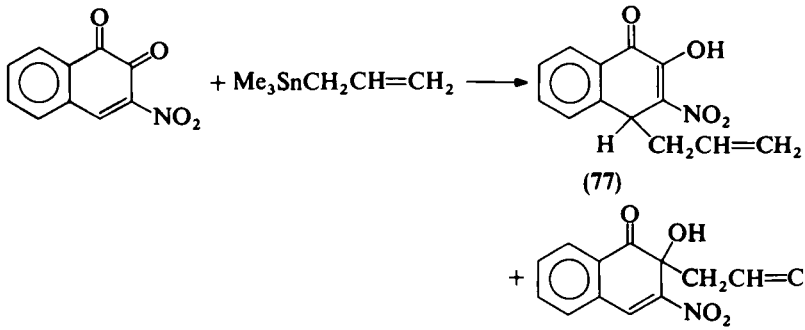
These workers have successfully applied these reactions, with many useful extensions, to the synthesis of a variety of complex, naturally occurring quinones[213–218]. Especially noteworthy contributions include: the inclusion of 1,2-benzoquinones[216], the addition of conjugated dienes without accompanying Diels–Alder chemistry[217] and addition to quinones containing the highly reactive formyl, acetyl, or methoxycarbonyl groups[218].



91% (89% total) (223)

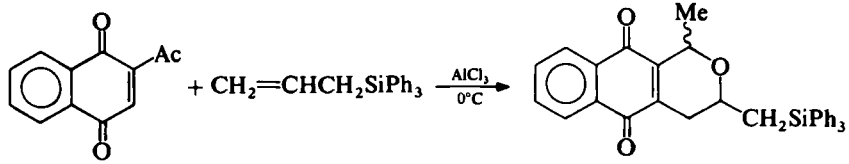


93% (75%total) (224)



(225)

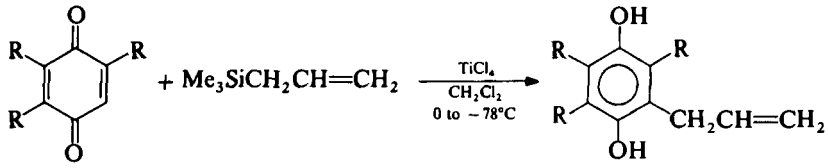
An interesting modification of these tin reagents is found in the allylation of 2-acetyl-1,4-naphthoquinone with allyltriphenylsilane (equation 226)[219]. The spontaneous cyclization



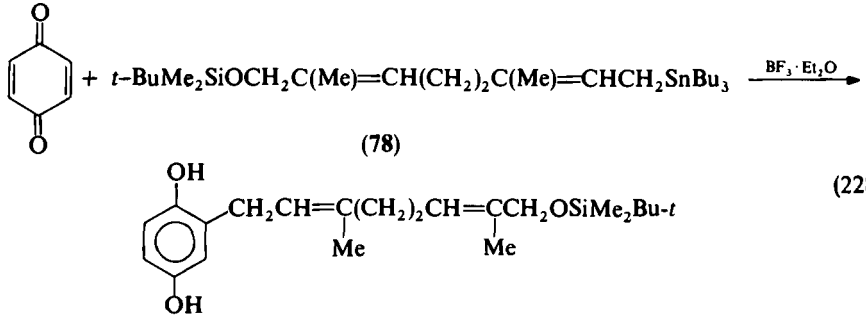
61% (226)

of the presumed intermediate makes this reaction of special interest in the synthesis of pyranonaphthoquinones. Hosomi and Sakurai have also investigated the use of silicon compounds in the allylation of quinones (equation 227)[220]. They found average yields of hydroquinone products except for 2,6-dimethoxy-1,4-benzoquinone which gave excellent yields of the more hindered *p*-allylquinol.

An especially intriguing reaction was carried out by Mori and coworkers involving an unconjugated allylic tin diene which also contained a siloxy group (**78**, equation 228)[221].



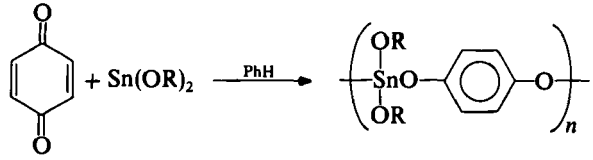
R = H, Me, MeO, —CH=CHCH=CH— (227)



(78)

91%

Tin(II) compounds containing a SnOC system have been prepared and react with 1,4-benzoquinone to give essentially quantitative yields of a reductive addition polymer (equation 229)[222].



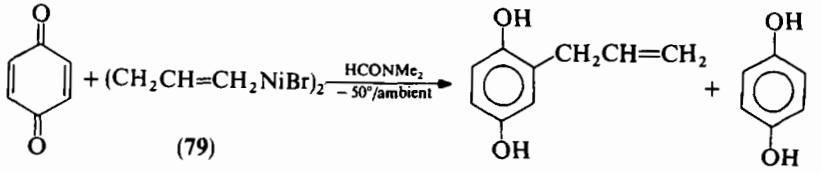
(229)

R = $(CH_2)_2NMe_2$, C(Me)=CHCOMe

Hegedus has examined a complimentary route to allylhydroquinones using π-nickel bromide complexes (**79**, equation 230)[223-225]. In all cases equal amounts of allylation and reduction are observed and quinones with a reduction potential more negative than − 70 V do not react. The correlation of the allylation site with the carbon of highest spin density makes it likely that electron transfer is followed immediately by coordination and alkyl transfer. Convincing evidence for allylquinol intermediates is presented in a subsequent and more detailed report[226]. The properties of these isolated, but relatively unstable, compounds was determined and the range of quinones extended. In conjunction with other alkylation methods the procedure proved to be especially versatile[227]. This chemistry has been applied to the synthesis of some naphthoquinone antibiotics and methods for trapping enolate intermediates with carbon electrophiles developed[228].

C. Alkylation by Radicals from Decarboxylation Reactions

Torssell and Jacobsen have developed a useful method related to the much earlier work of Fieser. Using silver ion and peroxydisulfate they were able to generate alkyl radicals from carboxylic acids (equation 231)[229]. These reactive species are effective alkylation



(79) 48% 47%

(230)

$$S_2O_8^{2-} + Ag^+ \rightarrow Ag^{2+} + SO_4^{2-} + SO_4^-$$
$$Ag^{2+} + RCO_2^- \rightarrow Ag^+ + CO_2 + R^\cdot$$

40–80% (231)

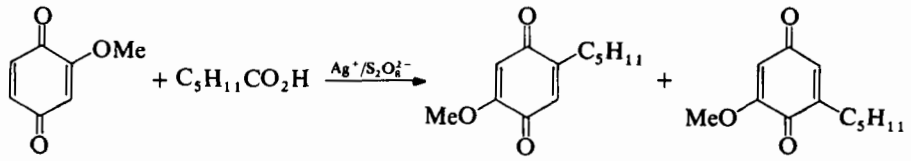
R = *i*–Pr, *t*–Bu, $EtOCH_2$, Bz, $PhOCH_2$

agents for quinones. Only one unsymmetrically substituted quinone, 2-methyl-1,4-benzoquinone, was reported and it gave roughly random amounts of the three isomeric products.

TABLE 4. Isomer distribution in the radical pentylation of monosubstituted 1,4-benzoquinones[229,230]

Substituent	2-Pentyl, 3-R	2-Pentyl, 5-R	2-Pentyl, 6-R
Me	25	40	35
MeO	5	68	27

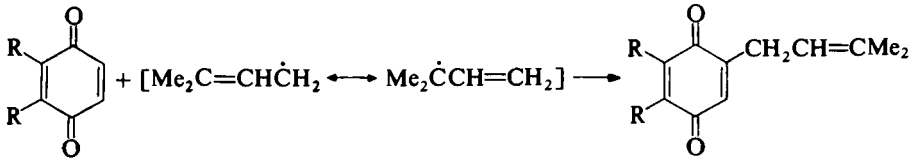
In a later paper they reported the preparation of the natural product primin (**80**, equation 232)[230]. Comparison of the isomeric distribution for monosubstituted 1,4-benzoquinones shows the stronger influence of the methoxy group and indicated the



34% (**80**) 13%

(232)

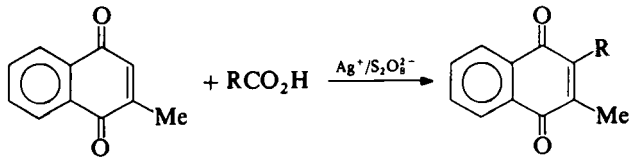
nucleophilic character of the radical involved (Table 4). Low yields of all three dipentyl 2-methoxyquinones were also obtained. Where the radical generated could be expected to react in more than one form only one product was observed (equation 233). These yields



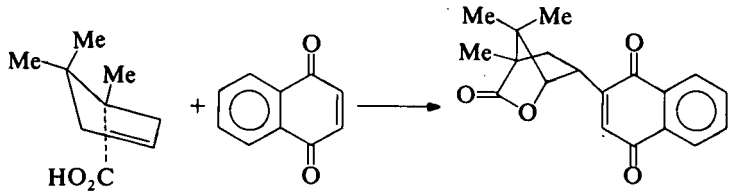
R = H, —CH=CHCH=CH— 34%, 58% (233)

leave some questions to be answered as does the observation that the decarboxylation of α, β-unsaturated acids in the presence of quinones gave only recovered starting material.

These studies have been extended to include cycloalkyl radicals where it was found that steric hindrance is extremely important. Fair yields of simple ring substitution products are obtained (equation 234), but only one product of reasonably complicated structure was produced in quite a few attempts (equation 235)[231].

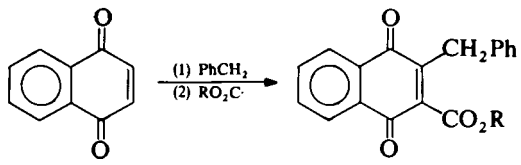


R = *c*-Pr, *c*-Bu, *c*-Pen, *c*-Hex 37–56% (234)



41% (apparently *endo*) (235)

Efforts to use this radical chemistry for the introduction of chains containing an ester group using the monoesters of oxalic acid met with limited success with naphthoquinone (equation 236)[232]. Such intermediates provide an attractive alternative entry to the naphthacene quinones.

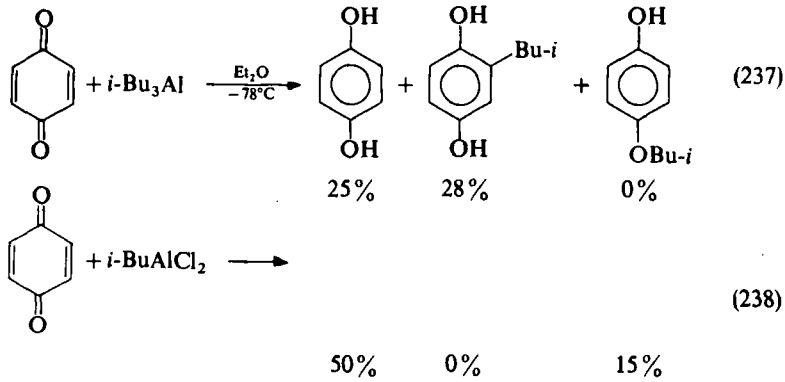


R = Me, Et 64%, 80% (236)

A variety of natural product syntheses using this decarboxylation chemistry have been reported[233-238]. In general yields have been satisfactory and certain developmental efforts are noteworthy: dicarboxylic acid esters[235], cyclopropyl radicals[236] and additional quinone substituents[238].

D. Quinones and Organoaluminums

Studies with aluminum compounds represent a recent interest. The chief reaction product with most alkylaluminum reactants is the corresponding hydroquinone[239]. Depending on the number of the alkyl groups present in the aluminum compound, ring substitution or monoether formation can occur (equation 237, 238). The authors propose



and support a carbanionic 1,4-addition mechanism for the carbon–carbon bond product and a radical 1,6-addition for ether formation. With chloranil higher yields of ether are obtained and the product ratio is dependent on both the structure of the aluminum reagent and the temperature (Table 5)[240]. Traces of ring substitution products are obtained. This aspect of the chemistry has been expanded to include a variety of alkyl groups and quinones (Table 5)[241]. The clear trends show yields dependent on the electron affinities of the quinone and that methylaluminum dichloride leads only to reduction.

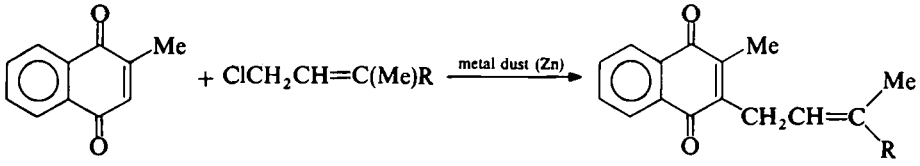
TABLE 5. Yields of reduction and 4-alkoxyhydroquinones from the reactions of alkylaluminums with 1,4-benzoquinones[240, 241]

Quinone	Aluminum	T (°C)	Hydroquinone (%)	Ether (%)
Unsubst.	Et_3	−78	64	6
Unsubst.		0	56	41
Unsubst.		25	65	18
Unsubst.		100	86	0
Unsubst.	Et_2Cl	−78	51	27
Unsubst.	$EtCl_2$	−78	23	53
Unsubst.	$BuCl_2$	−78	35	43
Unsubst.	*i*-$BuCl_2$	−78	52	12
2,5-Cl_2	$EtCl_2$	−78	9	59
2,6-Cl_2			12	60
2,3,5-Cl_3			13	67
2,3,5,6-Cl_4			23	58
1,4-Naphtho-			26	44

Alberola and his coworkers have made extensive investigations of the interaction of organoaluminum compounds and quinones[242]. They have added a great deal of detail to our understanding of this chemistry and shown that in certain instances useful yields of ring alkylation can be obtained[243]. In addition these workers have examined triphenylaluminum[244] and tribenzylaluminum[245], finding similar chemistry and raising questions about its possible future development along synthetic lines.

E. Miscellaneous Metal Catalyzed Alkylations

Tachibana studied the synthesis of vitamins K_1 and K_2 using phytyl and geranyl chlorides and various metallic dusts (equation 239)[246]. He found that good yields (60–

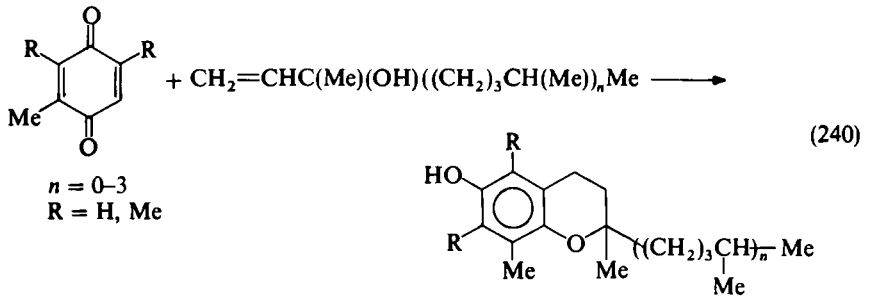


$R = C_6H_{11}, C_{16}H_{33}$ (239)

65%) of the desired product can be obtained with zinc in tetrahydrofuran and that no reduction of the quinone occurs. The by-product from reaction at the 2-methyl position is well limited in this process. Finally, the order of reactivity of various metal dusts is: Zn > Pd > Fe > Ce > Sn > Cu.

Further application of this chemistry has been reported and a variety of naturally occurring quinones prepared[247]. The range of quinone substituents was increased and while the yields are not great the starting materials and process make it an attractive approach.

Good to excellent yields of tocopherols, including vitamin E, are obtained using copper–zinc powder in the presence of formic acid (equation 240)[248]. Various isoprenyl alcohol-related compounds were used.

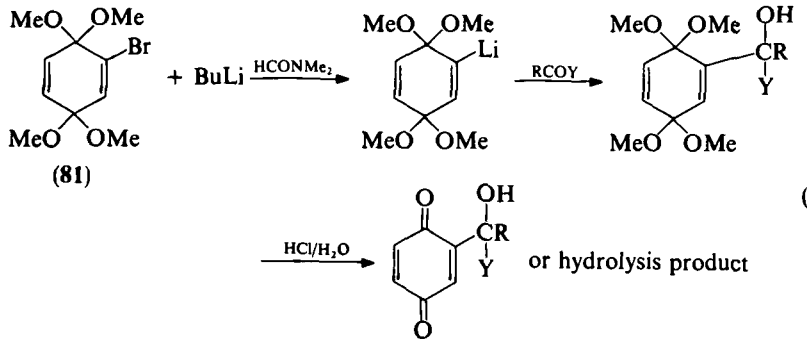


(240)

The use of zinc-amalgam or palladium have both been proposed for the prenylation of 1,4-benzoquinones or their corresponding hydroquinones[249]. Yields appear to be comparable to the other related studies already cited, but the possibility of working with either the oxidized or reduced starting material suggests this approach should be examined further.

Palladium has been shown to be an effective catalyst for the methylation of quinones by methylcobalt complexes[250]. The authors claim yields as high as 70%, but 30% or less is the rule.

A particularly exciting application of organolithium chemistry has been proposed and deserves more extensive study and application (equation 241)[251]. The oxidation of 2-bromo-1,4-dimethoxybenzene provides a good route to the quinone ketal (**81**) which reacts smoothly with lithium compounds.

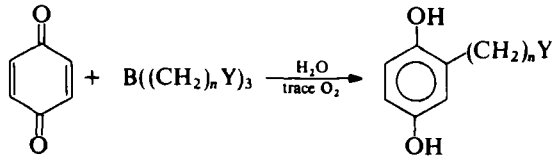


(241)

Y = H, R′, OR, Cl, NR_2

F. Hydroboration of Quinones

Kabalka has extended his earlier study to include chloro, cyano, methoxy, and ester groups in the alkylating agent (equation 242)[252]. The yields of substituted hydroquinone

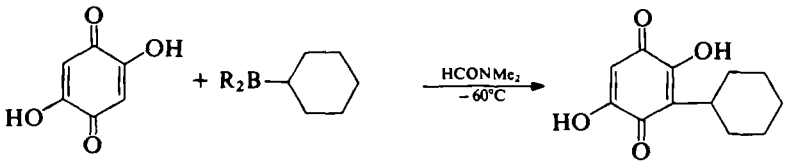


(242)

n = 3, 4, 10; Y = Cl, CO_2Et, CO_2Ph, CN, MeO

are all nearly quantitative, but the syntheses of the required trialkylboranes are subject to electronic effects which produce isomers. The products are generally easy to separate by gas chromatography and the difficulty can be minimized using one of several alternative hydroborating agents available.

An attempt to prepare 3-substituted 2,5-dihydroxy-1,4-benzoquinones by hydroboration showed that the quinone rather than hydroquinone is produced (equation 243)[253].



(243)

The yield of the desired product is low as a result of polyalkylation and hydroxyl group displacement. However, the presence of a large excess of trialkylborane in dimethylformamide or protection of the hydroxy groups gave good results. The latter approach resulted in the reduced product.

The hydroboration procedure is also applicable to the preparation of mole scale amounts of alkylhydroquinones[254]. Yields of 70 to < 90% were obtained for alkylations involving ethyl through dodecyl chains. Several branched chain groups were also prepared; however, it should be noted that both 2,4,4-trimethylpentene-1 and 2,4,4-trimethylpentene-2 gave the 1-pentyl product. Much longer reaction and workup times are required for the higher homologs.

V. CYCLOADDITION TO QUINONES

A. The Diels–Alder Reaction

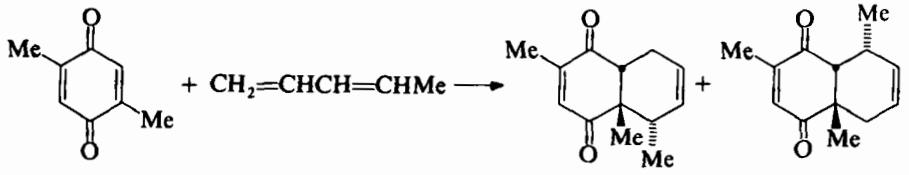
1. Theoretical studies

In recent years there has been a great deal of interest in the synthesis of quinonoid natural products and the Diels–Alder reaction has been employed to great advantage. This utility has had the happy consequence of supporting a continued high level of interest in the mechanistic details of this family of reactions. As a result of these two concurrent efforts, in several cases by the same research group, one finds quinones playing a role in the theoretical study of the process in general. The number of literature references to quinones in Diels–Alder reactions is so large and diverse that many difficult choices had to be made. In spite of efforts to select the most detailed and significant studies the reader must refer to the usually extensive citations in the original papers to be sure of seeing all relevant material.

Houk and Paquette presented thoughtful and readable accounts of their efforts in cycloaddition chemistry[255, 256]. Houk's interest is in general much more directly concerned with quinone chemistry while Paquette has simply used quinones where appropriate in his emphasis on gaining full appreciation of Diels–Alder chemistry. While Houk's review was published much earlier it is especially valuable as an introduction to the concepts of frontier molecular orbitals as an approach to understanding chemical processes. In their more recent publications both authors have essentially left quinone chemistry in an effort to resolve fine, perhaps important, details concerning stereoselectivity in cycloadditions[257, 258].

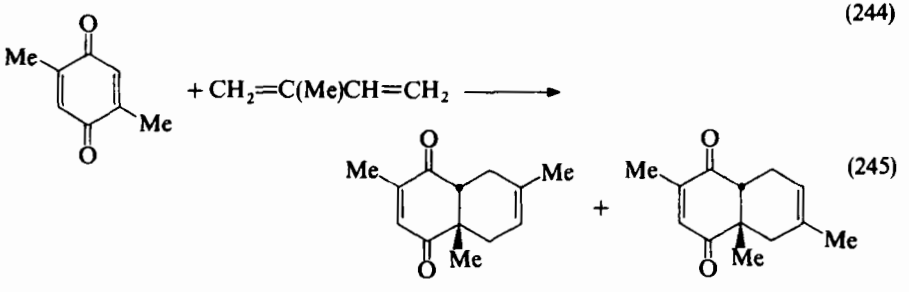
Of greatest significance in quinone–cycloaddition chemistry are the studies by Houk and his collaborators which deal directly with theoretical applications. The unifying potential of frontier molecular orbital theory has already been mentioned in discussing the reductive Michael addition so typical of the quinones[1]. The basic assumption is that reactivity depends on the interaction of the lowest unoccupied molecular orbital (LUMO) of the quinone and the highest occupied molecular orbital (HOMO) of the nucleophile[255]. The closer these orbitals are in energy, the more strongly they interact. The computational results are presented in detail and comparisons with published results, both experimental and theoretical, are made along with predictions for unexamined cases. The prediction that substituent effects can be transmitted through many bonds is coupled with an implied plea for more carefully organized studies.

Shortly after the appearance of this general study Houk and his collaborators published the results of their efforts to account for cycloaddition reactions in which the products represent regioselectivity opposite to that predicted by consideration of LUMO coefficients[259]. Three different dienes reacted with 2,5-dimethyl-1,4-benzoquinone (equations 244–246) and showed similar product compositions also with 2,6-dimethyl-, 2,5-, or 2,6-dimethoxy-1,4-benzoquinone and 2-methyl- or 2-methoxy-1,4-naphthoquinone. Houk argues that since all of these examples lead to the more nucleophilic end of the diene reacting preferentially at the less highly substituted carbon of the quinone it is likely that



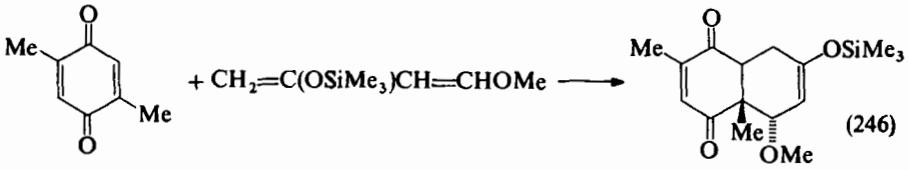
5 : 1 (75%) (total yield)

(244)



1 : 1 (70%)

(245)

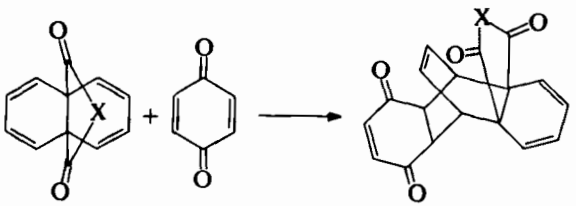


90%

(246)

secondary orbital repulsive effects offer the most attractive rationale for the experimental observations. These ideas are generalized and the applicability of the frontier molecular orbital approach expanded in a subsequent publication[260].

Others have examined the importance of secondary orbital overlap in Diels–Alder reactions; for example, Ginsburg and his coworkers have added specific evidence from the reaction of propellanes (**82**, **83**) with 1,4-benzoquinone (equation 247)[261]. In contrast to

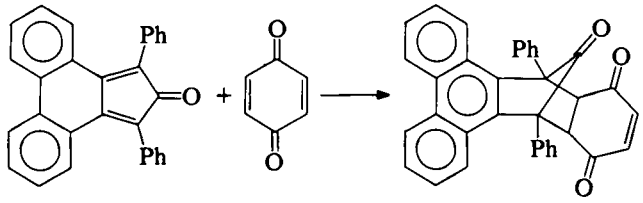


(247)

(**82**, X = O) 68%,
(**83**, X = NMe) 88%

N=N dienophiles which add to the *syn*-face of compounds like **82** and **83**, the C=C system of quinones add exclusively to the *anti*-face.

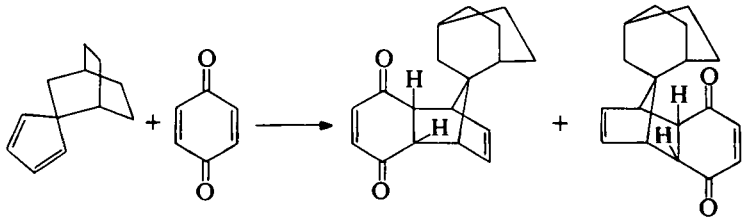
Kanematsu and his collaborators made an extensive examination of the kinetics of phencyclone (**84**) with various dienophiles including 1,4-benzoquinone (equation 248)[262].



(84) (248)

They classify those reactions in which the HOMO–LUMO separations are similar and either electron attraction or release should increase reactivity as neutral or type B. They too draw the conclusion that secondary orbital interactions are important, especially in cases like this where the planarity of the diene is nearly perfect.

In his early work Houk stated that Lewis acid-catalyzed Diels–Alder reactions promote stronger secondary orbital interactions[263]. However, it has been found that with the rather unusual diene spiro[bicyclo[2.2.2]octane-2,1'-[2,4]cyclopentadiene] (**85**) no change in the *syn/anti* ratio occurs in the two reactions (equation 249)[264]. The rates of the two processes

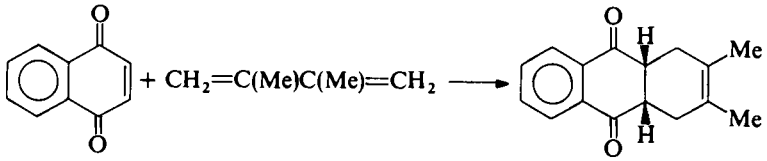


(85)	thermal	86	:	14 (100%)
	catalysed	90	:	10 (95%)

(249)

do change dramatically; several hours at 0 °C versus 30 minutes at − 78 °C in the presence of boron trifluoride etherate. The authors point out that their results do not necessarily demand more than a modification of Houk's hypothesis. They suggest that the *endo* reaction transition state may simply lie further along the reaction coordinate than the corresponding *exo* reaction.

The effect of solvent on the rates of the Diels–Alder reaction of 2,3-dimethyl-1,3-butadiene and 1,4-naphthoquinone (equation 250) has been studied[265]. Seventeen solvents



100% (250)

ranging from cyclohexane to acetic acid were used and all of the traditional correlation techniques failed to rationalize the small (31-fold) change observed. The much less widely applied donor/acceptor interactions of Mulliken not only served to explain the data, but the associated acceptor numbers correlate with the LUMOs of the solvent. The frontier molecular orbitals interactions of these LUMOs and the HOMO of the quinone leads to a qualitative explanation of the rate increases. A detailed treatment of the hyperbolic shape

of the plot of log second-order rate constants versus acceptor numbers is also given. This study appears entirely consistent with a reaction in which weakly polar reactants, transition states and products are dominant.

In a related study a comparison of 1,4-benzoquinone with several other dienophiles also ruled out a zwitterionic intermediate; the evidence involving substituent and solvent effects favored a concerted mechanism[266]. By contrast a less detailed examination of the reaction of 1,3-butadiene with 1,4-naphthoquinone was interpreted as favoring a charge separated transition state[267].

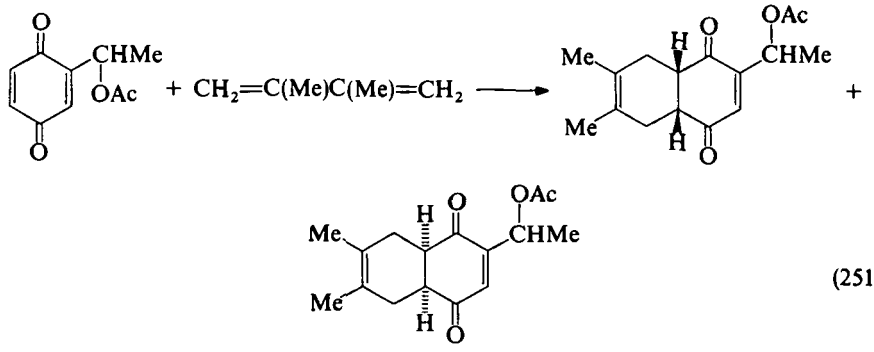
In an effort to apply the logic of isoselective relationships to the Diels–Alder reaction, competitions between 1,4-benzoquinone and maleic anhydride were carrried out with dienes representing normal and reverse electron demands[268]. The evidence shows clearly that these reactions do possess a common isoselective relationship and therefore a common reaction mechanism.

The instability of simple quinonoid systems toward water is well documented and may be part of the reason so few representatives are known beyond those contained exclusively in a single six-membered ring. Boldt and his coworkers used perturbation molecular orbital theory to examine both of these questions[269]. On the basis of their theoretical studies a 1,7-naphthoquinone was selected for preparation and a 13-step synthesis was carried out! This quinone, the 3,7-di-*t*-butyl-8-methyl derivative, proved to be unstable, thus supporting the thesis that the alkyl substituents which provide shielding from water also cause great steric strain.

2. *Stereochemistry and catalysis*

In addition to the considerable theoretical interest in the Diels–Alder reaction there has continued a steady stream of more experimentally oriented studies relating to the details of this important process. For example, various questions concerning stereochemical requirements are of central concern for the application of cyclization reactions to natural product synthesis. It has been observed that Lewis acids can change the product orientation dramatically and that reaction under high pressure provides a route to otherwise inaccessible compounds. The chemistry of quinones makes one aware of the modern trend to all but erase any clear distinction between mechanistic and synthetic studies.

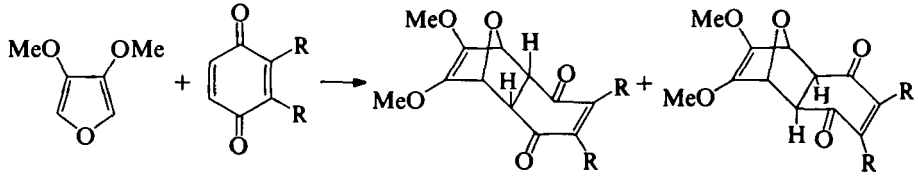
Jurczak has shown that quinones greatly restrict freedom in the transition state and enhance the utility of asymmetric induction as a synthetic tool[270]. In the reaction of *d,l*-1′-acetoxyethyl-1,4-benzoquinone with 2,3-dimethyl-1,3-butadiene, cyclization takes place in a completely regiospecific manner and the two diastereomers are produced in a ratio of 70:30, i.e. one is produced in 40% excess (equation 251). Reaction with 1,3-cyclohexadiene



(251)

gave identical results. The application of these observations to a model proposed earlier is discussed[271].

In the study just described the author points out that such differentiation is sensitive to the reaction pressure. Along with their coworkers Jurczak and Eugster have shown that 1,4-benzoquinones react smoothly with 3,4-dimethoxyfuran to give a highly stereospecific product (equation 252)[272]. With increasing pressure the *endo/exo* ratio decreased

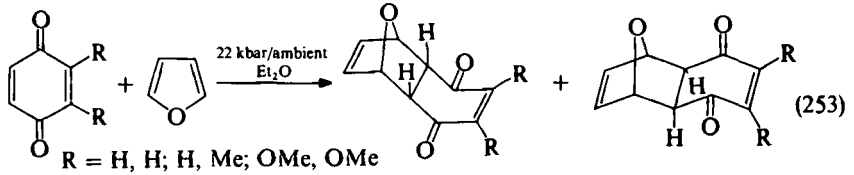


t = 25°C.	R = H, H *endo/exo*	R = H, Me *endo/exo*
7 kbar	89/11	89/11
11 kbar	83/17	76/24
19 kbar	54/46	68/32

(252)

dramatically. Raising the temperature produced an even larger change in the same direction, but the relationship between the two was not investigated. The situation for 2,3-dimethyl- and 2,3-dimethoxy-1,4-benzoquinones appears still more complicated and needs further work. The former gave only a 46% yield of the *exo* isomer at the lowest pressure and was not investigated further. The latter showed only a very small change in product composition with changing pressure. These reactions were first reported by Eugster and coworkers and apparently only the isomer which crystallized was considered[273]. A kinetic study shows that substituents in the furan ring play an important role in determining the thermodynamic stability of the adducts formed[274]. Activation energies for retro-Diels–Alder reactions of such adducts show the rather small effect of substituents in the quinone ring and make clear the necessity of the high pressure modification for success in their synthesis.

Application of the Diels–Alder reactions at high pressure can provide a synthesis of unstable adducts such as those of simple 1,4-benzoquinones with furan (equation 253)[275]. The two stereoisomers have different stabilities, but neither survive 12 hours at 5°C.

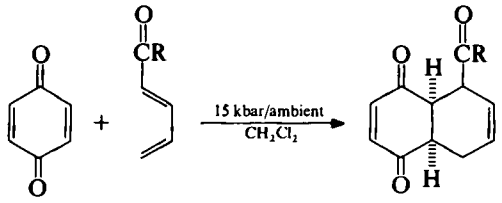


R = H, H; H, Me; OMe, OMe

(253)

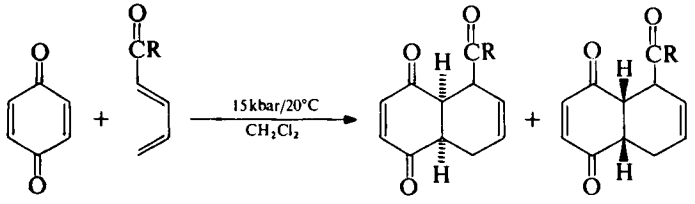
Dauben and Baker have also examined Diels–Alder chemistry at high pressures for the synthesis of heat-sensitive quinones[276]. Of particular interest is the use of electron-poor dienes and the avoidance of aromatization (equation 254). Unless the diene has an unfavorable stereochemistry or an electron-withdrawing substituent at its terminus, adequate to excellent isolated yields are obtained. The *t*-butyldimethylsilyloxy group is an exception (84%), but it required a 65-hour reaction time.

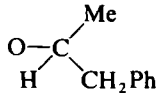
Dauben and Bunce have applied this technique to the synthesis of quinonoid chiral esters (equation 255)[277]. The bulk of the ester is the principal determinant of the enantiomeric excess obtained. A variety of examples representing intermediate degrees of



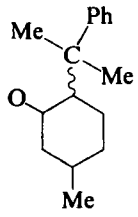
(254)

R = OMe, OEt, (−)-menthyl



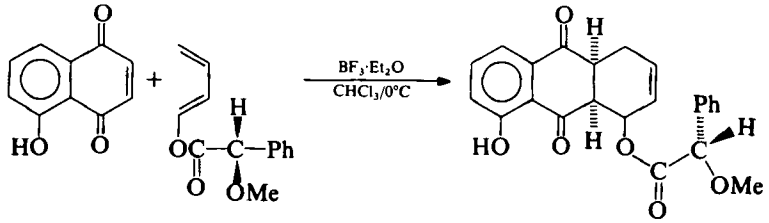
R = (+)  98% yield 2% enantiomeric excess

(255)

(−)  62% yield 50% enantiomeric excess

asymmetric induction are given. In all cases the adducts could not have been prepared by classical methods.

Trost and his coworkers have given an especially clear example of the control possible in molecules of great significance to the synthesis of natural products (equation 256)[278]. This

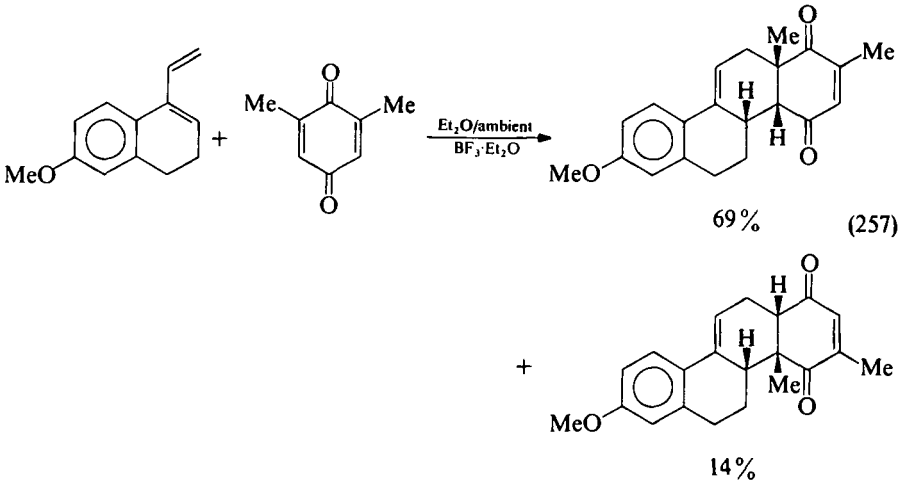


(256)

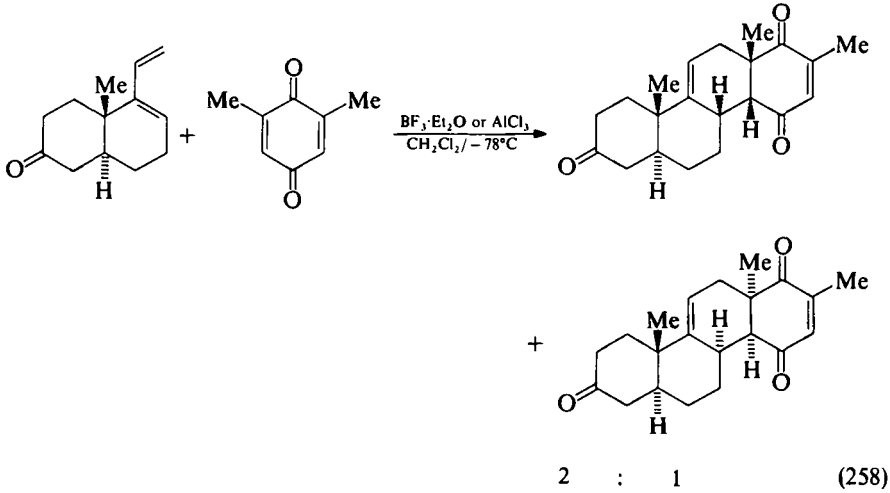
98% (> 97% optical purity)

complete stereochemical control is attributed to the interaction referred to as π-stacking which may be promoted by enhanced charge transfer.

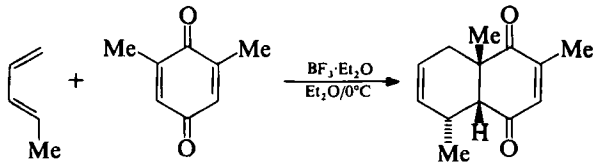
The presence of a Lewis acid catalyst in the preceding Diels–Alder reaction illustrates what may well be the most important single synthetic discovery in the quinonoid field during the past decade and a half. Valenta and coworkers reported that in the presence of boron trifluoride etherate a key step in the synthesis of a steroid showed almost complete



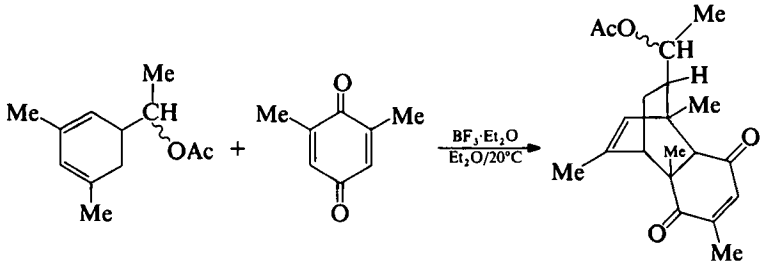
reversal of product orientation (equation 257)[279]. The minor product is the only isomer obtained from reaction in refluxing benzene. In this first publication the authors indicated that similar exciting results had been found for an example in the saturated steroids (equation 258). No yields were given and the structures were only proposed, but neither of the products is found in the uncatalyzed reaction.



The generality of such great regioselectivity was demonstrated by a study involving simple (equation 259) as well as complex (equation 260) dienes[280]. In the latter example both the starting material and product are mixtures of stereoisomers. No specific figures are cited, but the authors claim that all yields are higher than 80% and the product represents complete reversal of orientation. They have rigorously demonstrated the stereochemistry and advance tentative arguments based on the frontier molecular orbital model.

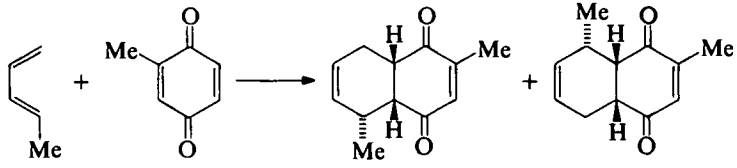


(259)



(260)

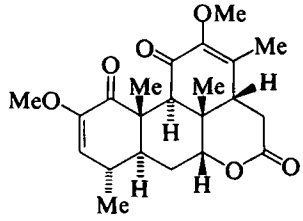
The chemistry just described is not as completely stereoselective with monosubstituted 1,4-benzoquinones, but even there the shift in product orientation is impressive (equation 261). The choice of solvent, with or without catalyst, provides 60–70% yields of either isomer.



(261)

toluene or acetone	2	:	1
dioxane	1	:	1
toluene/$BF_3 \cdot Et_2O$	1	:	2

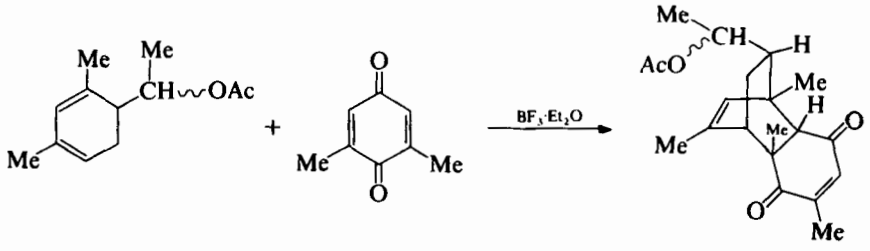
Valenta and his collaborators have used their method to advantage in several natural product syntheses. For example, the molecule quassin (**86**) presents a serious stereo-



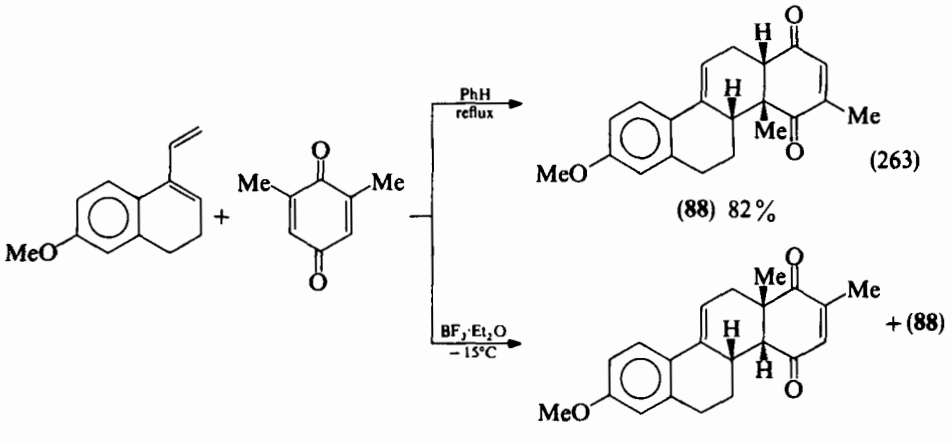
(**86**)

chemical challenge with seven chiral centers[281]. The application of a Lewis acid catalyzed Diels–Alder reaction gave an excellent yield of **87** which shows exactly the opposite stereochemistry to that predicted and obtained from the thermal reaction (equation 262).

A later publication gives a brief overview of the utility of Diels–Alder based steroid syntheses followed by an impressive set of examples of the complementary possibilities of



(87) 80% (262)



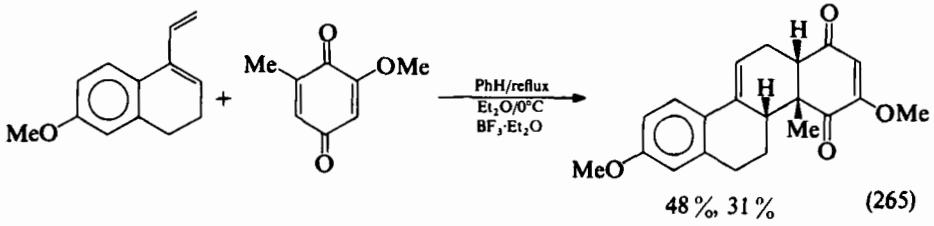
(263)

(88) 82%

69% 11%

(264)

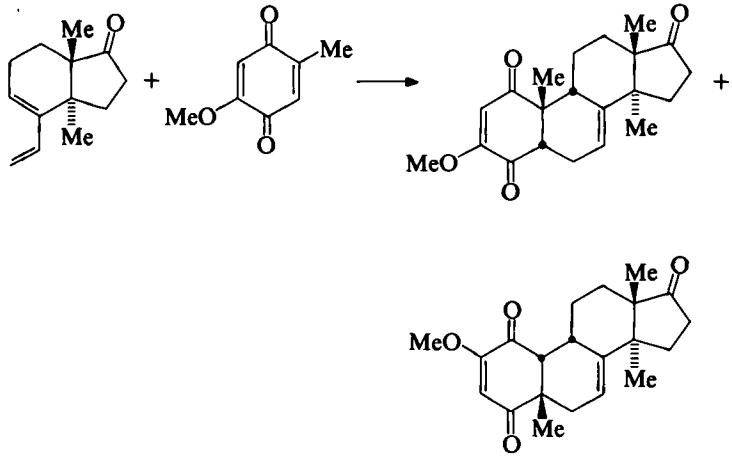
the thermal and catalyzed reactions (equations 263, 264)[282]. One compound, 2-methoxy-6-methyl-1,4-benzoquinone proved to be an exception in that under both reaction conditions a much lower yield of the thermal product is obtained (equation 265).



48%, 31% (265)

A variety of fragmentary experimental evidence exists and the authors discuss the problems involved in interpretation of these extraordinary results. The overall conclusion is that a great deal of additional detailed research is required before any useful mechanistic conclusions can be reached. Unfortunately, the expected later studies have not yet appeared, but the synthetic applicability of the reaction is clear and available.

With methyl-methoxy quinones the choice of Lewis acid catalyst can have an impressive effect on the product structure (equation 266)[283]. These variables were also applied to the



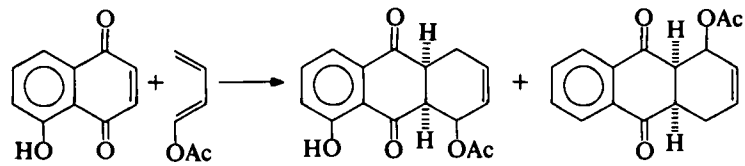
(266)

PhH/reflux	24%	16%
$SnCl_4/CH_2Cl_2/0\,°C$	0%	75%
$BF_3.Et_2O/-16\,°C$	55%	< 10%

reactions of 2-methoxy-6-methyl-1,4-benzoquinone with piperylene or isoprene with very similar results.

Several research groups have been active in relating these catalyzed Diels–Alder reactions to a variety of synthetic problems. A great deal of important chemistry has been produced and several mechanistic proposals have been put forward, but the debate has hardly reached a point of substantial agreement. For the moment the best approach seems to be to collect the experimental data and await the design of critical experiments.

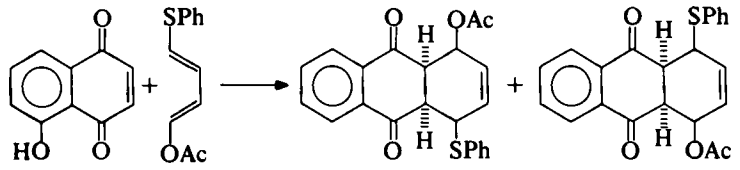
Trost and his collaborators have been among the most active investigators of the potential of the two paths of Diels–Alder chemistry combining them with their own elegant studies of the utility of sulfur and oxygen for regiospecific control[284]. Their work, like much of recent chemistry in this field, has involved the naturally occurring quinone juglone (**89**) as a substrate (equation 267). Thus, with oxygen alone in the diene the Lewis acid



(**89**) (267)

thermal addition	3	:	1
$BF_3.Et_2O$	> 20	:	1

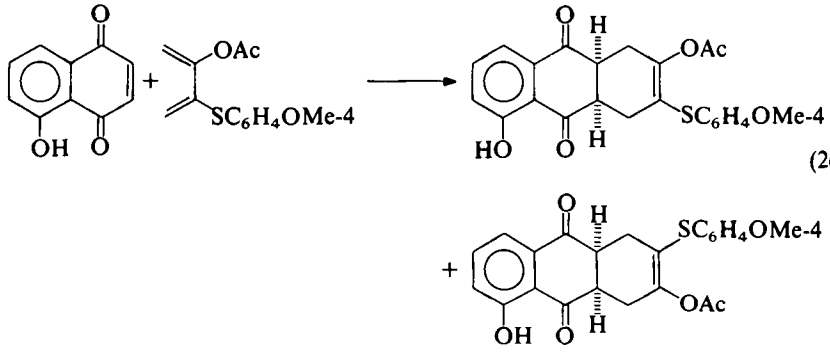
catalyst greatly enhances the formation of the major isomer. When a diene substituted with both oxygen and sulfur is employed thermal addition shows a marked preference for sulfur control of the regiochemistry, but a Lewis acid can completely reverse the product distribution (equation 268). When these observations are coupled with the wealth of sulfur chemistry available the procedure becomes extremely versatile.



(268)

thermal addition	2.3	:	1
$BF_3.Et_2O$			sole product

The use of a 2,3-substituted 1,3-butadiene allows the same extraordinary control in both thermal and catalyzed reactions (equation 269). In a subsequent full paper these

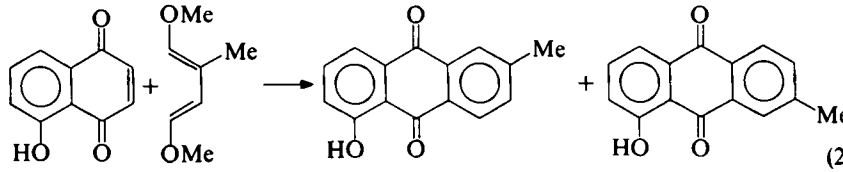


(269)

thermal addition	1	:	2
$BF_3.Et_2O$	sole product		

observations are described in greater detail and the product structures assigned unambiguously[285]. The synthetic result is clear; the minor isomer of the thermal reaction (oxygen control) becomes the exclusive product of the catalyzed reaction.

The original ideas advanced by Valenta[280] dealt with the effect of catalyst on the quinone dienophile while the evidence advanced by Trost places emphasis on the diene structure. Boeckman and his collaborators have examined the importance of the diene and catalyst in Diels–Alder reactions of juglone and its derivatives[286]. Like Trost, they find that the polarity of the diene is of the greatest importance in regiochemical control. Like all workers in this area, they conclude that the complete explanation is very complex and much additional experimentation is required. Of immediate practical interest is their observation that for juglone and certain dienes a complete reversal of regiochemistry can be obtained by a change in the Lewis acid catalyst (equation 270). Such an observation



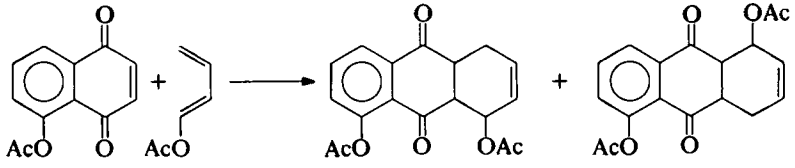
(270)

thermal addition	1	:	1.8
$BF_3{\cdot}Et_2O$	1	:	4.5
$AlCl_3$	4.7	:	1

recalls the work of Tou and Reusch[283]. Both Trost and Boeckman have expanded their investigations to much more complex dienes and applied the results to the synthesis of tetracyclic antibiotics[287, 288].

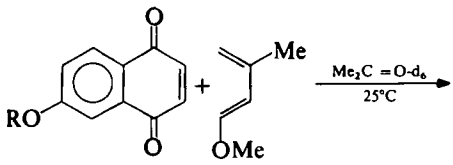
The synthesis of these important pharmaceuticals with their complex functionality and stereochemistry has occupied the time and talents of several research groups over the past decade. One of the pioneers is Kelly who, with his collaborators, has significantly enhanced our practical and theoretical knowledge of quinone–Diels–Alder chemistry.

In early work[289] Kelly suggested that the regiochemical outcome of the reaction of 5-acetoxy-1,4-naphthoquinone (acetyl juglone) with 1-acetoxy-1,3-butadiene (equation 271)

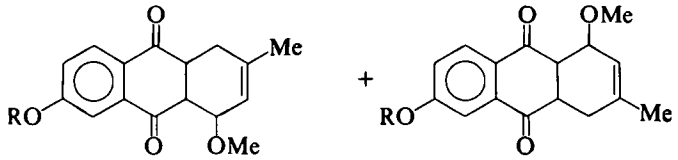


1 : 3 (271)

can be rationalized on the basis of resonance electron donation. While the idea led to useful predictions[290,291] it is not in accord with the Hammett treatment showing the acetoxy group as electron-withdrawing. This situation resulted in a series of experiments designed to remove the substituents in question to a more remote site and avoid alternative explanations based on direct interactions (equation 272)[292]. The results shown are clearly



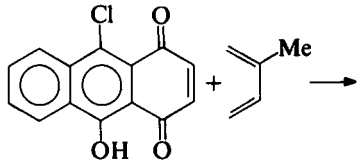
(272)

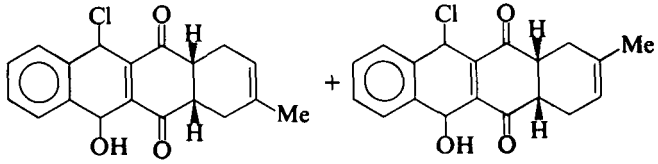


R = H	75	25
Me	75	25
Ac	60	40

consistent with the acetoxy group behaving as an electron donor, a result which is supported by a more refined treatment of its electronic properties. The authors also document the fact that 5-acetoxy-1,4-naphthoquinone shows identical regiospecificity in this reaction. Extensive additional experimental support and applications published by Kelly's group allow one to follow the development of these ideas and to imagine useful new extensions of them[293–299].

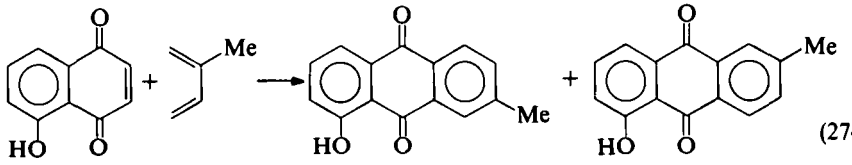
Another impressive example of the change in regiochemistry made possible by selecting the appropriate catalyst is found in the work of Stoodley and coworkers (equation 273)[300]. They also repeated the work of Boeckman[286] using boron triacetate and observed a complete reversal of orientation (equation 274).





(273)

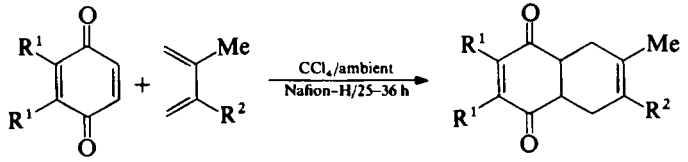
PhH/reflux	1	:	1	(88%)
$BF_3 \cdot Et_2O$	sole product			(70%)
$AlCl_3$	sole product			(68%)
$B(OAc)_3$	1	:	10	(72%)



(274)

$BF_3 \cdot Et_2O$	8	:	1 (66%)
$B(OAc)_3$	1	:	7 (63%)

Olah has employed the resinsulfonic acid Nafion-H as a catalyst for Diels–Alder cyclizations (equation 275)[301]. The excellent yields and easy workup make this an



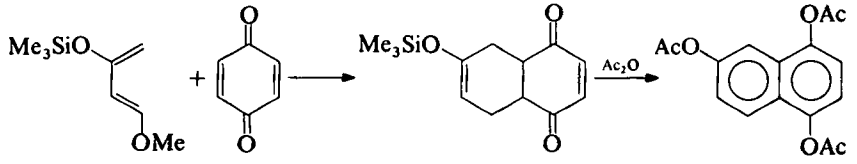
(275)

R^1 = H,	;	R^2 = H,	80%
$-CH=CHCH=CH-$	;	Me	93%

especially attractive reaction for further study in spite of the fairly long reaction times required. Several dienophiles, including 1,4-benzoquinone, react with anthracene in high (92%) yield. Such products have importance in the study of stereochemical questions by NMR spectroscopy[302].

The need for reactive dienes which can easily be converted to oxygen functions is of major synthetic importance in preparing many classes of natural products. Danishefsky's group has made investigations of silyl enol ethers in Diels–Alder reactions. His account[303] is an interesting survey of these important reagents but fails to mention their relationships to quinone chemistry. A limited number of quinonoid reactions is presented by Brownbridge in his extended synthetic review[304].

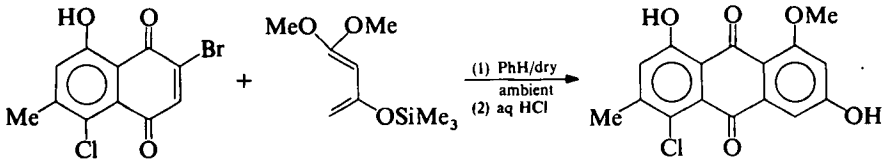
Danishefsky and Kitahara described the requirements of an improved diene, prepared *trans*-1-methoxy-3-trimethylsilyloxy-1,3-butadiene (**90**) and demonstrated its reaction with 1,4-benzoquinone (equation 276)[305].



(**90**) 87%

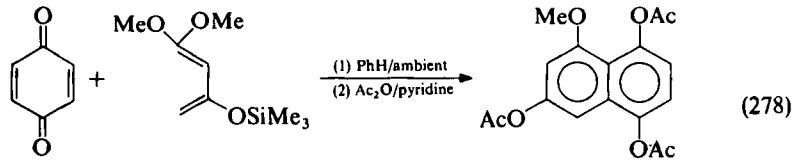
(276)

Later, Brassard and his group prepared 1,1-dimethoxy-3-trimethylsilyloxy-1,3-butadiene (**91**) and some longer chain derivatives[306]. They found that reaction with 2-bromo-5-chloro-8-hydroxy-6-methyl-1,4-naphthoquinone took place rapidly and cleanly (equation 277). After pyrolysis and hydrolysis, 87% yield of the corresponding



(**91**) 87% (277)

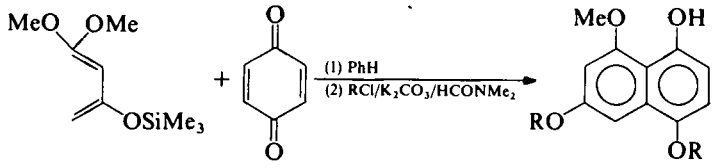
anthraquinone was obtained. The presence of the hydroxy group is not necessary and the corresponding methyl ether formed its anthraquinone in 90% yield. Failure to heat strongly prior to hydrolysis leads to a mixture of alcohol addition products. Three naturally occurring anthraquinones were prepared in excellent yields using this diene and its ethyl and butyl homologs. Subsequently, Danishefsky and coworkers were making a more detailed study of the range of Diels–Alder chemistry possible with this new reactive diene[307]. Reaction with 1,4-benzoquinone continued to support the general observation that the initial adducts are unstable and best isolated after conversion to an aromatic derivative (equation 278). Two competitive experiments showed that this diene is more reactive than the monomethoxy compound reported earlier[305].



78% (278)

If the intermediate adduct first formed is alkylated with a bulkier group such as isopropyl or benzyl, the major product retains one free hydroxy substituent (equation 279)[308].

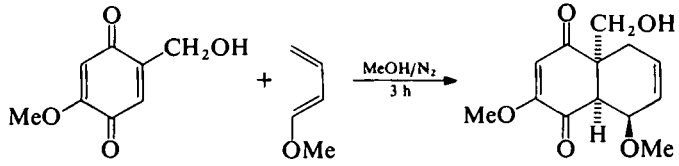
Further work by Danishefsky and his colleagues greatly expanded the practical application of this synthetic method without introducing novel quinonoid chemistry[309-313]. They have also been able to demonstrate that in certain instances enol ether



(279)

R = *i*-Pr, Bz 69%, 42%

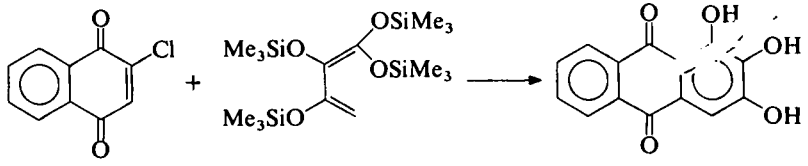
dienes can display extraordinary regioselectivity (equation 280)[314]. Many other workers have recognized the importance of polymethoxy or polysiloxy dienes in Diels–Alder chemistry[315–330].



(280)

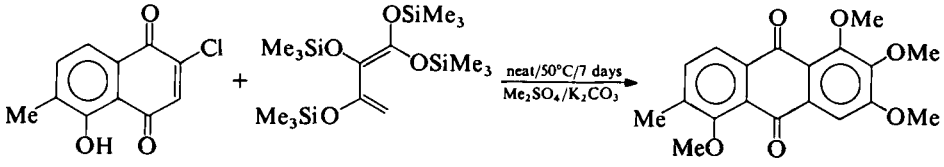
94%

Brassard and his collaborators developed different routes and explored modifications of the silyl enol ethers. One major thrust of their research has been the exploration of ketene acetals (see Section V.C.1) and this has often led them to examine silylated derivatives. One such reagent has proven especially useful in synthetic efforts directed toward the anthragallols (equation 281)[331]. These compounds are somewhat less sensitive than



82% (281)

corresponding naphthoquinones which could not be obtained by this chemistry. The reaction takes place with great regiospecificity as indicated by the synthesis of the tetramethyl ether of the natural product copareolatin (**92**, equation 282). This reagent and



(**92**) (282)

the analogous 2-methoxy derivative were employed in the synthesis of a variety of naturally occurring anthraquinones[332]. This work also allows some useful comments on the factors affecting the reaction mechanism. The yields and ease of reaction for various halojuglones studied present a consistent picture of the electronic demands of these reactions. While no analysis is given it seems clear that the trends from these resonance

arguments correspond closely to those of frontier molecular orbital calculations, a comparison outlined fully by Houk (see Section V.A.1).

A major shortcoming of the siloxylated 1,3-butadienes is their failure to provide an entry to the naphthoquinones. While they apparently react easily with 1,4-benzoquinones, the hydrolysis to highly hydroxylated naphthoquinones leads to extensive decomposition. In a series of explorations Brassard and his collaborators have steadily improved the efficiency of these synthons by modifying the balance between silyloxy and methoxy substituents in the 1,3-butadienes[333-338]. There are still limitations to be overcome[339], but the great progress made is documented by the vastly improved syntheses of a broad range of naturally occurring quinonoid compounds. A number of other research efforts have recognized the importance of Brassard's contributions[340-342].

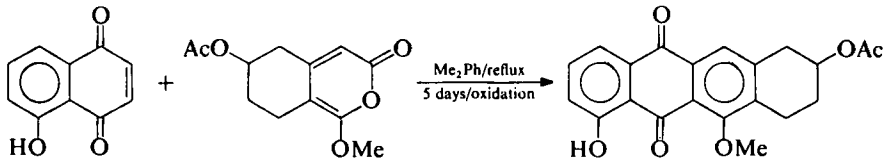
Fleming and his collaborators[343], while their major interest has not been in quinone reactions, also provided a great deal of insight to these reactions; see especially the detailed survey of allyl compounds[344].

3. *Synthetic survey*

The amount of synthetic studies in the past 15 years is such that a systematic treatment is not possible within the limitations of this chapter. Also, these reports are so diverse that their proper contribution to understanding the mechanistic implications demand many carefully constructed and controlled future studies. In order to promote such work the available chemistry has been grouped in what seem to be logical subdivisions coupled with illustrative equations and with leading references.

a. Pyrones as dienes

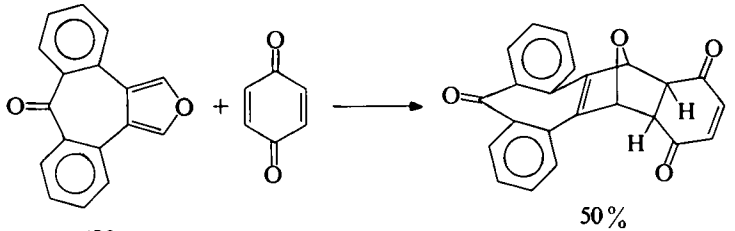
Several groups, most notably that of Jung and his collaborators[345-347], have used various alkylated and alkoxylated derivatives of these lactones in effective approaches to the anthracycline antitumor antibiotics (equation 283)[348].



63% (283)

b. Heteroatom bridges from furans and thiophenes

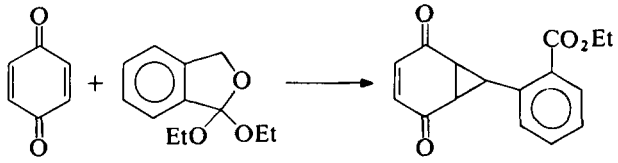
As a complement to their extensive investigations of the cycloaddition chemistry of phenylcyclone[349,350] Sasaki and his coworkers have studied the related furotropone (**93**, equation 284)[351]. Warrener[352,353], Rickborn[354] and Smith[355,356], with various collabor-



(93)

50% (284)

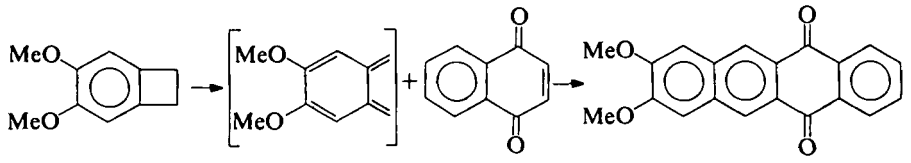
ators, have greatly expanded the range of isobenzofuran cycloaddition chemistry. Still other studies have involved the analogous sulfur heterocycles[357,358] and the *in situ* generation of the furan[359]. One interesting report concerns the formation of a cyclopropane ring in an apparently similar reaction (equation 285)[360].



30% (285)

c. Exocyclic dienes

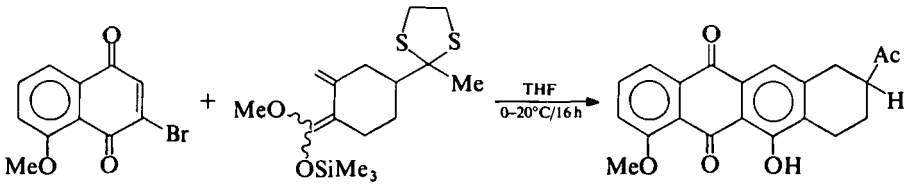
The polycyclic structure of so many natural products makes the ability to create a new ring with predetermined structure particularly attractive. Thus, the application of exocyclic dienes in Diels–Alder reactions has attracted a great deal of interest. Of special importance are recent investigations of *o*-quinodimethanes generated from benzocyclobutenes and related compounds (equation 286)[361-365].



75% (286)

Yields are generally much lower than this example, and some odd competing reactions do occur, but the variety of functionality that can be introduced in a single step make this a potentially important route. Other methods for the generation of the reactive intermediate show promise of good regioselectivity[366].

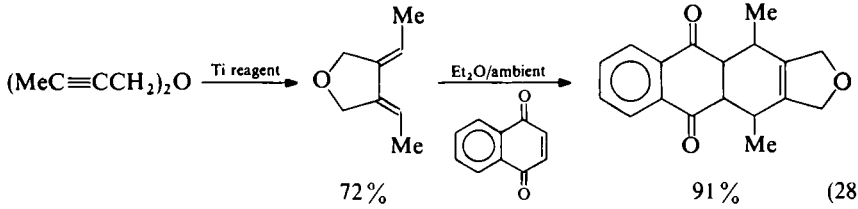
Gesson and his coworkers have used siloxylated enol ethers in the form of exocyclic dienes with excellent results in the synthesis of anthracyclines (equation 287)[367-369].



71% (287)

A variety of related dienes have been prepared and used in imaginative ways[370-377]. The cyclization of diynes with dicyclopentadienyltitanium leads to five-, six-, or seven-membered rings bearing both the exocyclic diene system and various other functional groups. These products with 1,4-naphthoquinone allow the production of some very interesting products (equation 288)[378].

A final point in the application of exocyclic dienes to Diels–Alder syntheses is the report by Scharf and his collaborators which shows the importance of 1,4-distances in the reactivity of such compounds[379]. The reaction rates, activation parameters, ionization

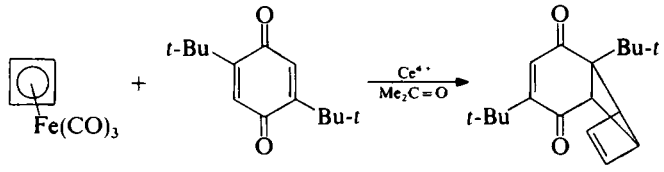


(288)

potentials, and molecular geometries combined to reduce the importance of the dihedral angle in such systems. While quinones played only a secondary role in these studies, the implications for them are clear.

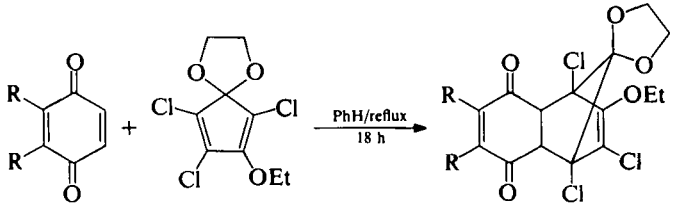
d. Cyclic dienes

For most of the reasons cited in the preceding section the Diels–Alder chemistry of conjugated alicyclic dienes occupies an extremely important position in modern natural product synthesis. These substrates have also been frequently involved in more theoretical investigations. The simplest representative of the series, cyclobutadiene, has been generated from its iron tricarbonyl complex and reacts with highly hindered quinones (equation 289)[380]. The tetramethyl analog shows similar reactivity toward quinones[381].



(289)

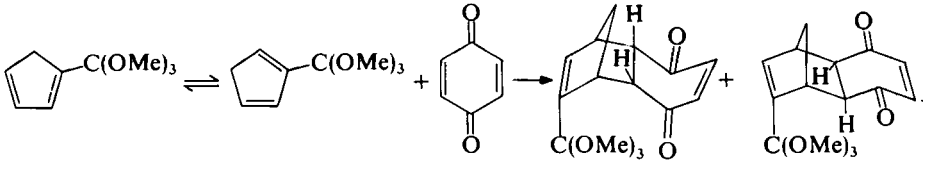
O'Connor and Rosen have applied Diels–Alder reactions of cyclopentadienes bearing alkoxy and chloro substituents to the synthesis of interesting aromatic quinones (equation 290)[382,383]. Yates and Gupta demonstrated that quinones are capable of reacting



(290)

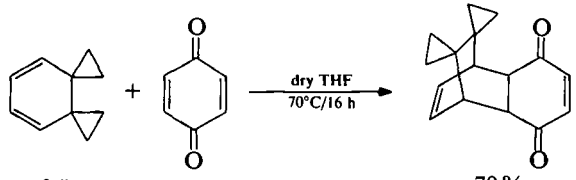
R = H, –CH=CHCH=CH– 97%, 90%

selectively with the 2-substituted tautomer of (trimethoxymethyl)cyclopentadienes (equation 291)[384]. A variety of cyclopentadiene applications have been reported[385–391].



3 : 2 (291)

In the cyclohexadiene series 1-methoxy or silyloxy derivatives have occupied a major position[392-398] along with the related cyclohexadienones[399,400]. Applications have proven fruitful in the study of steric strain[401], cage compounds[402,403] and intramolecular hydride transfer[404]. In the latter two citations some useful comparisons of the influence of ring size are made. One of the more exotic examples of these compounds involves two spirocyclopropyl substituents (**94**, equation 292)[405]. The delicate balance observed



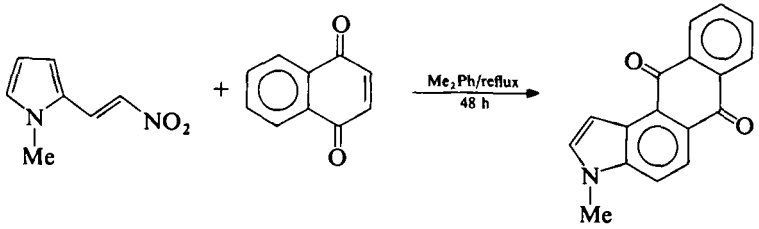
(**94**) 70%

(292)

between electronic and steric effects in this cycloaddition suggests a great deal of future interest.

e. Vinyl pyrroles, indoles and benzothiophenes

Hiremath and his colleagues have contributed to the synthesis of complex polyaromatic heterocyclic molecules with their discovery of the utility of an added nitro substituent (equation 293)[406-408]. Porter and his coworkers have extended the range of vinylindoles



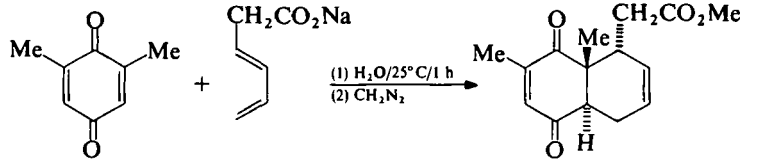
64%

(293)

and investigated the analogous chemistry of benzothiophenes with considerable success[409-411]. This latter work has been applied by others to more complex[412] and to simpler systems[413].

f. Sorbates and aqueous reactions

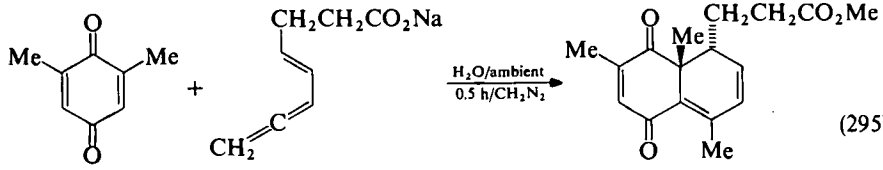
Grieco and his collaborators have had an interest in aqueous Diels–Alder reactions and employed the salts of sorbic and related acids in these studies[414-417]. Very high yields, mild conditions, short reaction times, and great regioselectivity characterize these reactions (equation 294) and stand in sharp contrast to the results obtained with the corresponding esters in hydrocarbon solvent. Methods of avoiding competition from complex sequential



77%

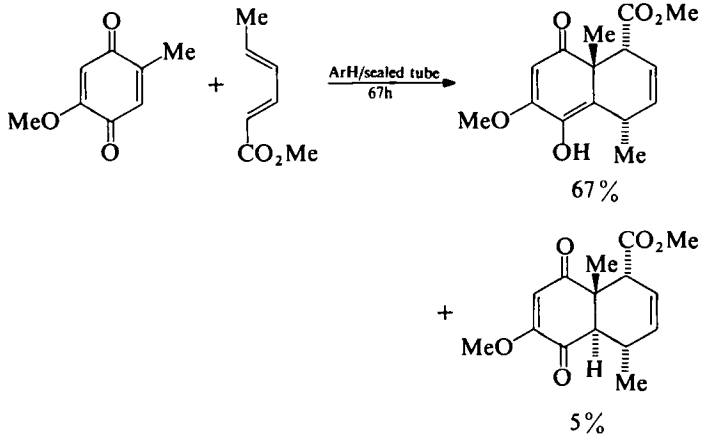
(294)

Michael additions have been found[414] and a promising allenic acid has been developed (equation 295)[417]. To obtain the same yield using the methyl ester in benzene, 21 hours at



(295)

50°C is required. On the other hand Kanematsu and his colleagues have used exactly this non-aqueous reaction to investigate the synthesis of stable enols (equation 296)[418,419]. It



(296)

seems clear that both the methoxy and the methyl group are essential to the success of this unusual chemistry. It should also be noted that other studies involving allenes in Diels–Alder reactions have been appearing[420,421]. While the extent of such applications is limited a method has been proposed for their preparation from vinylacetylene[420].

A number of more limited studies involving these salts and esters have been reported[422–424].

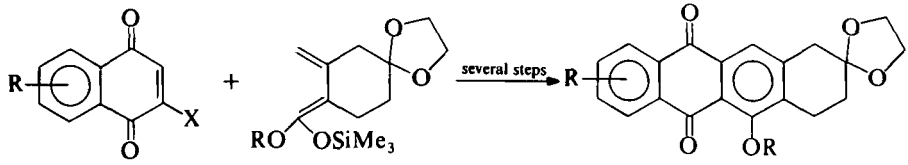
g. Tetracyclic antibiotics

Beyond all doubt the synthesis of derivatives of the anthracycline antibiotic compounds, which also show great promise for the treatment of various tumors, has exerted a huge influence on the application and development of Diels–Alder chemistry. Gesson and coworkers have studied especially ketene acetals (equation 297)[425–428]. Much of this work has been summarized[427] and applied to a total synthesis[428].

Other research groups have made approaches to the synthesis of these stereochemically demanding molecules[429–442]. Some of the chemistry described will show the way to broad improvements in synthetic methods, but for the moment they remain isolated examples awaiting further systematic development.

h. Polycyclic aromatic syntheses

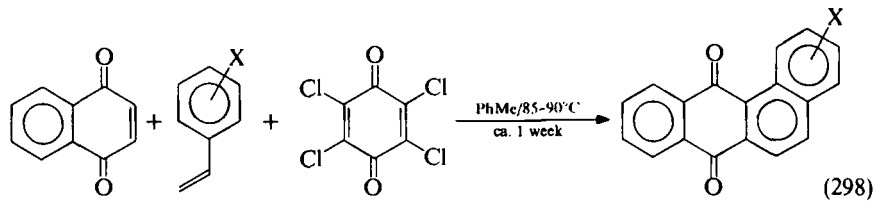
The great interest in polycyclic aromatic compounds as carcinogens has provided an ideal area for the application of Diels–Alder chemistry. One research group has dominated



(297)

R = H, OH, OMe, OAc
X = H, Cl, Br

the work and obtained results of the highest quality. In five short years Manning, Muschik and Tomaszewski produced a formidable number of syntheses which represent a major contribution to our understanding of the mechanism of these reactions[290,443-452]. The two most important aspects of their work may be illustrated in the general synthesis of benz[*a*]anthracene-7,12-diones (equation 298)[444].



(298)

30–40%

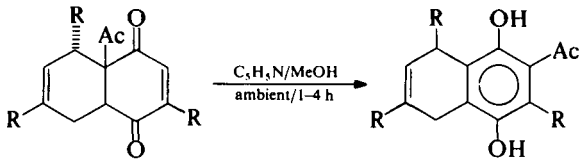
X = Me, 2,5-Me_2, F, Cl, Br, OMe

The use of substituted styrenes allows the preparation of specific product isomers, and the presence of chloranil improved the yields significantly.

Rosen and Weber have applied the same methods to the reactions of 1,4-phenanthraquinones[453]. Here too Manning's group improved the original work and showed that steric interaction, while important, does not by itself preclude a successful Diels–Alder reaction in these compounds[451].

i. Acyl rearrangements

Bruce and his coworkers recognized that the Diels–Alder adducts bearing angular acyl substituents can undergo a very specific migration (equation 299)[454-457]. The importance



(299)

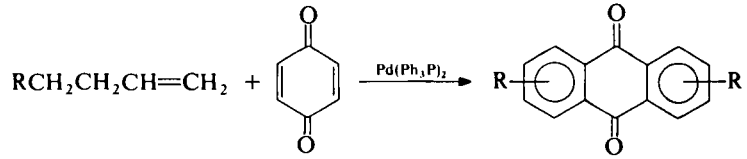
R = H, Me

50–80%

of substituents in both the quinone and the diene are fully developed and the intramolecular nature of the shift demonstrated. The reasonable yields and mild conditions coupled with high regiospecificity make this an attractive synthesis. This rearrangement was first observed by Cooper and Sammes[458] who later published a detailed study of the effects of substituents and conditions on the yield and ease of the reaction[459]. The general mechanistic conclusion seems to demand at least a partial retro-diene process[457].

j. Unusual isolated observations

Some more reports represent work that deserves to be developed in greater detail. For example, there is a report that palladium metal in the presence of triphenylphosphine dimer acts as a powerful catalyst for the conversion of terminal alkenes into conjugated dienes which undergo addition and aromatization with 1,4-benzoquinone (equation 300)[460].

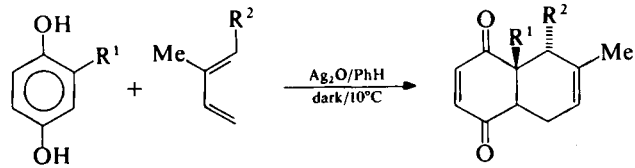


(300)

R = Me, Et, Bu 69–75%

Keana and Eckler[461] continued study of an interesting report by Jung[462] concerning the detailed effect of enol–ester diastereomers on reactivity in Diels–Alder chemistry. Three of the four isomers are reported and in view of the importance of these reactive dienes this investigation should be made more quantitative. There also seems to be a lack of clear communication among the authors and some irritating typographical problems occur in the first article.

While the *in situ* generation of 1,2-quinones has been a common practice, this method is rare with the corresponding 1,4-quinones. Kraus and Taschner have applied the procedure to quinones bearing destabilizing electron-withdrawing substituents (equation 301) with excellent results[463].



(301)

94–100%

R^1 = CO_2Me, CHO, Ac; R^2 = $OSiMe_3$, CH_2CO_2Et, $(CH_2)_2OBz$

An extraordinary formation of a polycyclic molecule deserves attention (equation 302)[464].

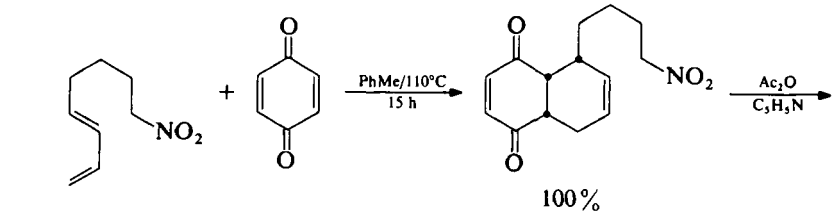
k. Non-Diels–Alder products

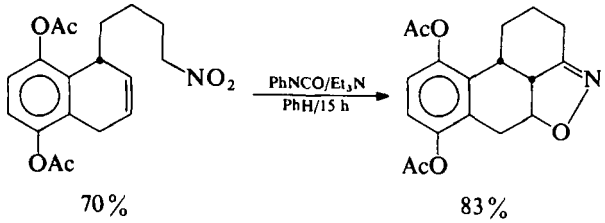
In some instances the formation of an unexpected product can be the most interesting outcome. The addition of 8-methoxyheptafulvene to 1,4-naphthoquinone produces a good yield of the azulene derivative (**95**, equation 303)[465]. This chemistry has been developed more fully showing the range of quinones which can be used[466].

There are several potential diene reaction sites in the indene **96**. A low yield of cycloadduct is obtained when 1,4-benzoquinone reacts at what might be considered the least likely of these sites (equation 304)[467].

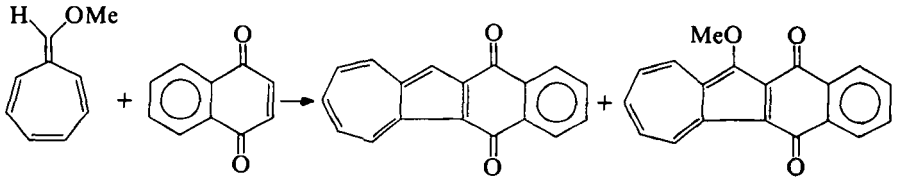
l. Miscellaneous Diels–Alder reactions

The reactions reported here represent a great many suggestions of worthwhile studies, but at the moment must be considered only as interesting examples of the still unrealized potential of this reaction. The vastness of the literature was made clearer to me when I

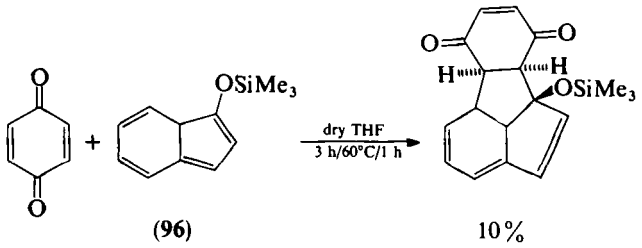




(302)



(95) 65 : 35 (67%) (303)



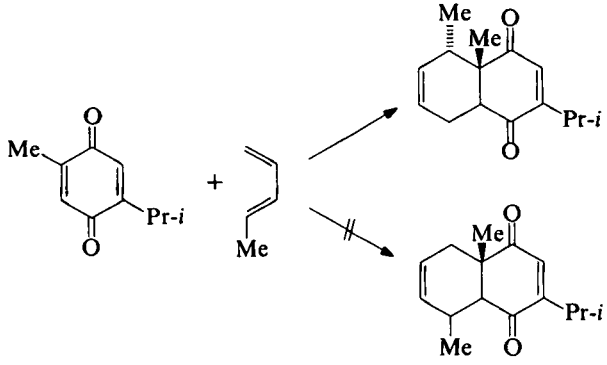
(304)

realized that my earlier intensive search of Fieser's work had failed to uncover a long and rather important paper from 1935[468]! The reaction product failed to form a semicarbazone and was assigned a structure shown to be incorrect by modern methods (equation 305)[469].

Additional references in this section note the wide variety of modifications that have resulted from the stimulus of Diels–Alder–quinonoid chemistry[470-503].

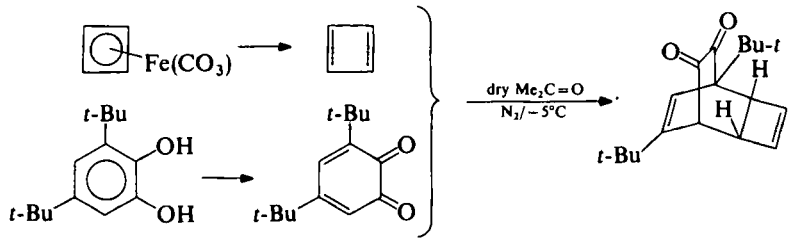
4. Diels–Alder chemistry of ortho*-quinones*

This area of cyclization chemistry has received much attention during the past decade. For example, Diels–Alder products involving 1,2-quinones are often of interest as unusual substrates for subsequent photochemical transformations. Paquette and his collaborators have introduced a novel synthetic approach to 1,3-disubstituted cyclooctatetraenes involving the adduct of 3,5-di-*t*-butyl-1,2-benzoquinone and cyclobutadiene[504,505]. Both



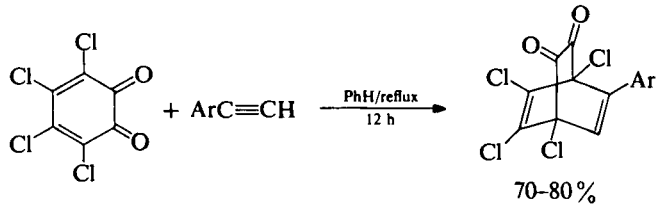
(305)

starting materials were generated *in situ* and the *endo*-adduct was obtained in 51% yield (equation 306).



(306)

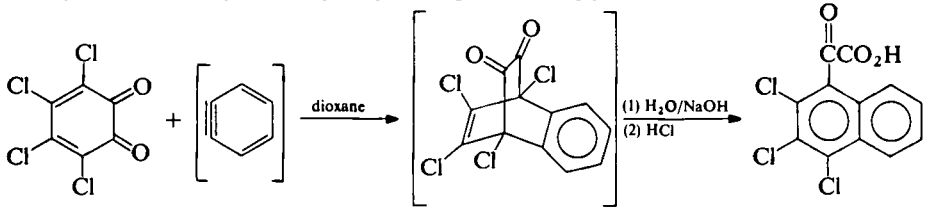
Unsymmetrical chlorobiphenyls for toxicological studies have been prepared from the adducts of *o*-chloranil and appropriate arylacetylenes (equation 307)[506]. In an earlier study



(307)

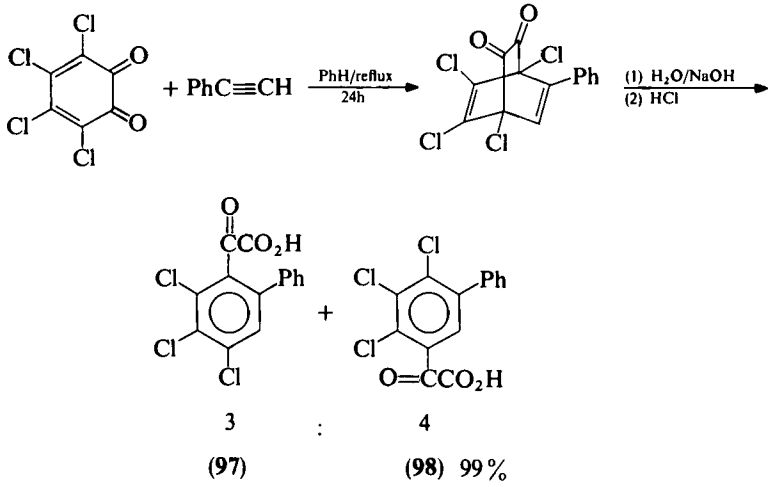
Ar = 3- or 4-ClC_6H_4, 2,4- or 2,5-$Cl_2C_6H_3$

Pyle and his colleagues had repeated a still earlier Diels–Alder reaction of *o*-chloranil with benzyne followed by basic hydrolysis to produce a glyoxylic acid (equation 308)[507].



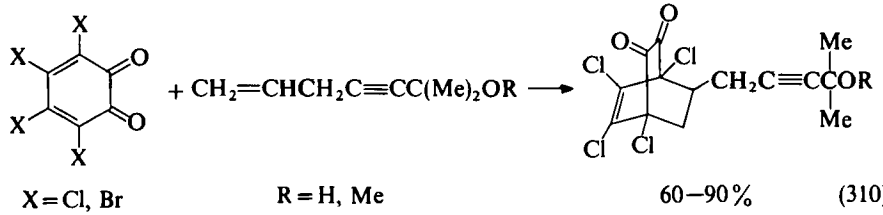
(308)

Realizing the synthetic potential of this sequence they employed phenylacetylene and obtained a nearly quantitative yield of two isomeric biphenylglyoxylic acids (**97** and **98**, equation 309).



(309)

The Diels–Alder chemistry of 1,2-quinones with alkynes has been the subject of several reports. For example, given a choice between reaction at alkyne or alkene linkages the tetrahalo-1,2-benzoquinones react as dienes and the alkene as a dienophile (equation 310)[508]. The yields are moderate, and no evidence is presented for the absence of the

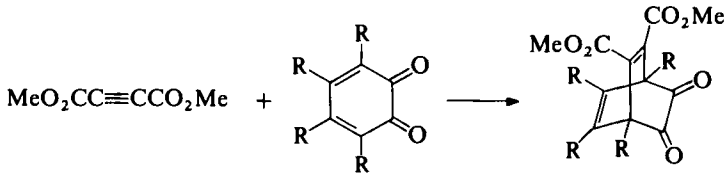


(310)

alternative product or bis-addition. A later, greatly expanded report shows that terminal conjugated dienes behave analogously, giving the adducts in high yield. The quinones proved to be the most reactive dienes studied, and a detailed account of their molecular orbitals is presented[509].

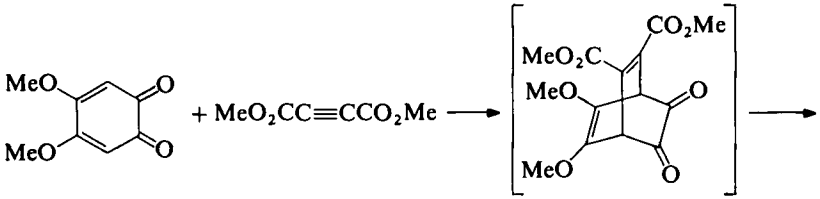
An interesting observation illustrates the relationship between the structure of the quinonoid starting material and that of the product[510]. Using dimethyl acetylenedicarboxylate as the dienophile alkyl and allyl substituted 1,2-benzoquinones gave only bicyclic α-diketones (equation 311). When the strong electron-donating effect of two methoxy groups is present the probable initial adduct decomposes under the reaction conditions (equation 312). Finally, when both types of substituents are involved in the fully substituted quinone, 3,6-di-*n*-propyl-4,5-dimethoxy-1,2-benzoquinone, decomposition without addition is observed.

Verboom and Bos have studied the reactions of 1,2-quinones with cyclooctyne and found several different product structures depending upon both the reaction conditions and the exact nature of the quinone[511]. The presence of the Lewis acid catalyst is essential for the 9,10-phenanthrenequinone reaction (equation 313) and leads to complete conver-

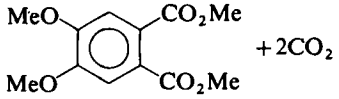


(311)

R = H, Pr, allyl, CH = CHMe variable 20—70%



(312)



42%

sion of the expected Diels–Alder product to the rearranged isomers shown with 3,5-di-*t*-butyl-1,2-benzoquinone (equation 314). The amount of catalyst, temperature and reaction time are important to the product distribution in equations 314 and 315. The second carbonyl bridged product (**100**) is not formed by rearrangement of either the first (**99**) or the normal Diels–Alder adduct.

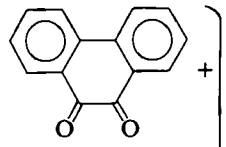
A ring-expansion reaction has been used in attempts to synthesize an intermediate related to the highly oxygenated natural product purpurogallin (**101**) (equation 316)[512]. While the product is not one expected from the Diels–Alder reaction, its relationship to those obtained by Bos and Verboom might be investigated.

The addition of cyclobutadiene to 1,2-naphthoquinone occurred in good yield (equation 317)[513].

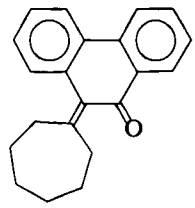
Danishefsky and his colleagues have added to their extensive investigations of regiospecificity in Diels–Alder reactions of oxygenated dienes and dienophiles with a few examples of 1,2-benzoquinones[514–516]. The use of 4-methoxy derivatives is generally successful and extremely structure dependent (equations 318, 319). Of even greater interest is their demonstration that the first reaction is very solvent dependent while the second is not. With either solvent, or their mixtures, a small amount of the other product was obtained, but the influence of the change in environment is far more dramatic than might be expected.

A kinetic study of the addition of substituted styrenes to the halo-1,2-benzoquinones (equation 320) shows normal Diels–Alder adducts in which the quinone acts as a diene and the characteristics of a neutral mechanism[517]. The results are discussed in terms of molecular orbitals.

A much more detailed orbital treatment accompanies the reported addition of cyclopropenes to 1,2-benzoquinone and its tetrachloro derivative (equations 321, 322)[518,519]. When *o*-chloranil reacts with 3-methyl-3-phenyl- or 3,3-diphenylcyclo-

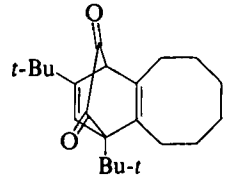


$BF_3 \cdot Et_2O$, $CHCl_3$



85%

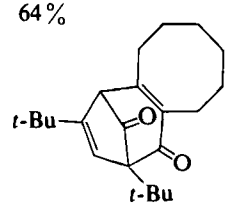
(313)



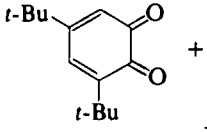
(314)

$CHCl_3$/4.5 h, ambient

64%



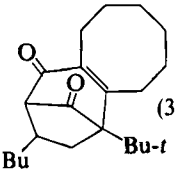
36% (**99**)



Products of equation 314

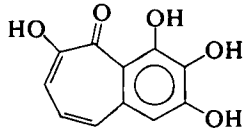
$BF_3 \cdot Et_2O$

(**99**) +

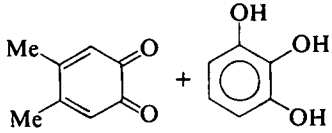


(315)

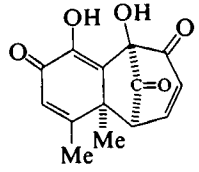
86% (**100**) 14%



(**101**)

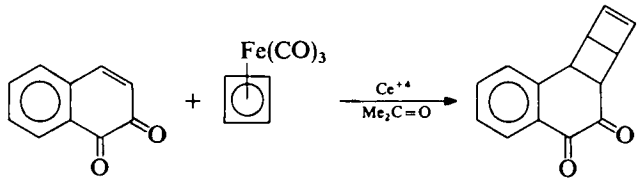


dry dioxane, [O]



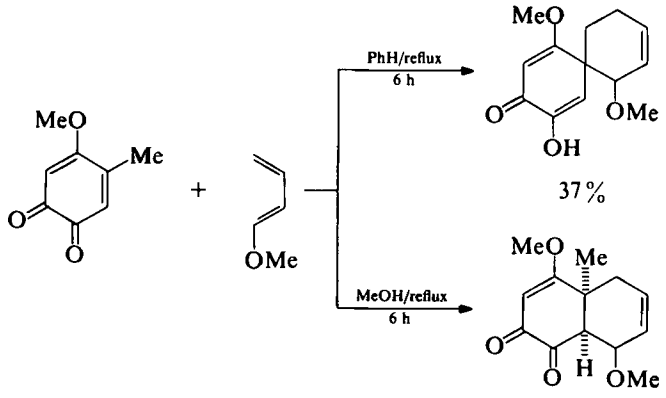
(316)

92%



75%

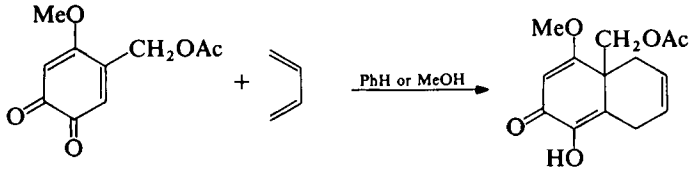
(317)



37%

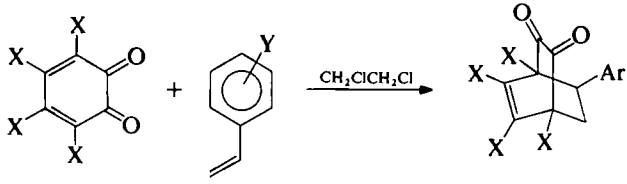
67%

(318)

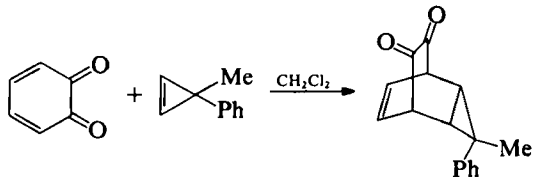


81%

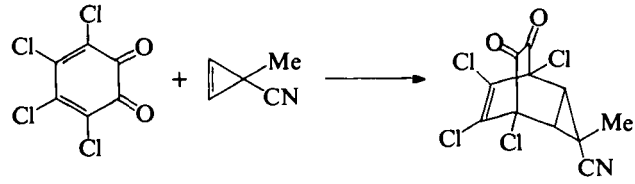
(319)



(320)

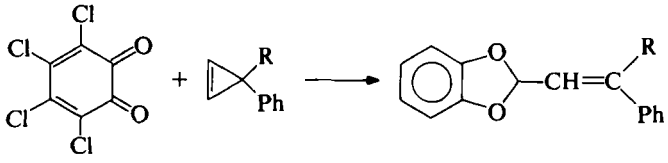


(321)



(322)

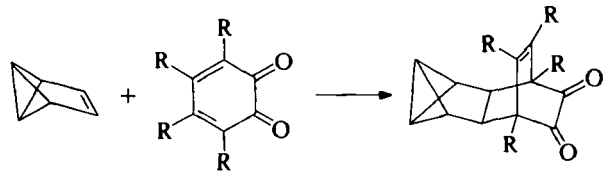
propene a very different product structure results (equation 323). A mechanism involving a charge transfer complex is presented and supported by ionization potential measurements.



(323)

R = Me, Ph

Simple 1,2-benzoquinones produce normal Diels–Alder adducts in which the quinone reacts as a carbon diene[520-524]. For example, both 1,2-benzoquinone and its tetrachloro analog add readily to the electron-rich double bond of benzvalene (**102**) to form the expected pentacyclic adduct (equation 324)[521]. The presence of four chlorine atoms led to

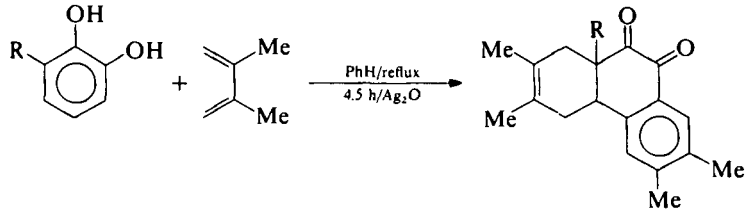


(324)

(**102**) R = H, Cl

a much higher isolated yield (90% compared to 58%) of product. The structures were determined using ^{13}C-NMR spectra.

When these fragile, but versatile, compounds contain strong electron-withdrawing substituents they can serve as carbon dienophiles. Al-Hamdany and coworkers have examined this chemistry using nascent 1,2-benzoquinones bearing such substituents in the 3- or 4-position. Their first report suggested a mechanistic pathway for the observed diadducts (**103**) summarized in Table 6 (equation 325)[525].



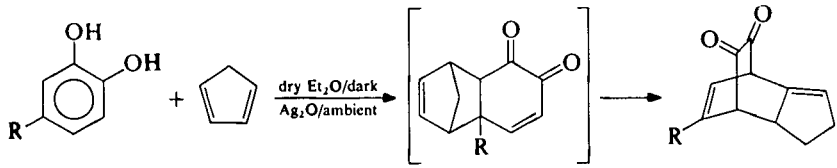
(325)

R = CHO, Ac, CO_2Me, CN, COPh, COEt (**103**)

Using analogous 4-substituted quinones and cyclopentadiene the isolated product (**104**) would be the result of the quinone acting as the dienophile (equation 326)[526]. An

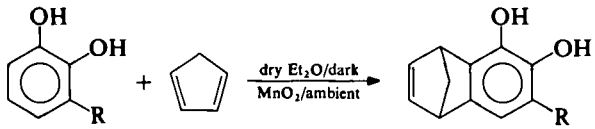
Table 6. Product yields from Diels–Alder chemistry of nascent 1,2-benzoquinones with electron-withdrawing 3- or 4-substituents[525-527]

R	Yield (%) 103	104
3-CHO	25	60
4-CHO		45
3-COMe	51	40
4-COMe		55
4-COEt		—
3-COPh	65	46
4-COPh		51
3-CO_2Me	78	63
4-CO_2Me		69
3-CN	43	62
4-CN		58



(105) (104) (326)

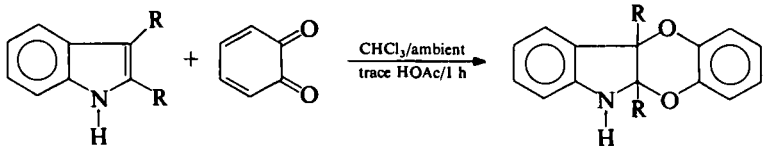
intermediate, the adduct **105** is postulated, but no evidence is presented. Yields similar to those just cited are also noted in Table 6. These results contrast markedly with those reported for 1,2-benzoquinones bearing electron-withdrawing groups in the 3-position (equation 327)[527]. While the authors are wrong in reporting that Ansell and his



(327)

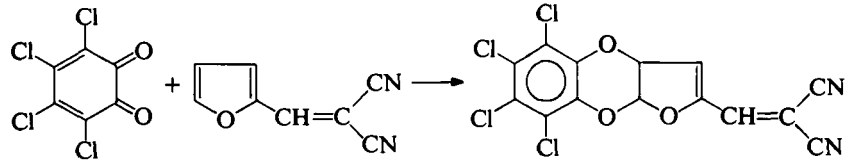
collaborators[528] did not study electron-withdrawing substituents, their studies do expand our understanding of those important compounds.

The α-dicarbonyl structure of 1,2-quinones provides a useful variant from the diene system, and it too has been the subject of several Diels–Alder studies, for example, the reactions of 3-substituted indoles with 1,2-benzoquinone occur in low yield (equation 328)[529]. However, when both the 3- and 4-position are part of a fused ring system, good yields are obtained.

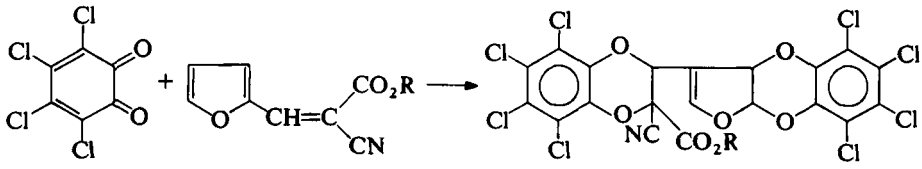


(328)

Latif and his collaborators, in a study with *o*-chloranil showed that with furfurylidenemalononitrile a mono-adduct involving the heterocyclic ring was obtained (equation 329); while with furfurylidenecyanoacetic ester a di-adduct was obtained (equation 330)[530, 531].

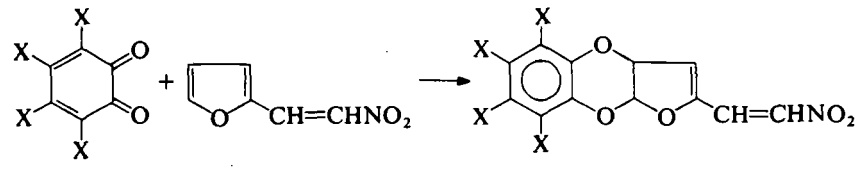


(329)



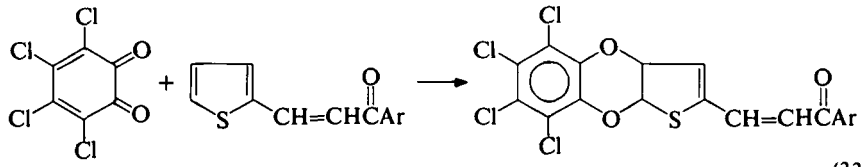
(330)

Furans substituted by a 2-nitrovinyl group cyclized in fair to good yield and only at the furan ring with either chloranil or bromanil (equation 331)[531].

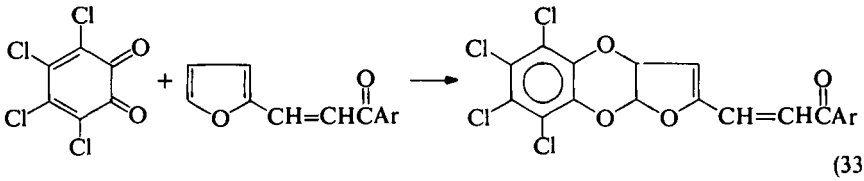


X = Cl, Br (331)

These studies have been extended in several directions. The thiophene ring (equation 332) and the furan system bearing acrylophenone substituents (equation 333) have both



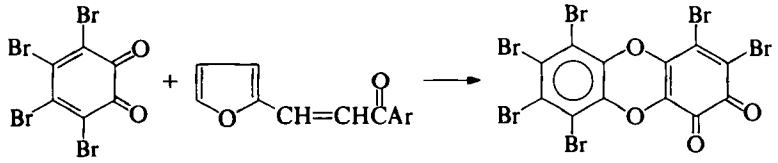
Ar = Ph, 4-ClC$_6$H$_4$, 4-An (332)



(333)

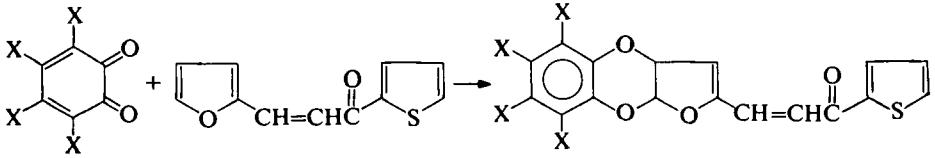
proven fruitful[532]. The yields reported are generally above average and the difference in reactivity is marked. The apparently analogous reaction of bromanil follows a different

path; only cyclization by dehydrohalogenation between two moles of quinone is observed (equation 334)[533].



(334)

Members of this same team have examined the situation when both the furan and the thiophene ring are present in the substrate (equation 335)[534]. In both cases the mono-

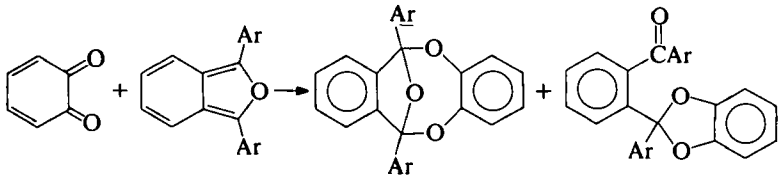


X = Cl, Br

(335)

adduct corresponded to furan ring addition. Even the more drastic conditions required to force addition of *o*-chloranil to the alkene failed to produce any reaction at thiophene. The di-adduct from *o*-bromanil was too unstable to isolate.

Latif and his colleagues have applied this useful dioxane preparation to other synthetic efforts[535] as have a number of other workers in studies ranging from rather theoretical[536-539] to the preparation of complex heterocyclic molecules[540,541]. Friedrichsen and colleagues have continued to experiment with reactions of 1,2-benzoquinone and isobenzofurans[542]. In addition to the eight-membered heterocycle (**106**) previously reported, they obtained a product which is possibly related to that found in certain reactions of cyclopropenes[520] (equation 336). The products distribution is discussed in



Ar = Ph, 4-Tol, 4-ClC_6H_4, 4-An

(**106**)

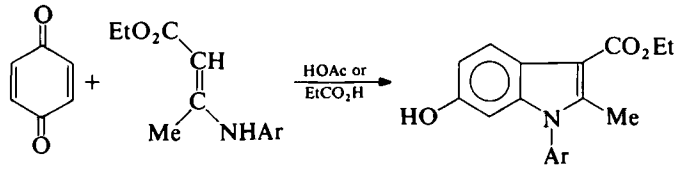
(336)

terms of solvent and temperature variations and evidence presented for a dipolar transition state.

B. Nenitzescu Reaction

Allen has not only made extensive contributions to the understanding and application of this singular synthesis of 5-hydroxyindoles, but has written a detailed review of the field[543]. Several additional studies have appeared by Kuckländer and his collaborators[544-550].

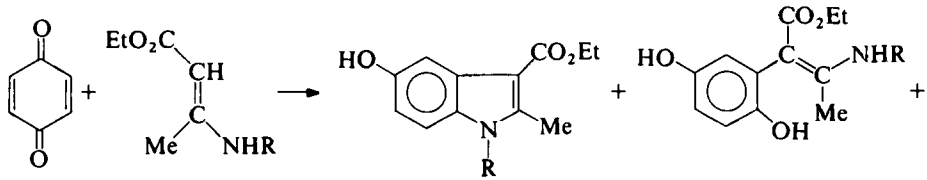
Studies in acetic and propionic acids show that a variety of *n*-arylindoles can be prepared, but in rather modest yields (equation 337)[544-547]. A more detailed investigation

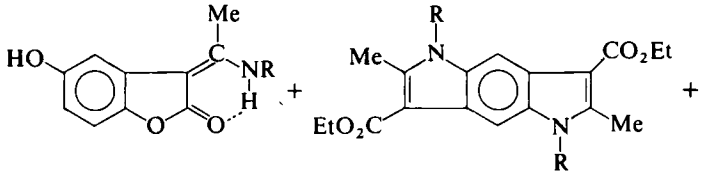


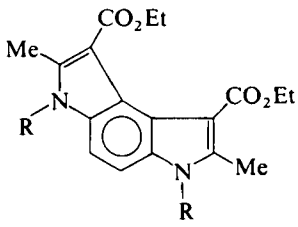
20–35%

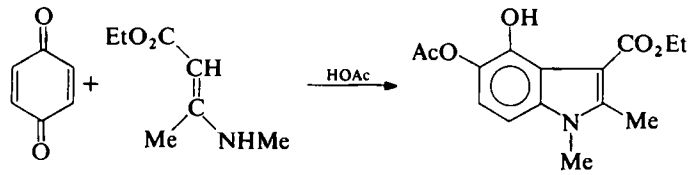
Ar = Ph, 3- or 4-Tol, 4-XC_6H_4, 4-$NO_2C_6H_4$, 4-NCC_6H_4, 4-An (337)

of the by-products from addition of two equivalents of enamine was made and a direct cyclization mechanism suggested (equation 338)[548]. These same workers have shown that acyl migration can take place under Nenitzescu conditions (equation 339)[549] and one is reminded of the studies of Bruce[457]

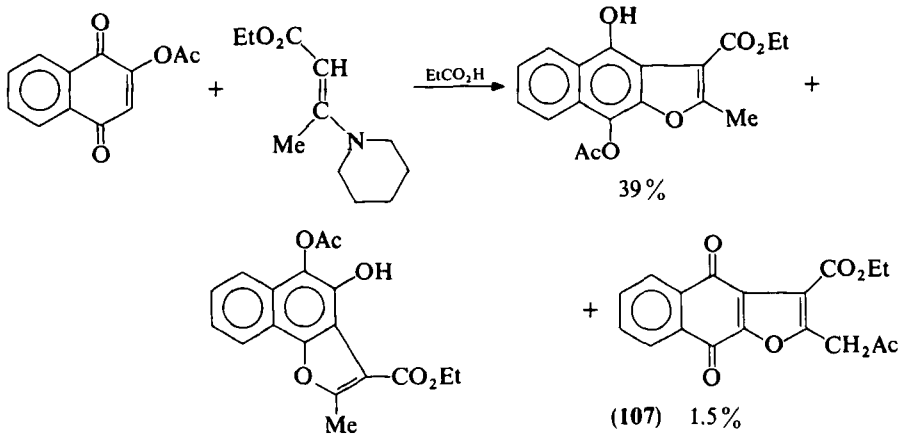






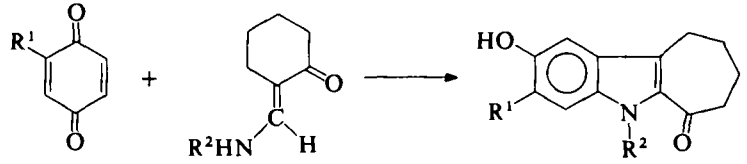


Kuckländer also studied the formation of furans derived from 2-acetoxy-1,4-naphthoquinone (equation 340)[547]. An acyl migration in this reaction leads to the formation of the minor by-product (**107**).



(340)

The reaction of cyclohexenones with quinones to produce carbazoles is known but when the enamine is external to the ketone ring, an interesting ring-expansion reaction takes place (equation 341)[549]. While the yields are low (ca. 20%) the method provides a simple

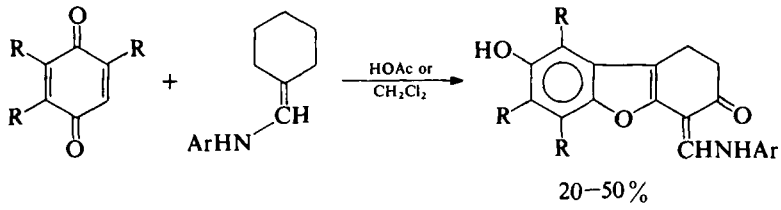


(341)

R^1 = Me, Bz, Ph, 4-Tol, 4-FC_6H_4, 4-An; R^2 = H, Me

entry to rather complex ring systems. The apparent regiospecificity remains to be deomonstrated.

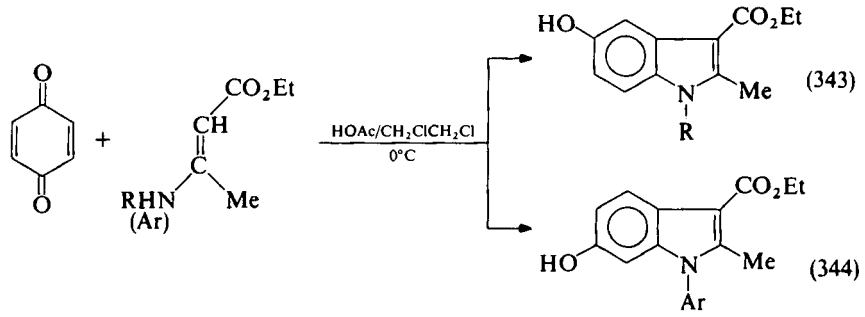
More recently Kuckländer and Töberich have examined the frequently observed formation of benzofurans under Nenitzescu conditions (equation 342)[550]. With 2,3- and 2,6-dichloro-1,4-benzoquinones the yields are exceptionally high.



(342)

R = H, Cl; Ar = 4-FC_6H_4, 4-An

Grinev and his colleagues have continued their studies of the influence of nitrogen substituents on the course of the condensation[551]. Hydrogen or a methyl group leads to 5-hydroxyindoles (equation 343) while phenyl or *p*-tolyl groups produced the corresponding 6-hydroxyindoles (equation 344). They have also examined the addition of enamines to

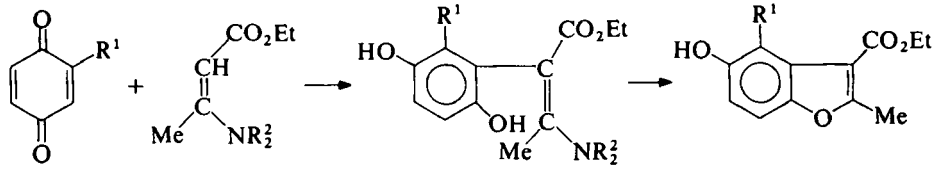


(343)

(344)

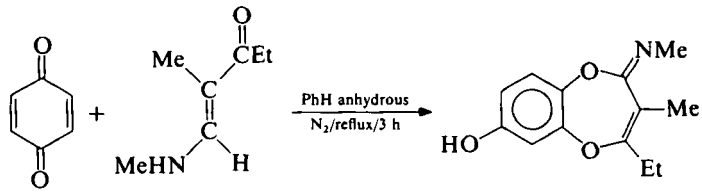
R = H, Me; Ar = Ph, 4-Tol

quinones bearing strong electron-withdrawing groups and found that the initial adduct leads to benzofuran but not to indole (equation 345)[552].



$R^1 = SO_2Ph$, $SO_2C_6H_4Me$-4; R^2 = H, Me, Ph (345)

The chemistry of enaminones has attracted some interest. Kozerski noted that the unusual 2*H*-1,5-benzodioxepine ring system (**108**) can be formed in 50% yield under Nenitzescu conditions (equation 346)[553]. In a later publication he offers interesting

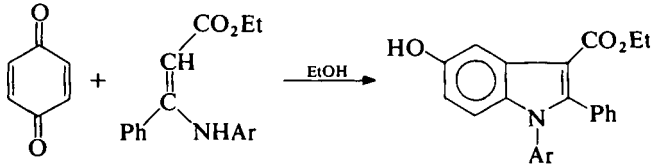


(346)

(108)

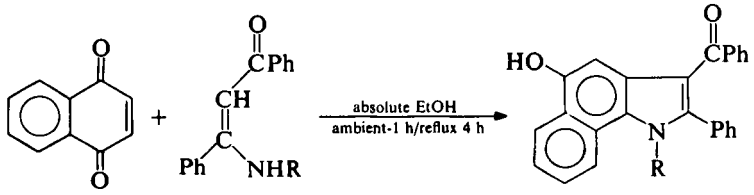
information concerning acyl rearrangements in intermediates but unfortunately fails to develop the earlier promising chemistry[554].

Siddappa and his colleagues have examined an example of the traditional cinnamate enamine (equation 347)[555, 556] and some newer unsaturated phenones (equation 348)[557]. In both instances the yields with few exceptions lie in the 30–40% range.



(347)

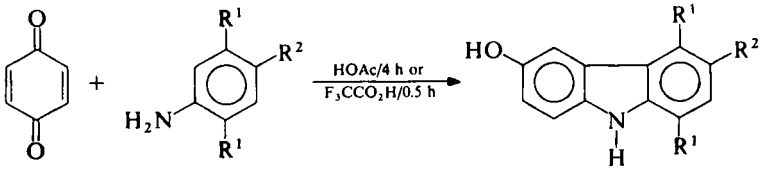
Ar = Ph, 4-BrC_6H_4



(348)

R = Pr, Bu, *i*-Bu, Ph, Bz

A number of research groups have reported isolated examples of the Nenitzescu reaction[558-562]. Of broader interest is the development of a procedure for the synthesis of enamines from *S,S*-acetals of ketene which expands the range of available starting materials showing average reactivity toward quinones[563]. Another extention is the use of anilines as the enamine reactant (equation 349)[564]. The yields are low, but important by-

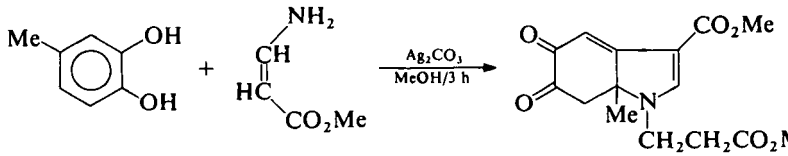


(349)

R^1 = H, Me; R^2 = NO_2, CN

products are obtained. This chemistry should be examined in more detail. A novel modification has been reported by Patrick and Saunders[565]. Using nitromethane as the solvent and methyl crotonates as enamines, they were able to obtain 2–3-fold improvement in yields with few exceptions, e.g. *N*-phenyl. The reasons for this will require additional study.

Allen suggested that studies of *o*-quinones with enamines should be undertaken[543] and one such report is available (equation 350)[566]. In spite of the very low yield this is a truly



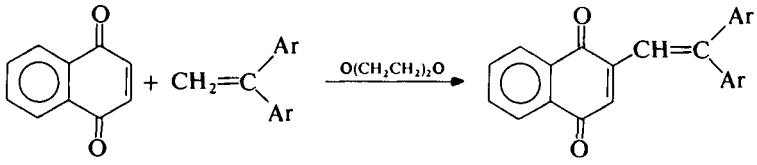
(350)

novel approach, and the authors indicate that it has an obvious relationship to the cross-linking of proteins by such quinones.

C. Other Examples of Cycloaddition Chemistry

1. Nucleophilic alkenes

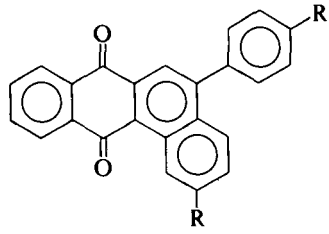
In 1944 Gates studied reactions between quinones and unsymmetrical diaryl ethenes and reported the formation of the expected Michael addition products (equation 351)[567]. Nearly 40 years later modern instrumentation and synthetic methods enabled him to show that a cyclization reaction to produce compound **109** had taken place[568]. The corresponding reaction of 1,2-naphthoquinone does lead to the Michael products originally proposed (equation 352). Gates suggests that differences in charge density at the reactive carbons



(351)

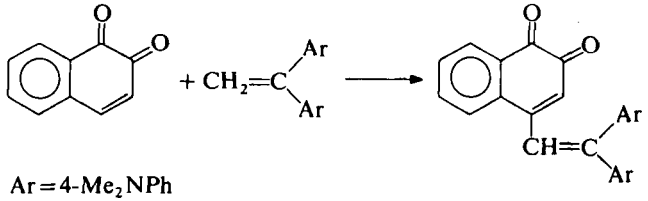
Ar = 4-$Me_2NC_6H_4$, 4-An

59%, 40%



(109)

R = NMe_2, OMe



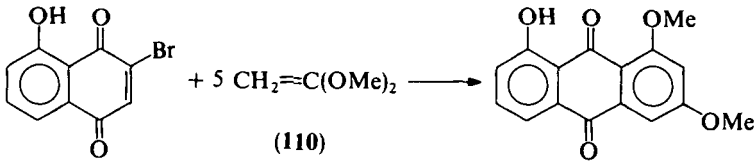
(352)

Ar = 4-Me_2NPh

84%

may account for this potentially useful distinction. At least one other group has noted and utilized this chemistry[569].

Other highly polarized alkenes have been explored extensively by Brassard and Cameron and their research groups. In 1973 Brassard's group published the first of a series of studies on the cycloaddition of ketene acetals (**110**) chiefly to halogenated juglones (equation 353)[570]. Their greatest contributions lie in determining the regiospecificity of

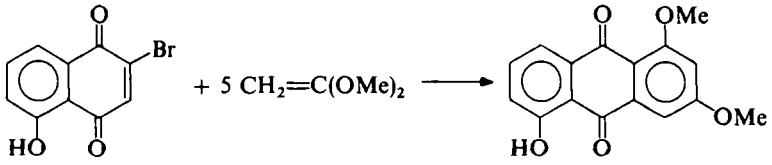


(353)

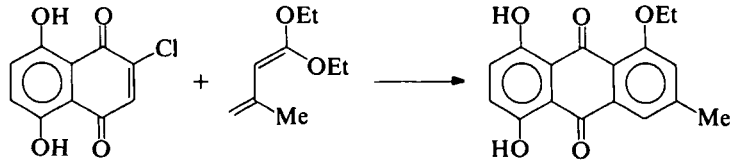
(**110**)

60%

these reactions. When 2-bromojuglone is used the isomeric anthraquinone is obtained (equation 354). In both experiments no evidence of the isomeric product was found. The reaction was also successfully applied to halonaphthazarins and isopropenylketene acetal can also be used (equation 355). An attempt to produce chloroanthraquinones showed that chloroketene acetals are too unreactive to be useful.

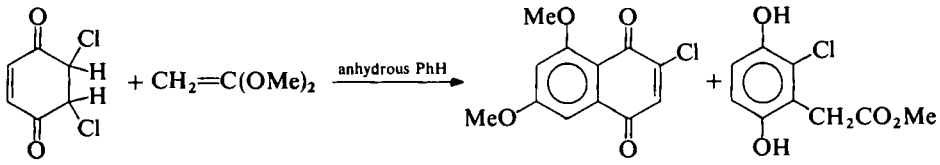


(354)



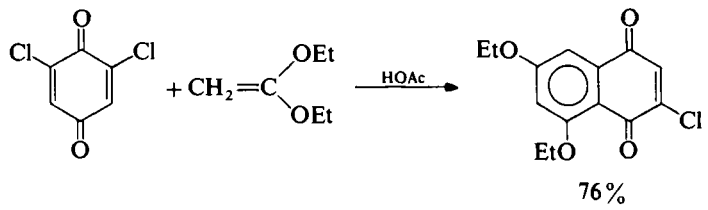
(355)

The extension of this chemistry to the benzoquinone series has been accomplished in low yield but does avoid the long reaction sequences previously required (equation 356)[571].



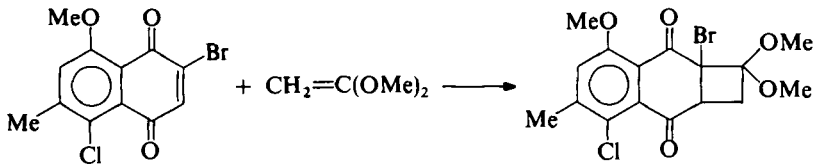
(356)

The major product also presents interesting potential applications. The use of acetic acid leads to good yields of the desired naphthoquinones (equation 357)[572].



(357)

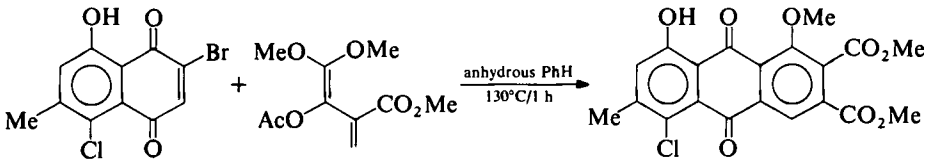
In later work Brassard and Banville found that juglone methyl ether, which gives low yields of the expected anthraquinone, reacts slowly with the ketene acetal to produce a cyclobutane derivative (equation 358)[573]. Neither acid nor base provide any catalysis and



(358)

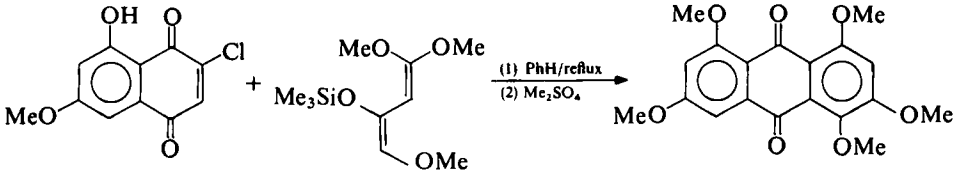
the cyclobutyl compound does not seem to be an intermediate in the anthraquinone reaction.

The same two scholars have found a method of converting the ketene acetals to vinylketene acetals showing promise as efficient dienes for a Diels–Alder synthesis of the anthraquinone system of important natural products (see Section V.A.2) (equation 359)[574]



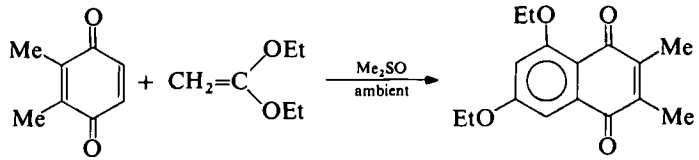
89% (359)

This chemistry has been applied to the preparation of a broad range of natural products through the introduction of the trimethylsilyloxy substituent (equation 360)[575].



78% (360)

Cameron and his coworkers have not only made excellent use of the chemistry of nucleophilic alkenes in the synthesis of natural products but have added their own original touches. Some of this chemistry is closely associated with Diels–Alder[120, 130] and bromination reactions[131] already cited. They have found dimethyl sulfoxide to be a useful solvent for these reactions (equation 361)[576, 577].



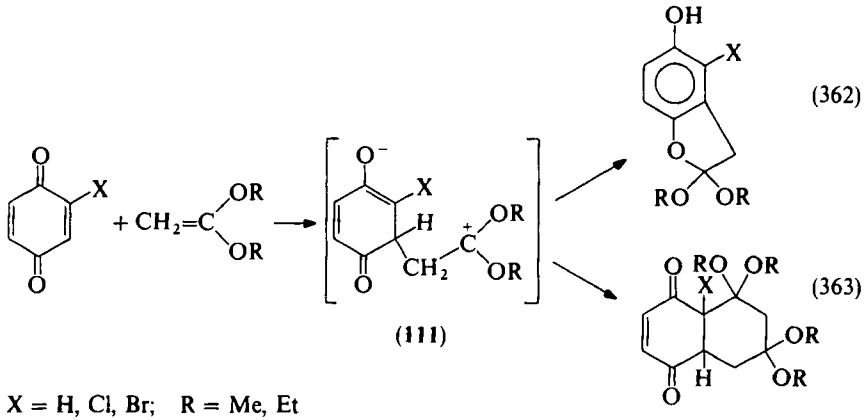
(361)

56%

In addition to its synthetic work[578] Cameron's group has contributed to our understanding of the mechanism of these cyclization reactions[579]. It has long been recognized that a competing 1 : 1 addition leads to benzofuran products and the presence of a zwitterionic intermediate (**111**) is strongly supported by the isolation of the initial adduct from both paths (equations 362, 363).

Cameron and Crossley used dimethyl sulfoxide to good advantage and complemented Brassard's studies by exploring the addition of nucleophilic alkenes to benzoquinones (equation 364)[580]. In benzene they were able to duplicate the earlier work which leads to benzofuran (equation 365). They were even able to isolate the initial orthoester adduct (**112**).

When 2-acetyl-1,4-benzoquinone was employed as the substrate rather different chemistry was found (equation 366)[581]. The overall yield was only 48% but the promise of this new route deserves to be explored.

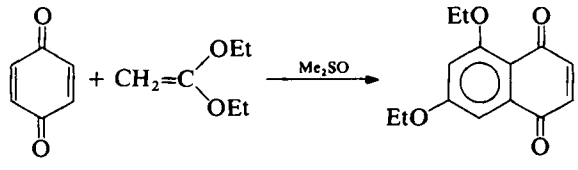


(362)

(363)

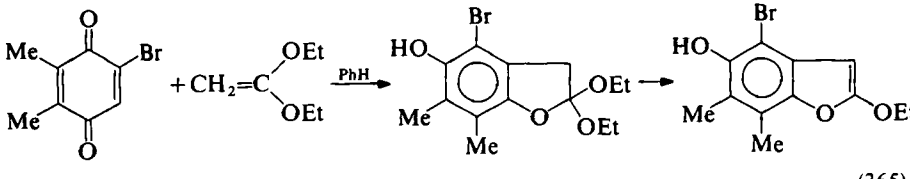
(111)

X = H, Cl, Br; R = Me, Et



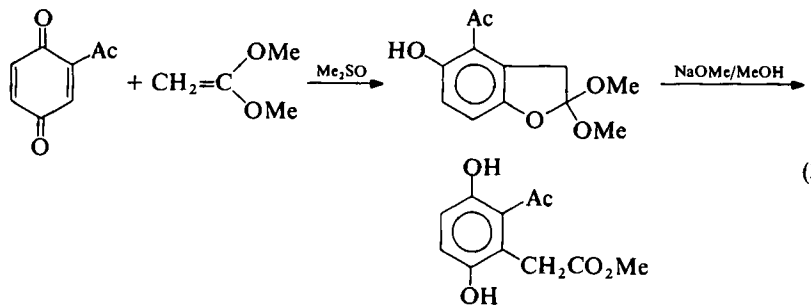
(364)

63%



(112)

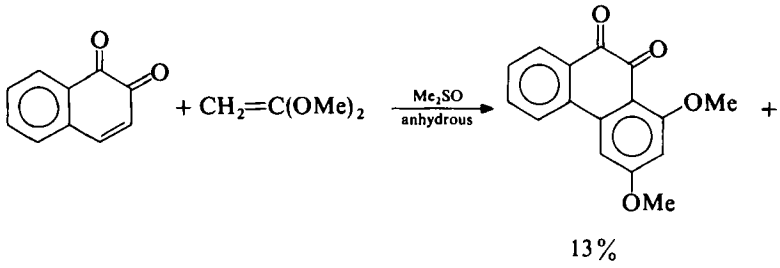
(365)



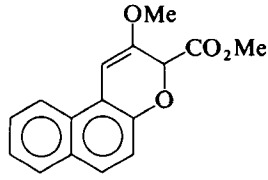
(366)

The addition of 1,1-dimethoxyethene to 1,2-naphthoquinones has also been carried out and as one might expect the product mixture is more complex and only the two major products were examined in detail (equation 367)[582].

In an attempt to expand this chemistry a 1,1-dianilinoethene was employed and good yields of a substitution product (**113**) and a dimeric quinone (**114**) were obtained (equation 368)[583a].

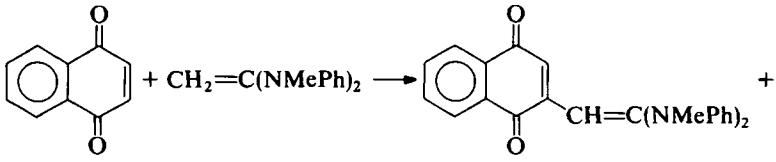


13%

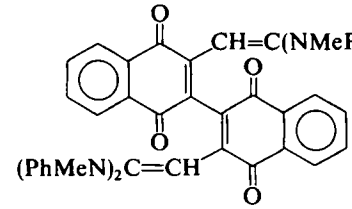


21%

(367)



(113) 52%



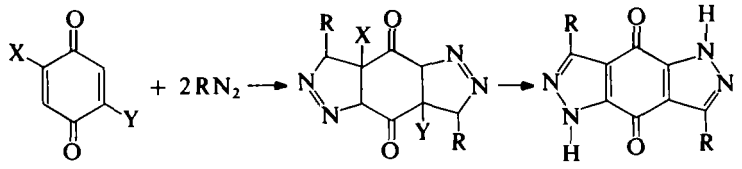
(368)

(114) 16%

Like Brassard, Cameron and his colleagues have extended their work to analogous alkoxy and silyloxy dienes in Diels–Alder approaches to their natural product goals[583b].

2. *Diazo cycloadditions*

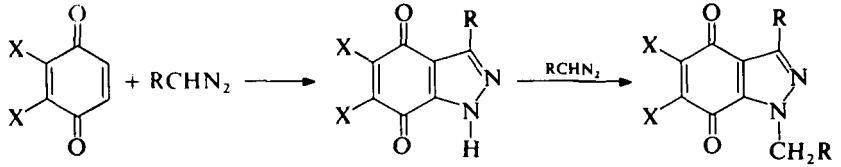
Interest has continued in the direct cycloaddition of diazomethane to quinones with Eistert and his colleagues making substantial contributions. Further studies on the von Pechmann reaction show that the unsymmetrical isomer is formed in either the addition or substitution route to the initial unstable intermediate (equation 369)[584]. Analogous chemistry is found with diazoethane and ethyl diazoacetate. Yields are much improved (35–50%) by the addition of alkali with the greatest change (ca. 85%) found in substitution chemistry. A later study showed that when three moles of diazoalkanes are added to 2,6-dichloro-1,4-benzoquinone, one of the carbonyl groups is epoxidized and the unsym-



(369)

X, Y = H, Cl, Br; R = H, Me, Et, CO_2Et

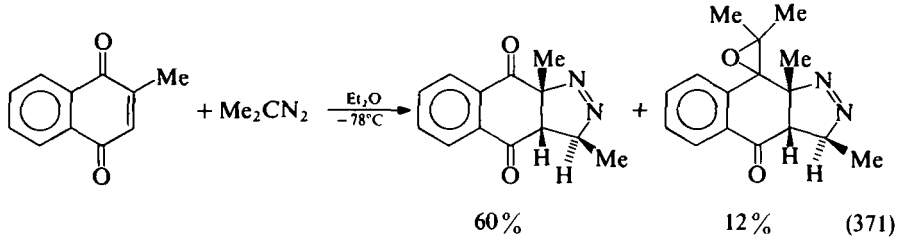
metrical adduct is formed[585]. The chemistry has been extended to 2,3-dichloro- and 2-anilino-1,4-benzoquinones (equation 370)[586, 587]. In all cases initial addition takes place at



R = H, Me; Ar = Ph, 4-Tol; X = H, Cl, ArNR (370)

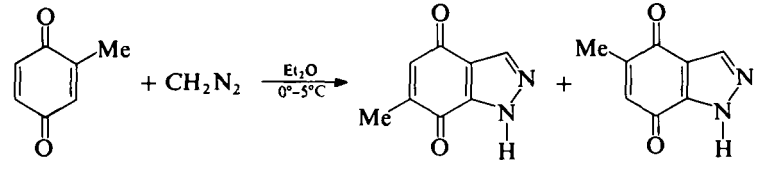
the unsubstituted carbon–carbon double bond and more diazoalkane attacks the pyrazole nitrogens.

An interesting and unexpected example of the ease with which diazomethane addition can overcome serious steric hindrance has been noted (equation 371)[588].



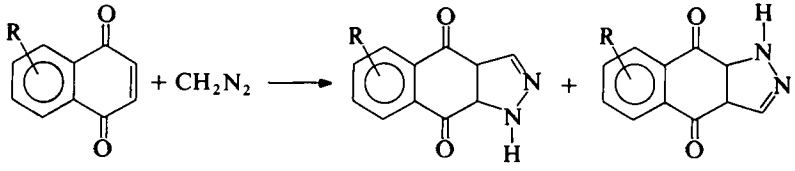
60% 12% (371)

A detailed study of the regiospecificity of diazomethane addition to 2-methyl-1,4-benzoquinone shows that one isomer is formed in significantly greater yield (equation 372)[589].



85 : 15 (30%)

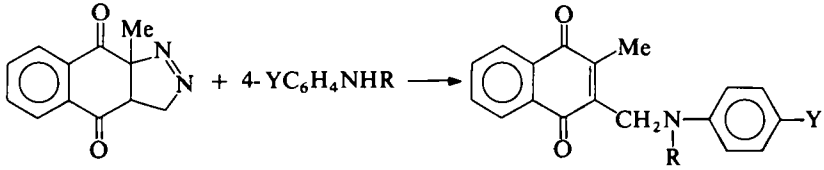
Laatsch, using the dimeric naphthoquinones to synthesize diazo addition products of known structure, has been able to investigate the isomer distribution when diazomethane is added to naphthoquinones substituted in the benzenoid ring (equation 373)[590]. These experiments provided data for a sensitive test of the predictive value of HMO calculations.



(373)

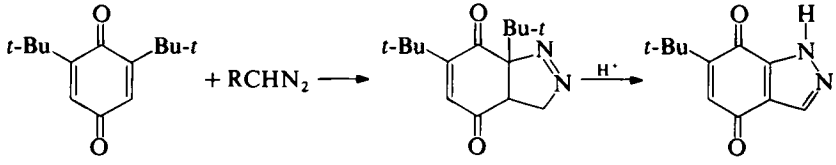
The following sequence of group effects was observed: 5-OAc > 5-OMe > 5-Cl > 5-Me > 6-Me > 6-Ac > 5-OH.

From a synthetic point of view the addition of diazoalkanes to quinones has been employed in a number of instances. For example, the adduct of 2-methyl-1,4-naphthoquinone served as a useful intermediate in the synthesis of 2-(anilinomethyl) derivatives (equation 374)[591]. Under acidic conditions the diazoalkane adducts of 2,6-di-*t*-

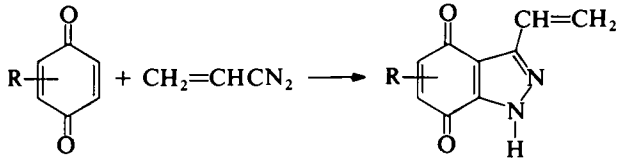


R = H, Me, Cl; Y = Me, MeO, NMe_2 (374)

butyl-1,4-benzoquinone suffer dealkylation (equation 375)[592]. The addition of vinyldiazomethane to various 1,4-benzoquinones provided monomers for the investigation of redox polymers (equation 376)[593].



R = H, Me (375)

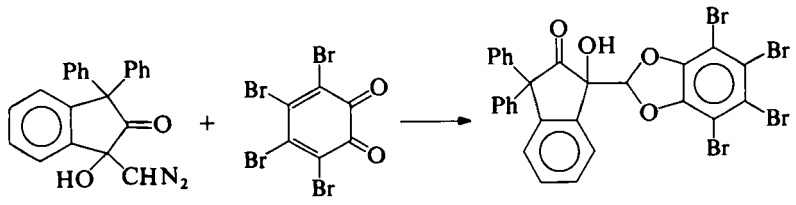


(376)

R = H, Cl, Me, OMe

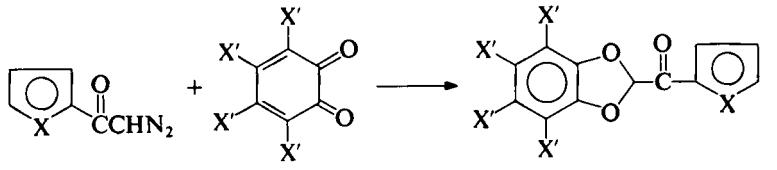
In general the reaction of tetrahalo-1,2-quinones with diazo groups leads to attack at a carbonyl group and the formation of a dioxole. Eistert and his coworkers trapped the 'diazo aldol' from 3,3-diphenylindane-1,2-dione (**115**) by reaction with *o*-bromanil (equation 377)[594].

Latif and Meguid have used this method to prepare a series of furyl and thienyl derivatives (equation 378)[595] The ease of the reaction and the good yields as compared with their earlier experience with analogous acetophenones suggest that the heteroatoms enhance the nucleophilic character of the carbanion intermediate.



(115) 50%

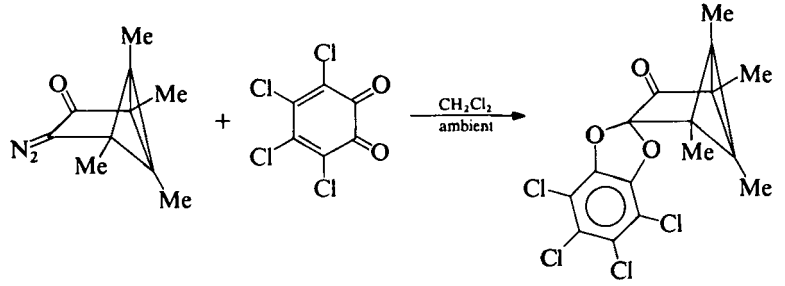
(377)



X=O, S; X′=Cl, Br 50–70%

(378)

The highly strained diazoketone of a bridged bicyclobutane forms a dioxole in good yield under mild conditions (equation 379)[596]. The authors point out that this observation

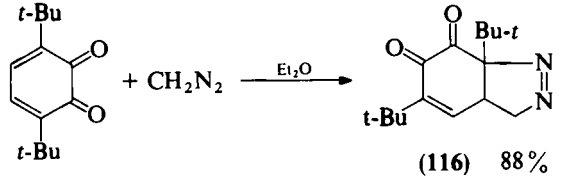


73%

(379)

is more consistent with a zwitterionic intermediate than a carbene since the latter would be likely to undergo intramolecular rearrangements.

Ershov and his colleagues have shown that the actual addition product obtained with 1,2-quinones depends heavily on the ratio of starting materials[597]. When 3,6-di-*t*-butyl-1,2-benzoquinone reacts with an equimolar quantity of diazomethane only the indazole **116** is obtained (equation 380). With additional diazomethane one of the carbonyl groups

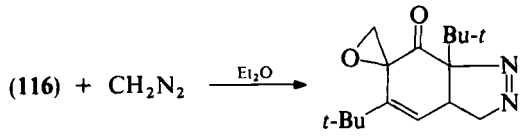


(116) 88%

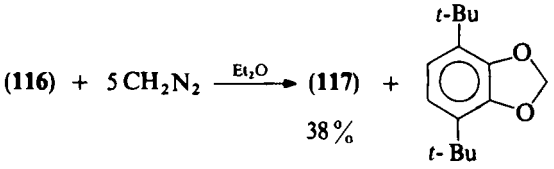
(380)

is converted to a spirooxirane (**117**, equation 381). Finally, with a 5–10-fold excess of diazomethane both **117** and the dioxole **118** are found (equation 382).

Unfortunately, while there are some excellent mechanistic studies in this field, most concern charge transfer complexes with chloranil and are of limited direct interest. Nagai

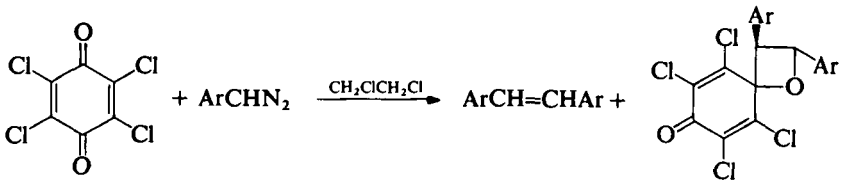


(381)



(382)

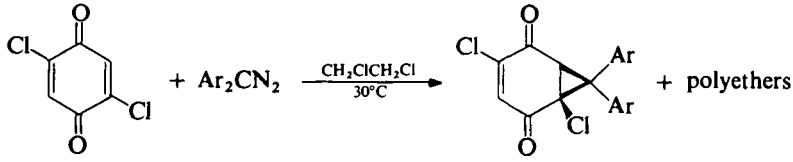
and Oshima have shown that aryldiazomethanes react with a carbonyl of chloranil to give modest amounts of spirooxetanes (**119**, equation 383)[598]. The required stereochemistry of



(383)

the products is important in the discussion of probable transition states consistent with that observed. When these workers expanded their studies to diaryldiazomethanes they observed a dramatic change of products. The total absence of alkenes and spirooxetanes is attributed to the greater steric hindrance of the two aryl substituents and the decreased nucleophilicity of the diazo carbon atom[599]. Only polyethers were found as products from these reactions.

Oshima and Nagai examined the products and kinetics of the reactions of various diaryldiazomethanes with 2,5-dichloro-1,4-benzoquinone (equation 384)[600]. The second-



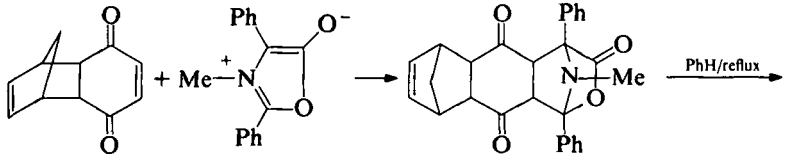
(384)

order rate constants increased with the electron-donating ability of the *para* substituent. A Hammett plot of the constants for the cycloaddition pathway display an excellent linear dependence indicating simple 1,3-dipolar addition.

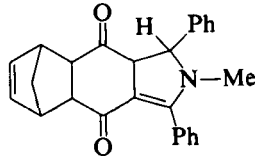
3. 1,3-Dipolar cycloadditions

The greatest interest in these additions has centered on the mesoionic oxazolium-5-oxide system. Myers and his colleagues showed that the 3-methyl-2,4-diphenyl derivative (**120**)

adds in good yield to the 1,4-benzoquinone–cyclopentadiene Diels–Alder adduct (equation 385)[601]. On refluxing in benzene this hexacyclic system loses carbon dioxide and opens



(120) 88%

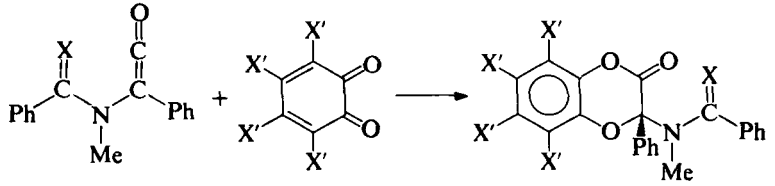


(121) 86%

(385)

a new pathway to the important 2*H*-isoindole-4,7-diones (**121**). Friedrichsen and his collaborators have been able to isolate the acid intermediate of the decarboxylation reaction and they obtained both the mono- and bis-adducts with 1,4-benzoquinone itself[602].

With 1,2-benzoquinones the reaction of either **120** or its sulfur analog takes place through an open-chain ketene form and a lactone results (equation 386)[603].

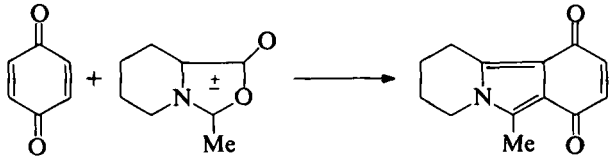


X = O, S X' = H, Cl

(386)

Matsukubo and Kato have questioned the structure of a pyrolysis product of the initial adduct and at the same time confirmed the structures of several important quinonoid products[604].

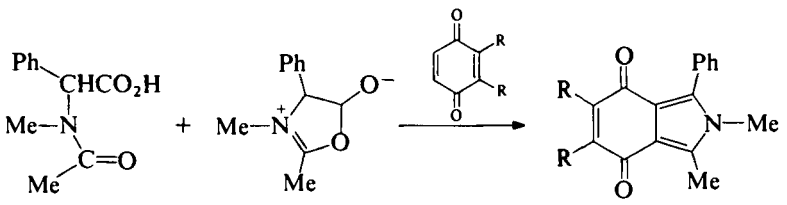
Matsumoto and coworkers have examined the more elaborate system, anhydro-5-hydroxyoxazolium hydroxide (**122**) and found useful yields of heterocyclic quinones (equation 387)[605].



(122)

(387)

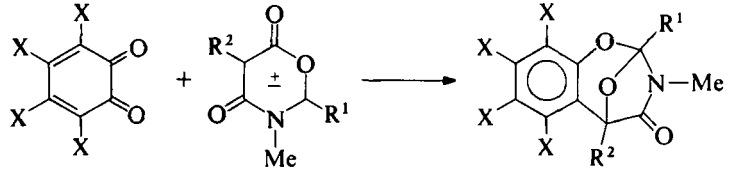
Myers has expanded the work of his group to include several more sensitive reactants by generating them *in situ* (equation 388)[606]. The yields are lower but the relative ease of making these heterocyclic systems makes the route attractive.



(388)

R = H, Me, OMe

The reaction of 6-oxo-6*H*-1,3-oxazin-3-ium-4-olate (**123**) with 1,2-benzoquinone or *o*-chloranil gives a product which must arise from a much more complex sequence of steps (equation 389)[607]. The high yields and the polycyclic structure make this too a promising

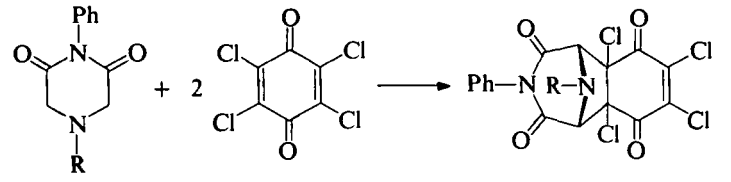


(389)

(**123**) 60–90%

X = H, Cl; R^1 = Me, Ph, Bz, 4-Tol 4-An; R^2 = Ph, Bz

route worthy of further investigation. A perhaps distantly related addition reaction involves 2,6-piperazinediones (**124**) and chloranil (equation 390)[608].



(390)

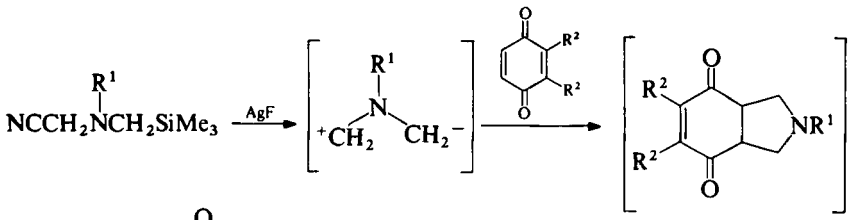
(**124**)

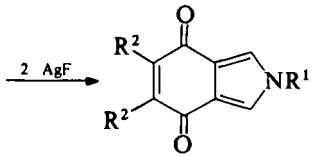
R = Me, Ph 59%, 31%

A recently published route to the isoindole quinonoid structure involves the addition of an azomethine ylide generated in the presence of a quinone (equation 391)[609]. Once again the ease of the reaction and the good yields make this an attractive route to an important class of compounds.

Still another route to the 4,7-isoindolediones involves the addition of aryl isocyanides to 1,4-benzoquinones (equations 392, 393)[610]. The yields of mono-adduct are quite good (30–70%) and the two isomeric di-adducts are formed in approximately equal yields. A zwitterionic intermediate involving carbon–carbon bond formation followed by reaction with a second equivalent of isocyanide is proposed as the mechanistic pathway.

The 1,3-dipolar addition of nitrile *N*-oxides have been studied extensively by Shiraishi and his coworkers. In reactions with chloranil only reactions at the carbonyl groups are observed (equation 394)[611]. Both mono- and di-adducts are obtained and the yields are generally excellent. With less highly substituted quinones both carbonyl and ring-carbon addition take place (equation 395)[612]. The dimethyl quinones give mainly isoxazolines.

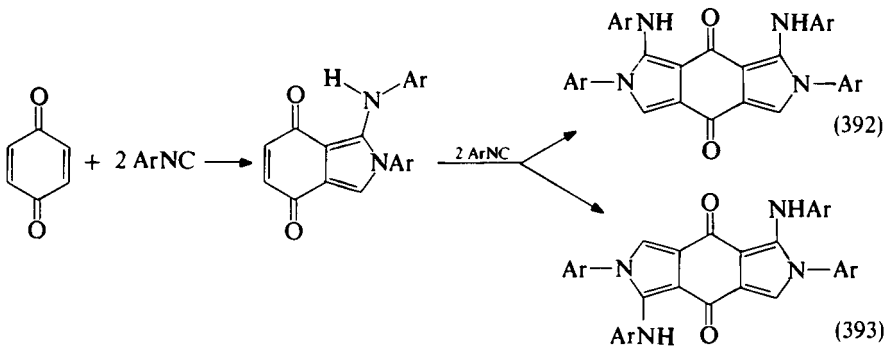




60–75%

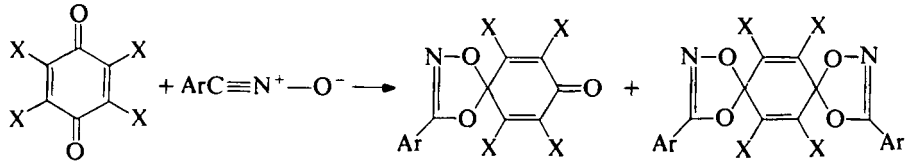
(391)

R^1 = Me, Bz; R^2 = H, Me, MeO

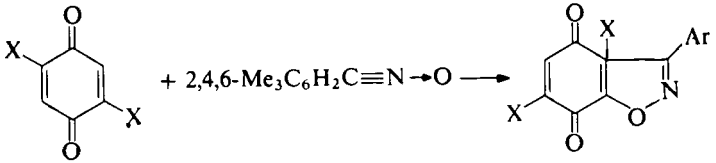


(392)

(393)

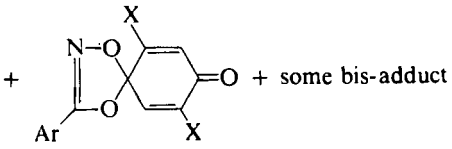


X = F, Cl, Br, I; Ar = Ph, 2,4,6-$Me_3C_6H_2$, 2,3,5,6-Me_4C_6H isomers 1:1 (394)



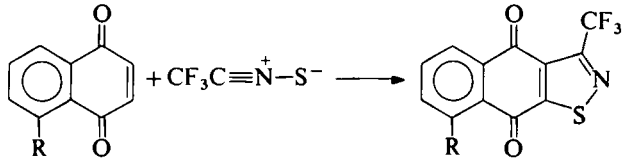
(395)

X = H, Me, Cl, MeO



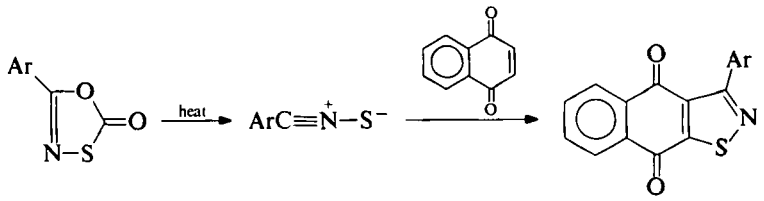
Electronic effects of the quinone substituents explain the reactivity of the carbonyl groups toward this reagent. These results have been extended to include a variety of alkyl and alkylhalo substituted 1,4-benzoquinones and the regiospecificity described[613]. The yields remain uniformly good, and it is apparent that steric effects are much less important than electronic ones. A detailed analysis of these reactions in terms of frontier molecular orbitals has been presented and some predictions confirmed by subsequent experimental studies[614].

Trifluoroacetonitrile *N*-sulfide, which bears a resemblance to the *N*-oxides just discussed, has also been prepared and reacts with 1,4-naphthoquinone and juglone in poor yields (equation 396)[615]. Such compounds also do add in reasonable yield to the simple quinones (equation 397)[616].



(396)

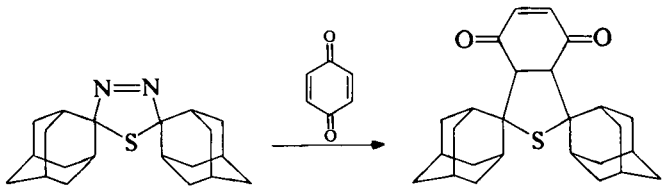
R = H, OH



(397)

Ar = Ph, 4-An 36%, 42%

Two interesting sulfur dipolar reagents have been reported. Sasaki and his colleagues have found that the highly strained bisspiroadamantane thiadiazine **125** loses nitrogen smoothly in refluxing xylene and the resulting ylide adds to 1,4-benzoquinone (equation 398)[617].



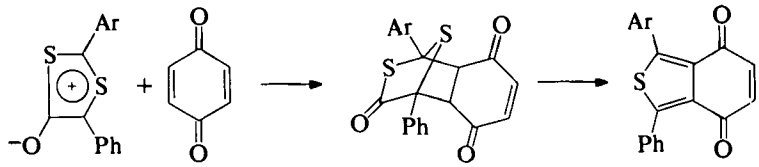
(398)

(**125**) 59%

The mesoionic 1,3-dithiolylium-4-olate (**126**) adds to 1,4-benzoquinone and loses carbon oxysulfide to form the corresponding thiophene quinone (equation 399)[618].

4. Homophthalic anhydride cyclization

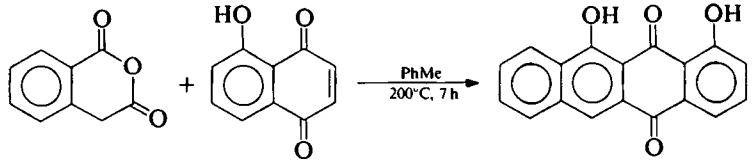
A new route to anthracyclinones was developed by Tamura and his collaborators by the condensation of quinones with homophthalic anhydrides (equation 400)[619,620]. This scheme has been applied successfully to the generation of key tetracyclic intermediates



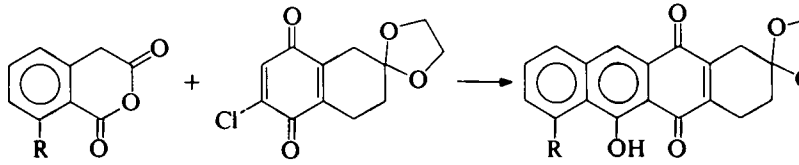
(126)
Ar = Ph, 4-Tol

60%, 55%

21%, 42% (399)



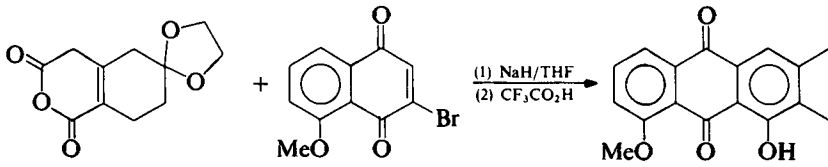
49% (400)



R = H, OMe

43% (401)

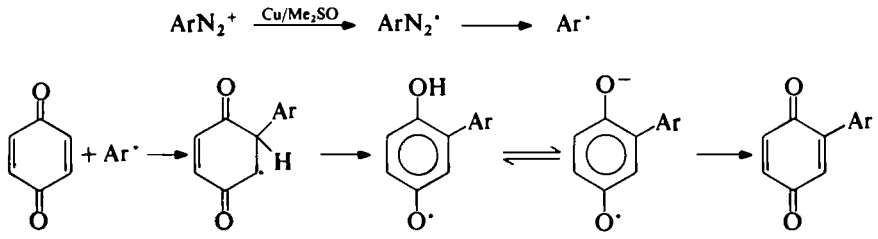
(equation 401). In the case of the 8-methoxy compound cycloaddition took place in poor yield but was greatly improved (65%) using the lithium salt of the anhydride. This technique has been explored and found to give excellent results[621,622]. The optimum method appears to be treatment of the anhydride with sodium hydride in dry tetrahydrofuran (equation 402). The application of this powerful new method to the synthesis of complex natural products continues at a high level[623,624].



95% (402)

VI. ARYLATION OF QUINONES

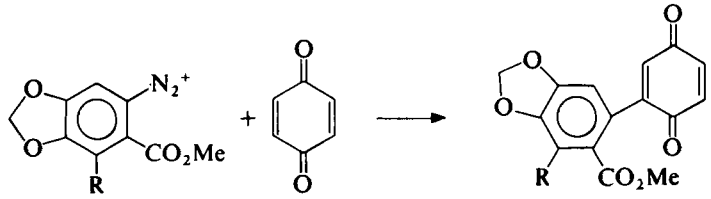
A lively interest has continued in joining aromatic rings to quinones. The use of diazonium salts, the Meerwein reaction, represents the method of choice in most instances, and a detailed review of it appeared[625], as well as a report of the absolute rate constants for the addition of aryl radicals to 1,4-benzoquinone (equation 403)[626]. The radicals show near diffusion-controlled rates and are not affected by significant polar considerations. The rate constant obtained for the phenyl radical ($8.8 \times 10^8\ dm^3mol^{-1}s^{-1}$) agrees well with that reported for radicals generated by radiolysis of diphenyl sulfoxide



Ar = 4-XC_6H_4 (X = H, Cl, Me, MeO, NO_2) (403)

(1.2×10^9 $dm^3mol^{-1}s^{-1}$)[627]. An electrochemical investigation supports the importance of the semiquinone radical ion as an intermediate[628].

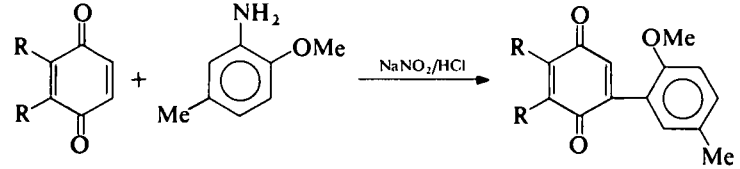
A few purely synthetic applications have appeared in connection with studies of natural products. Mondon and Krohn have used some highly oxygenated diazonium salts to good advantage (equation 404)[629]. The low yield with a free hydroxyl group is not surprising



(404)

R = H, OH, OBz 87%, 24%, 68%

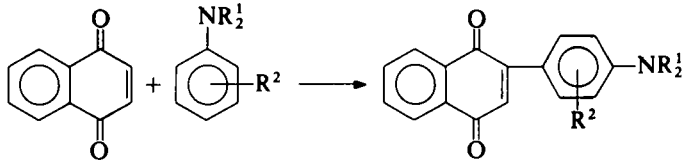
and it is easily overcome as indicated. Cameron and his coworkers have observed that a trace of hydroquinone is a significant catalyst for the Meerwein reaction[120]. They found a large difference in yield for two closely related reactions but did not offer any explanation (equation 405).



(405)

R = H, Me 53%, 20%

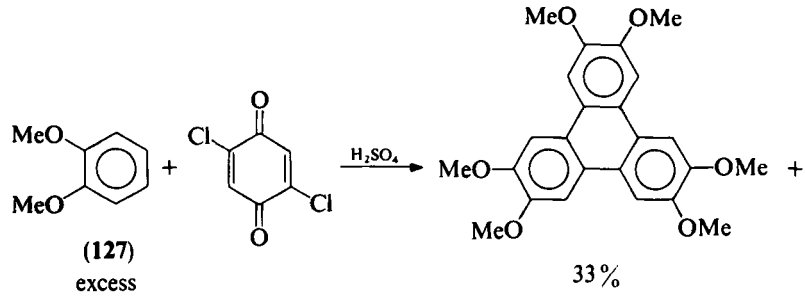
Tertiary aromatic amines can be effective arylating reagents (equation 406)[630] The yields are variable (10–66%) and the corresponding substitution chemistry with 2,3-dichloro-1,4-naphthoquinone was especially disappointing.

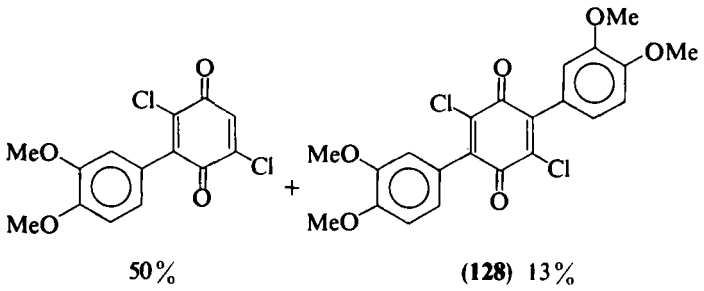


(406)

R^1 = Me, Et; R^2 = 2-Me, 2-MeO, 2-Cl, 2,6-Me_2

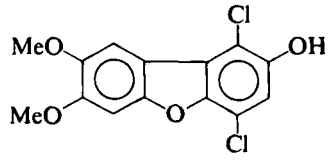
Reactions between aromatic ethers and quinones constitute a means of arylation and have received a good deal of study, particularly by Musgrave and his collaborators. They have examined in great detail the reactions of veratrole (**127**) with 2,5- and 2,6-dichloro-1,4-benzoquinone (equation 407)[631]. The quinone products were obtained after oxidation





(407)

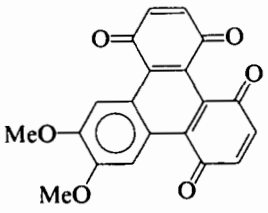
with ferric chloride. If the ratio of reactants is reversed the principal products are the diarylquinone (**128**) and a dibenzofuran (**129**) both formed in 38% yield. The chemistry of



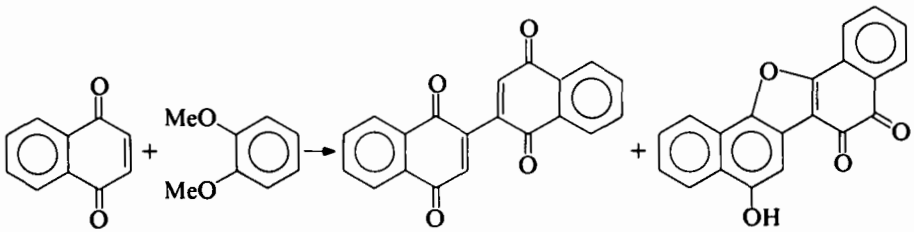
(**129**)

the 2,6-dichloro analog produces a closely related product distribution, and show similar results with 1,4-benzoquinone and its 2-chloro derivative[632,633]. In the latter case aluminum chloride in carbon disulfide is an effective catalyst while several other traditional Lewis acids fail completely. Evidence is presented that the arylbenzoquinones isolated from the reaction mixtures are true intermediates in the formation of the major product which is a triphenylenediquinone (**130**). In demonstrating the structure of these quinonoid products several applications of the Meerwein reaction have been employed[634,635].

By extending these studies to naphthoquinones and aryl ethers Buchan and Musgrave found also two other product types, a dimeric quinone (**131**) and a dinaphthofuran with the 1,2-quinonoid structure (**132**, equation 408)[636]. The latter structure was demonstrated by the unambiguous synthesis of the isomeric 1,4-quinone.



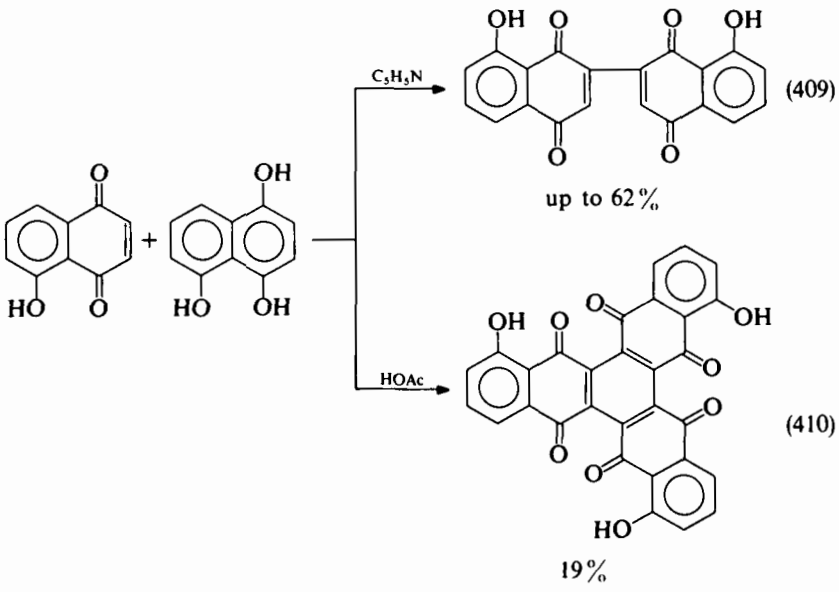
(130)



(131) 18% (132) 5%

(408)

The synthesis and study of dimeric naphthoquinones has been a principal interest of Laatsch. Working with juglone and various methoxynaphthoquinones in pyridine or acetic acid, he has been able to obtain synthetically useful yields of dimers and tricyclic quinones analogous to those found by Musgrave (equations 409, 410)[637] These results are



(409)

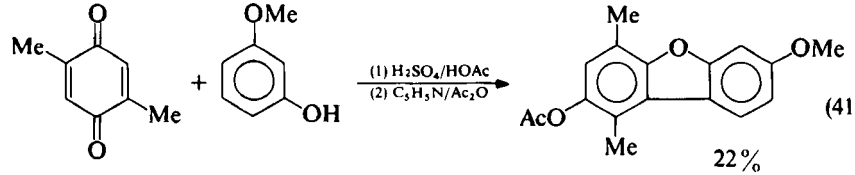
up to 62%

(410)

19%

applicable to the synthesis of natural products and to the understanding of their biosynthesis[638, 639].

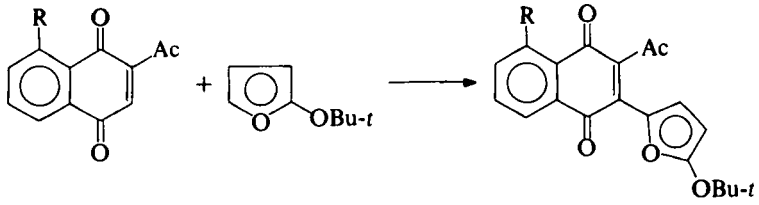
The frequent presence of benzofurans in natural products makes the preparation of this heterocyclic system especially desirable and the quinone–phenol route attractive. Both benzo-[640] and naphthoquinones[641] react with phenols to give key intermediates in reasonable yields (equation 411). The analogous reactions with resorcinol have been



(411)

studied in some detail; an ionic intermediate and the alkyl substitution pattern of the quinone appear to explain satisfactorily the widely differing yields observed[642].

The arylation of quinones by substituted furans also plays a potentially important role in developing new synthetic methods. Kraus and his coworkers have examined the use of butenolide anions for this purpose (equation 412)[643,644]. The presence of the 2-acetyl



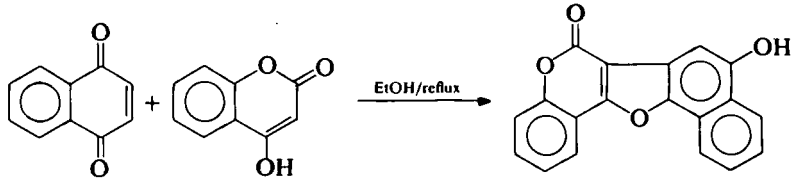
(412)

R = H, OMe

62%, 59%

group is essential since in its absence no reaction took place even with added Lewis acid.

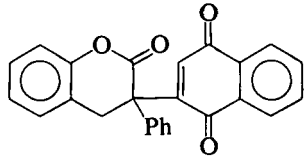
4-Hydroxycoumarin (**133**) has been studied by several groups in efforts to prepare compounds with potentially useful medicinal activity. This lactone adds to 1,4-naphthoquinone and the product has a furan ring (**134**, equation 413)[645]. Slower reactions of 3-



(413)

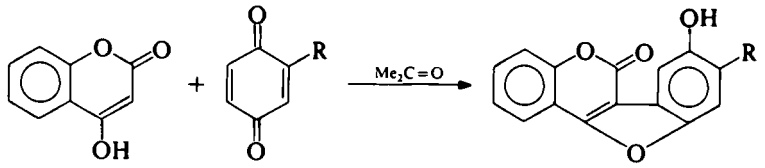
(**133**) (**134**)

phenylcoumarin with either 1,4-benzo- or 1,4-naphthoquinone produce the initial adduct (**135**) in lower (41 and 25%) yields. Similar chemistry with 1,4-benzoquinones (equa-



(**135**)

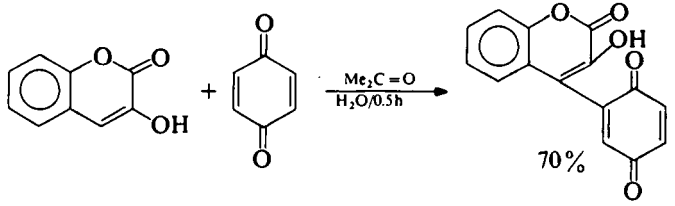
tion 414)[646] gives very reasonable yields. The addition of 3-hydroxycoumarin to 1,4-benzoquinone has also been demonstrated (equation 415)[647]. The statement is made that



R = H, Me, Cl

40–50%

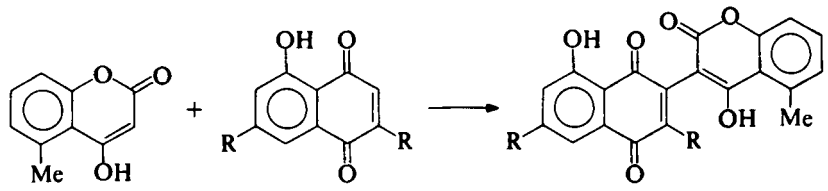
(414)



(415)

the reaction can be used with substituted quinones and 1,2-benzoquinone but no data are presented.

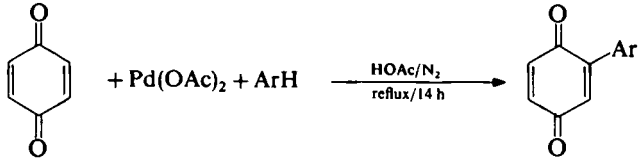
The addition of 4-hydroxy-5-methylcoumarin to 2- and 7-methyljuglones led to the efficient new synthesis of two natural products[648]. The former reaction is notable for the ease with which two bulky groups are introduced at adjacent positions (equation 416).



R = H, Me

(416)

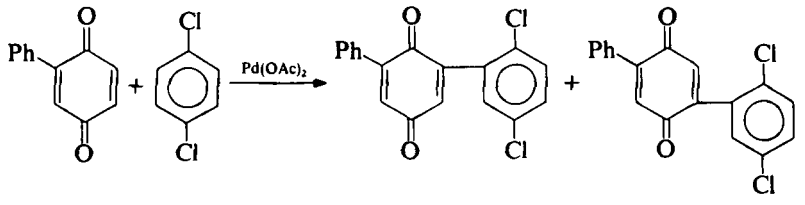
A new and exciting route to aryl quinones has been pioneered by Itahara[649,650]. In acetic acid, palladium(II) acetate reacts with aromatic compounds and couples them in good yield to a variety of quinones (equation 417). In the case of 1,4-benzoquinone, 2,5-



(417)

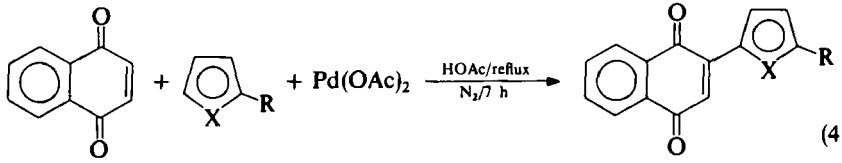
Ar = Ph, 2,5-$Me_2C_6H_3$, 2,5-$Cl_2C_6H_3$

and 2,6-diaryl products are also found. The single instance in which a monosubstituted quinone was studied produced a mixture of two isomeric products (equation 418). Still the result shows that unsymmetrical diarylquinones can be made using this chemistry. Itahara



36% 19% (418)

has also made some progress in the use of reoxidants to improve the efficiency of the palladium[651]. Naphthoquinones and 1,2-quinones are useful in this reaction and its further study seems important, especially in the synthesis of heterocycles bearing quinonoid substituents where it gives excellent results over a broad range of structures (equation 419)[652]. Itahara overlooked an earlier report describing similar chemistry with

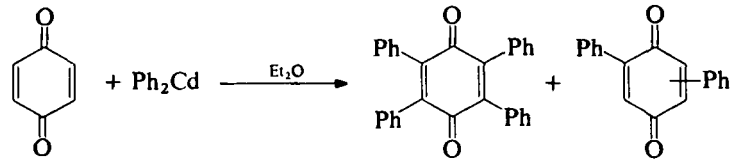


(419)

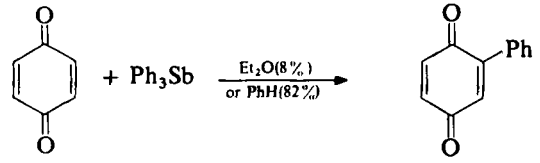
X = O, S, NSO_2Ph; R = CHO, Ac, H 50–70%

palladium dichloride and sodium acetate[653], but he did make a large improvement in yields and has investigated the range of the reaction in detail.

Brief reports of several other organometallic arylation reactions of quinones have appeared. The treatment of 1,4-benzoquinone with diphenylcadmium (equation 420)[654] and with triphenylstibine (equation 421)[655] are examples. The change in degree of



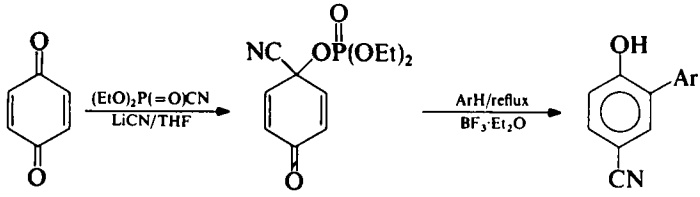
10% 3% (420)



(421)

substitution and the influence of solvent in the latter reaction are both remarkable and deserve further study.

The use of a carbonyl protection reaction and boron trifluoride etherate as a catalyst produces good yields of biaryls with several potentially useful functional groups (equation 422)[656].

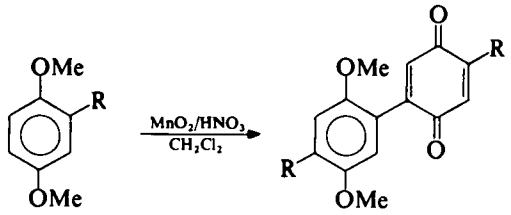


(422)

78% (Ar = Ph)

Ar = Ph, 4-Tol, 2,3- or 2,4-Xylyl, 4-HOC_6H_4, 4-An, 4-ClC_6H_4

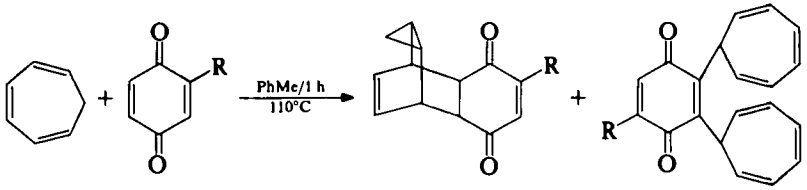
While studying the oxidative demethylation synthesis of quinones Valderrama and his colleagues obtained significant yields of arylated products under certain conditions (equation 423)[657]. These results which were obtained when the reaction mixture was shaken slowly have not yet been further developed.



(423)

R = Me, MeO 39%, 24%

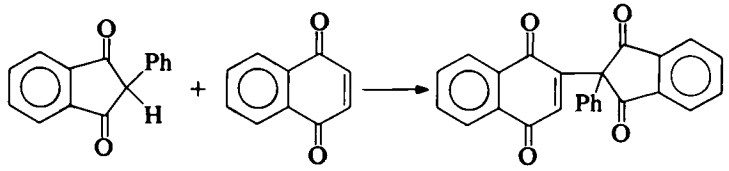
In a study of the thermal addition of cycloheptatriene to 1,4-benzoquinones a surprising arylation product is obtained along with the normal Diels–Alder product (equation 424)[658]. The formation of the crowded 2,3-product was studied and a stepwise



R = H, Me, Ph Me 16% 18% (424)

mechanistic pathway proposed. In a subsequent publication the chemistry has been extended to 1,4-naphthoquinone and the expected monotropyl product isolated[659].

Buggle and her collaborators added 2-phenylindane-1,3-dione (**136**) to a variety of 1,4-naphthoquinones (equation 425)[660]. The ease of addition as opposed to dimerization of

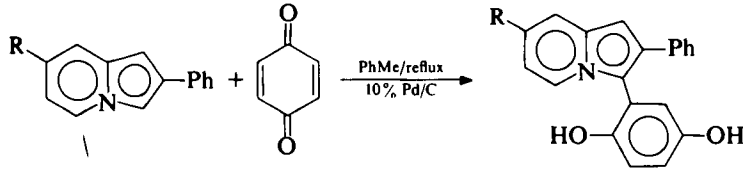


(425)

(136)

136 appears to depend on the redox potential of the quinone, its steric requirements and the solvent.

A potentially useful route to nitrogen bridged heterocyclic compounds is found in the reaction of indolizines (**137**) with 1,4-benzoquinone (equation 426)[661].



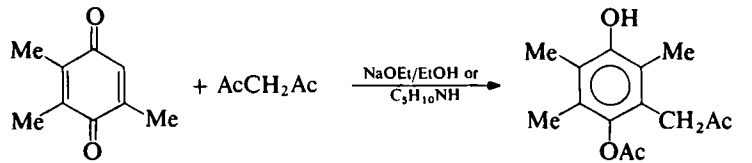
(426)

(**137**) R = H, Me 42%, 59%

VII. ACTIVE METHYLENE QUINONE CHEMISTRY

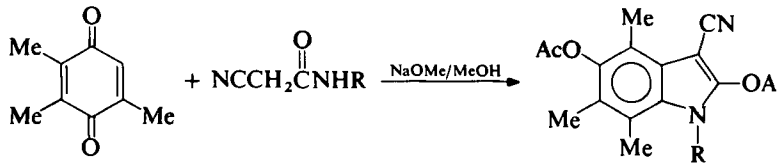
In contrast to the situation in the first half of this century no one person dominates this field. It is a tribute to Lee Irvin Smith and his numerous students to notice the number of recent publications in which their work is given credit for its pioneering spirit.

With the profound effect of modern instrumentation on structure determination it is hardly surprising that changes of the earlier work have been proposed. Under basic conditions 2,3,5-trimethyl-1,4-benzoquinone reacts with acetylacetone to give the hydroquinone half ester **138**, not the simple addition product previously reported (equation 427)[662]. In a similar fashion cyanoacetamide forms an indole rather than a furan (equation 428)[663]. In this case the earlier workers had pointed out that they could not rigorously



(427)

(**138**) 67%

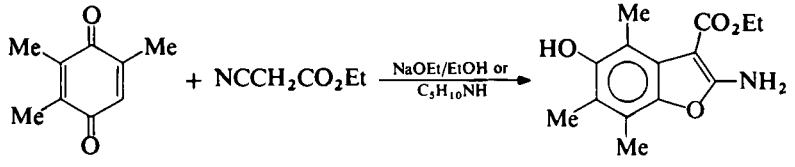


(428)

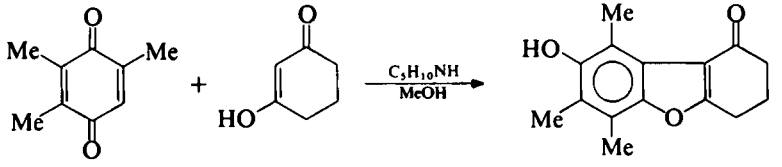
R = H, Me 78%, 71%

exclude this structure although they favored the furan. The closely related active methylene addition–cyclization sequence of ethyl cyanoacetate does lead to 2-aminofurans (equation 429)[664]. This chemistry is also observed, in slightly lower yield, with 2-methyl-1,4-naphthoquinone and 2-methyl-5-isopropyl-1,4-benzoquinone. The use of 1,3-cyclohexanedione leads to partially reduced dibenzofurans bearing the useful carbonyl group (equation 430)[665].

Wikholm has expanded the study of the addition of the acetylacetone anion to 1,4-benzoquinones in two directions. First, after confirming the report cited above and its

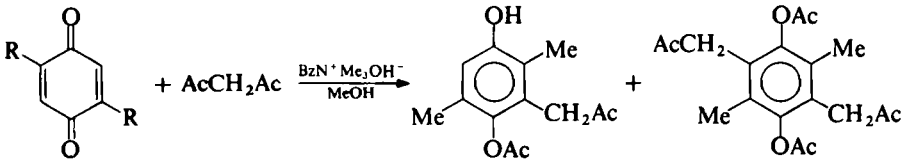


(429)



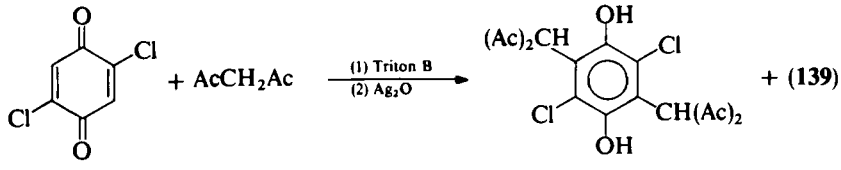
(430)

proposed new structure for the initial adduct, he shows that similar chemistry takes place with less highly substituted quinones (equation 431)[666]. The bis-adduct (**139**) also



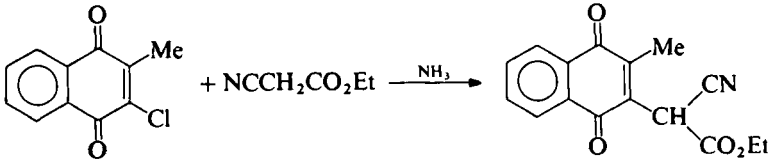
(431)

undergoes cyclization in refluxing acidic methanol. The second route involves the dichloroquinones which do give the simple Michael product analogous to those described by Smith (equation 432). The rearranged product can be obtained quantitatively by treating the initial adduct with Triton B in tetrahydrofuran. Apparently the combination of high oxidation potential and limited solubility prevent further reaction in this case and for the 2,6-dichloro isomer as well. A simple reoxidation–recycling procedure improves the yields substantially.



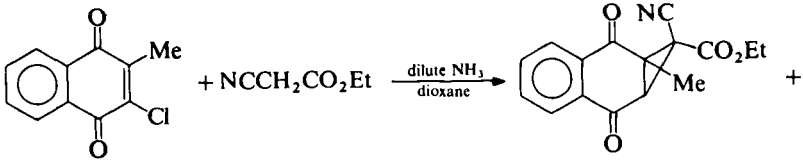
(432)

A very new product type results when the anion of ethyl cyanoacetate reacts with 2-chloro-3-methyl-1,4-naphthoquinone. In the presence of ammonia the simple products (**140**, equation 433) is formed but under slightly modified conditions two epimeric fused cyclopropyl products are obtained (equation 434)[667]. These compounds are especially interesting in that the initial attack of the carbanion must be at the alkyl-quinone carbon

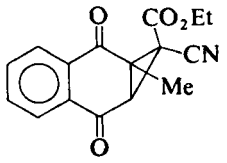


(433)

(140)



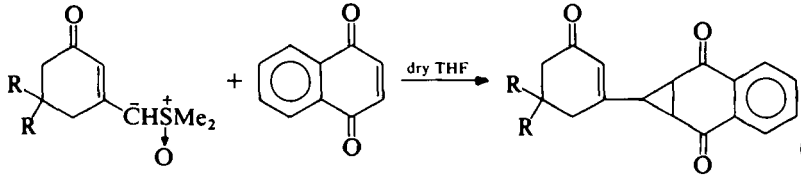
2 :



(434)

1 (75%)

site followed by chloride displacement–cyclization. These compounds are not intermediates in the synthesis of the simple chlorine displacement product **140**. Another carbanion synthesis of a cyclopropyl ring-fused dihydro-1,4-naphthoquinone system has been reported (equation 435)[668].



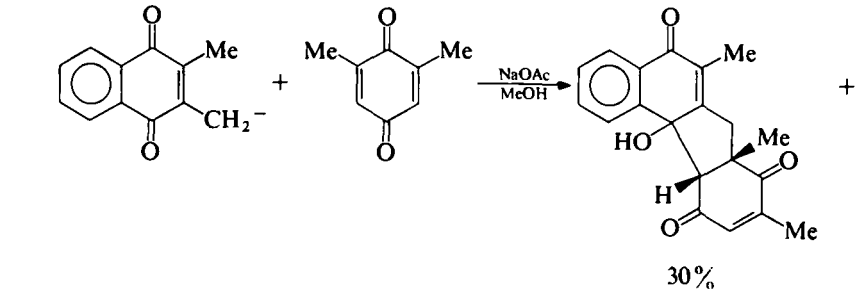
(435)

R = H, Me

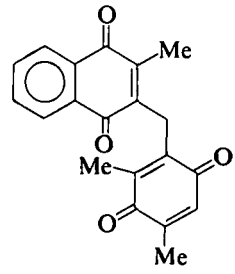
26%, 36%

Dean and his colleagues studied the chemistry of the 3-methyl-1,4-naphthoquinone-2-ylmethyl carbanion which they have generated in the presence of 2,6-dimethyl-1,4-benzoquinone[669]. The chemistry and the product structures are complex but surprisingly good yields of some can be obtained (equation 436). The authors attempted to obtain a xanthen derivative (**141**) or to trap its unstable carbanion with an excess of the quinone. Such an experiment (equations 437, 438) produced only the bridged trione **143** resulting from the carbanion of the diquinone product (**142**).

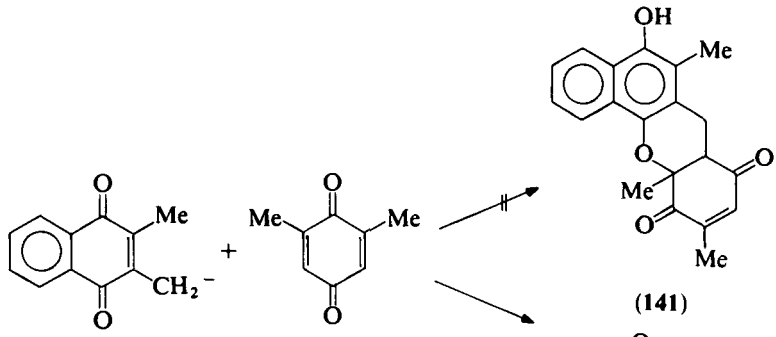
With 2,5-dimethyl-1,4-benzoquinone they were able to produce a cage compound (equation 439)[670]. Similar results are obtained but with greater difficulty in the cases of 2,6-dimethyl-1,4-benzoquinone and the combination of 2,5-dimethyl- and 2,3,5-trimethyl-1,4-benzoquinone. The last compound does not form a cage with itself indicating that steric effects are very important in these systems.



(436)

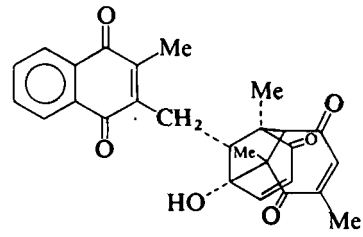


(142) 43%



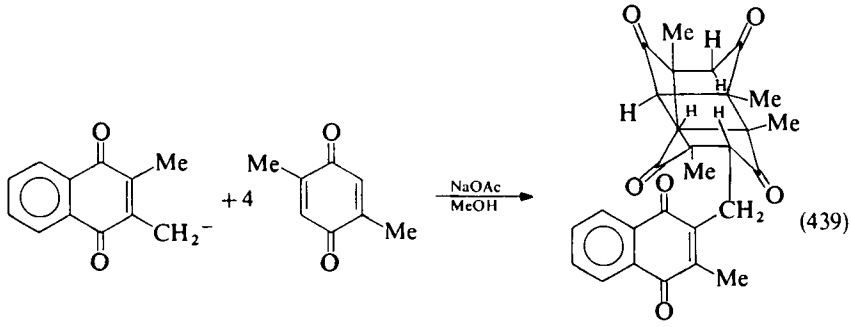
(437)

(141)

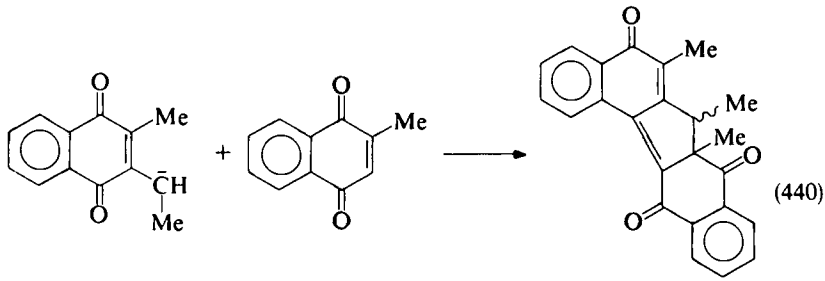


(143) 70% (438)

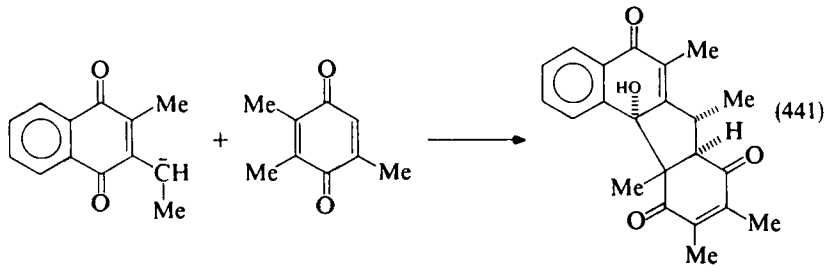
An extension of these studies to the analogous carbanion of 2-ethyl-3-methyl-1,4-naphthoquinone showed that while the chemistry does differ somewhat from that previously observed, these differences are not as great as might be inferred from earlier studies[671]. The chief difference lies in the regiospecificity of addition to 2-methyl-1,4-



(439)



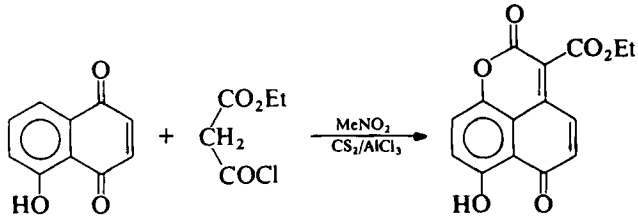
(440)



(441)

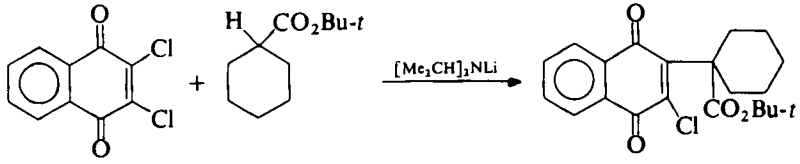
naphthoquinone (equation 440) and 2,3,5-trimethyl-1,4-benzoquinone (equation 441). In the former case the orientation corresponds to that often observed before, while in the latter a unique arrangement is found. In a later study these workers sought to assess the generality of the cage-forming reactions of quinones and quinonoid carbanions[672]. They were able to verify the negative results with a variety of carbanions reported by several different laboratories. Even with an excess of quinone designed to optimize cage compound formation, these reactions are not observed. The conclusion is that such reactions are indeed rare.

A particularly surprising reaction is reported by Thomson and his colleagues in their search for naphthoquinone methide lactones[673]. The aluminum chloride catalyzed reaction of juglone with chloroformylacetate (**144**) produced neither of the expected products (equation 442). A detailed study of related compounds shows that the carbanion reaction is at the C(8) position and suggests that the reduced quinone may first form an ester with the acid chloride. The results thus far are not conclusive, but further studies are promised.



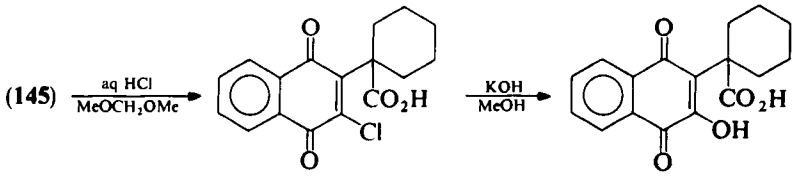
(144) 45% (442)

A different type of lactone results when carbanions are produced bearing a single activating group (equation 443)[674]. It is possible to hydrolyze the ester and the chlorine in near quantitative yields (equation 444). When the acid (**146**) is heated under nitrogen,



(443)

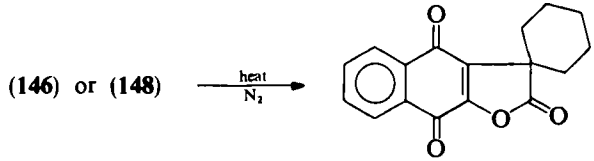
(**145**) 50%



(444)

(**146**) 94% (**148**) 92%

evolution of hydrogen chloride takes place and the lactone **147** is formed in 35% yield; from the hydroxy compound (**148**) the yield is more than doubled (equation 445). A minor



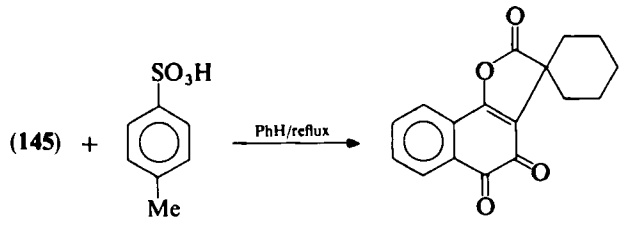
(445)

(**147**) 35%, 74%

product in these reactions is the analogous spirolactone of 1,2-naphthoquinone (**149**) but it can be produced in good yield from the initial ester (**145**, equation 446).

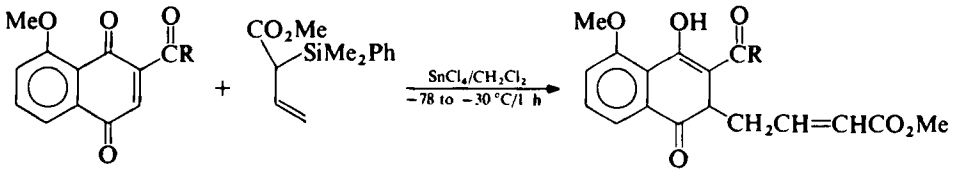
An example of an allyl carbanion has been explored by Maruyama and his coworkers (equation 447)[675, 676]. The high yields, mild conditions and excellent regiospecificity make this a potentially important route. Once again we note the requirement for a Lewis acid catalyst as the synthetic alternative to the traditional base-induced carbanion–Michael chemistry. This chemistry is also applicable to 2-acetyl-1,4-benzoquinone.

In the preparation of a substituted quinone for a photosynthetic study Akiba and his colleagues made an observation concerning the metal cation involved in these active



(149) 64%

(446)

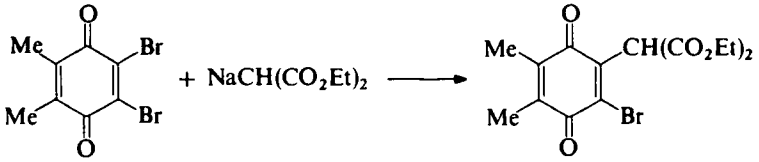


R = Me, Pr

74%, 82%

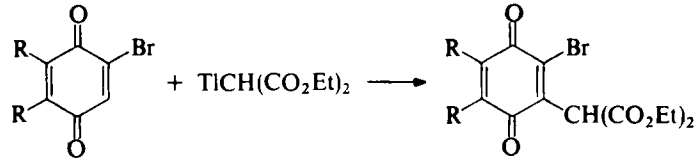
(447)

methylene reactions. Diethyl sodium malonate reacts somoothly with 2,3-dibromo-5-6-dimethyl-1,4-benzoquinone (equation 448) while the 2-bromo-5-methyl- and 2-bromo-6-



(448)

methyl- analogs gave only intractable mixtures[677] Using the thallium malonate salt moderate yields of the desired quinones are obtained (equation 449). Notice that some



R = H, Me

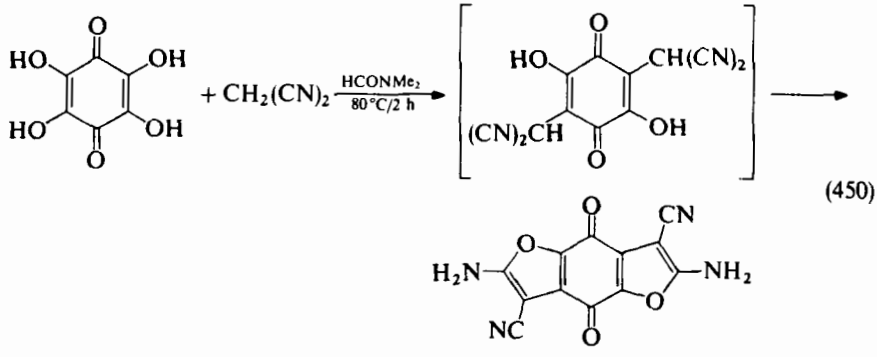
(449)

intriguing questions arise concerning the competition between addition and substitution; what would happen with 2-bromo-5,6-dimethyl-1,4-benzoquinone?

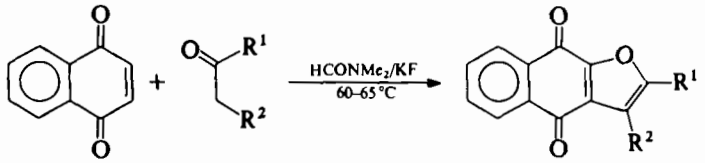
A reinvestigation of the reaction between 2,3,5,6-tetrahydroxy-1,4-benzoquinone and malononitrile in the absence of either acid or base shows that the principal product results from formal displacement of two hydroxyl groups (equation 450)[678]. While the yield is not great the functionality of this representative of the furan–quinone system promises useful chemistry.

A more traditional method for the synthesis of quinones with a fused furan ring involves the use of potassium fluoride (equation 451)[679]. Unfortunately, chloranil failed to react.

A third route involves the condensation of benzoylacetonitrile with 2,3-dichloro-1,4-naphthoquinones in the presence of pyridine (equation 452)[680]. An analogous product

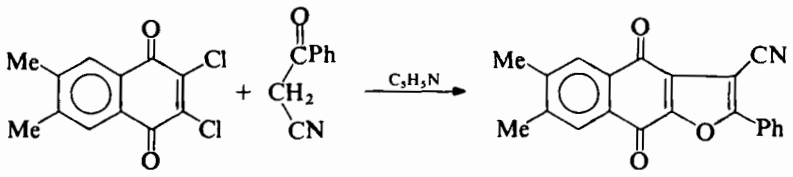


(450)



(451)

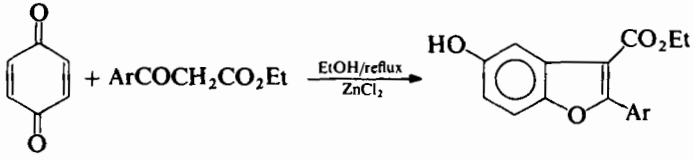
R^1 = Me, Ph; R^2 = CN, Ac, Bz, CO_2Et



(452)

from 6-methyl-5-phenyl-1,4-naphthoquinone was obtained in 48% yield but its regiochemistry was not determined.

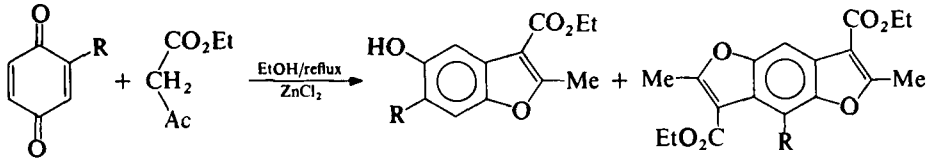
Benzofurans are another related structural type derived from quinones. McPherson and Ponder have shown that various benzoylacetates condense with 1,4-benzoquinone in the presence of a Lewis acid catalyst (equation 453)[681]. They have also examined the addition



(453)

Ar = 2-An, 2,4-, 2,5-$(MeO)_2C_6H_3$

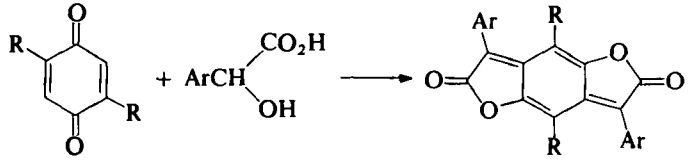
of ethyl acetoacetate to 1,4-benzoquinone and its 2-chloro and 2-methyl derivatives (equation 454)[682]. The use of an excess of quinone or its rapid addition tends to increase the yield of the difuran. The reinvestigation of several earlier preparations of these



R = H, Me, Cl 25% (R = H) 17% (R = H) (454)

compounds showed that the structures proposed without modern instrumental methods are correct in most instances.

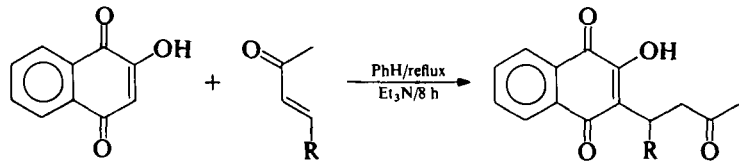
A search for dyestuffs has produced a novel preparation of benzodifuranones (equation 455)[683]. The yields are modest (up to 35%) but the range is quite broad. The authors attribute the poor yields to the instability of the mandelic acid and promise further studies.



(455)

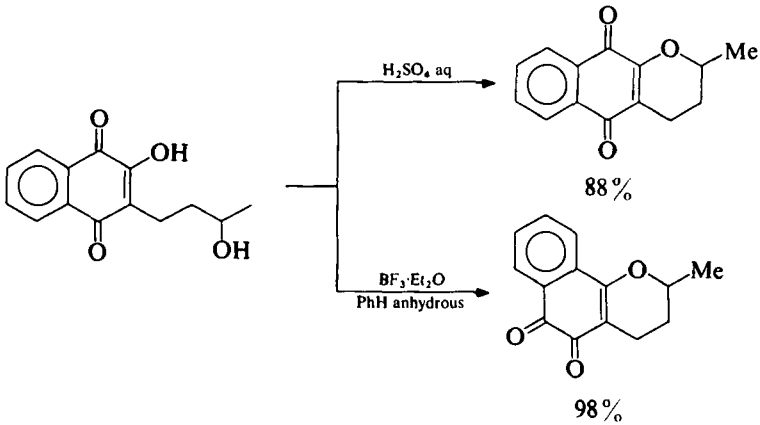
R = H, Me, Cl; Ar = Ph, 4-HOC_6H_4, 4-$AcOC_6H_4$, 4-An

Certain α,β-unsaturated ketones add well to 2-hydroxy-1,4-naphthoquinone (equation 456)[684]. When the carbonyl group is reduced it is possible to cyclize by two paths depending on the choice of catalyst (equations 457, 458)[685].



(456)

R = H, Me, Ph 68%, 28%, 35%

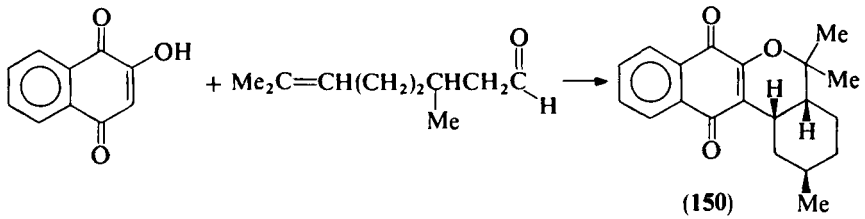


(457)

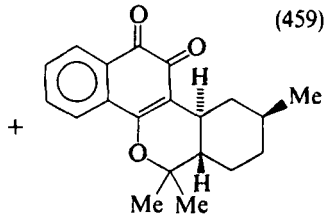
88%

(458)

98%



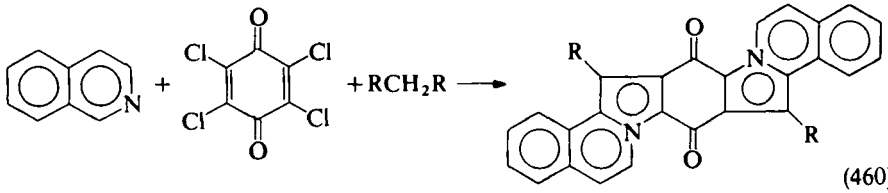
(150)



(151) 70% total (459)

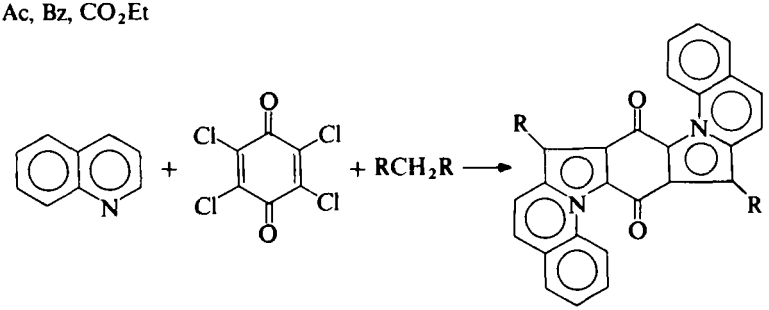
Quite similar compounds have been prepared in a one-step reaction (equation 459)[686]. The observation that **150** can be converted into **151** by treatment with sulfuric acid at 0°C deserves attention in the light of the study discussed above[684, 685].

In some instances the presence of a nitrogen base can produce rather complex polyheterocyclic quinones of importance in the dye industry (equation 460)[687]. This chemistry has been extended to the use of quinoline (equation 461), but again no yields are



(460)

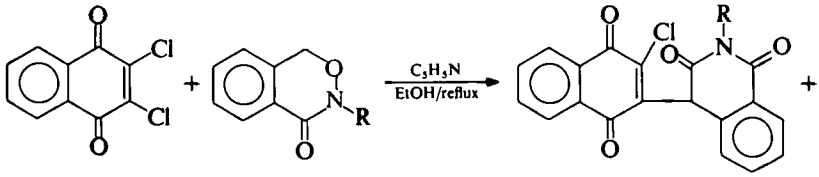
R = Ac, Bz, CO_2Et

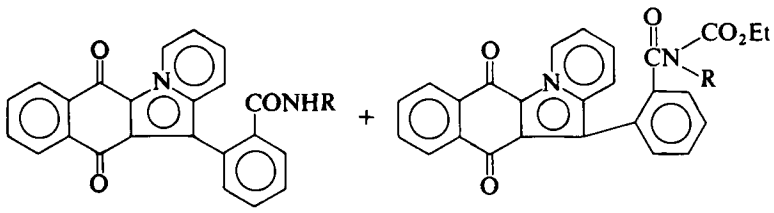


(461)

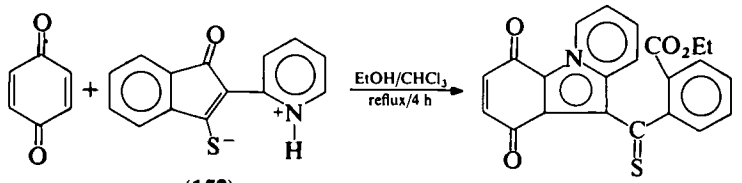
given[688]. A related reaction involving a homophthalimide and pyridine has been presented (equation 462)[689]. The chemistry is discussed in detail and a reasonable account of the product mixture presented.

A report of an analogous heterocyclic quinone system has been made by Buggle and Power (equation 463)[9]. In view of her earlier work this failure to react at the thiol group is exciting. Another interesting note is that the quinoline derivative of **152** fails to add to





(462)

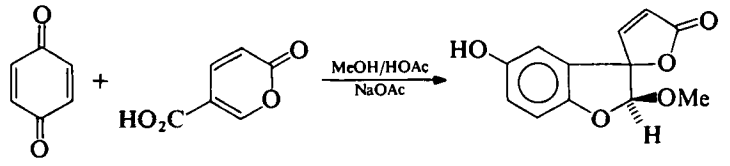


(463)

(152)

quinones while the isoquinoline does. Presumably for similar steric reasons **152** fails to react with 2,3-dichloro-1,4-naphthoquinone.

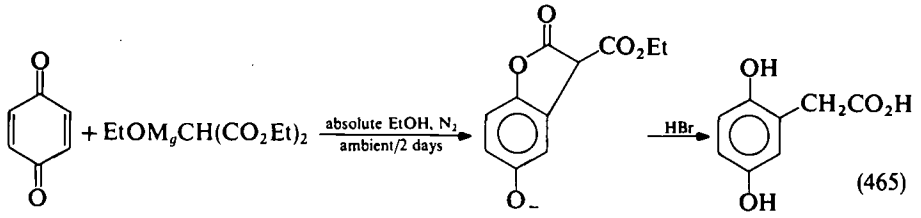
Three short notes are of interest for their promising hints of future development. Wheeler and his coworkers obtained a small amount of the unusual spirobutenolide **153** when coumalic acid was added to 1,4-benzoquinone (equation 464)[690]. All stated components of the reaction mixture must be present for this reaction to take place.



(464)

(**153**) 22%

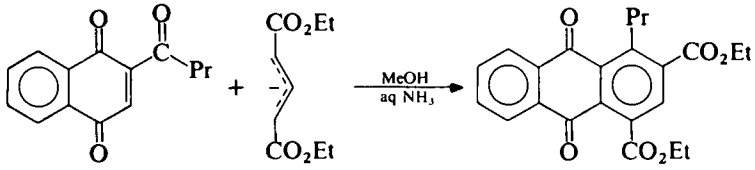
Bloomer and Damodaran have published a synthesis of homogentisic acid (**154**) with an intermediate lactone of additional interest (equation 465)[691].



(465)

(**154**) 47%

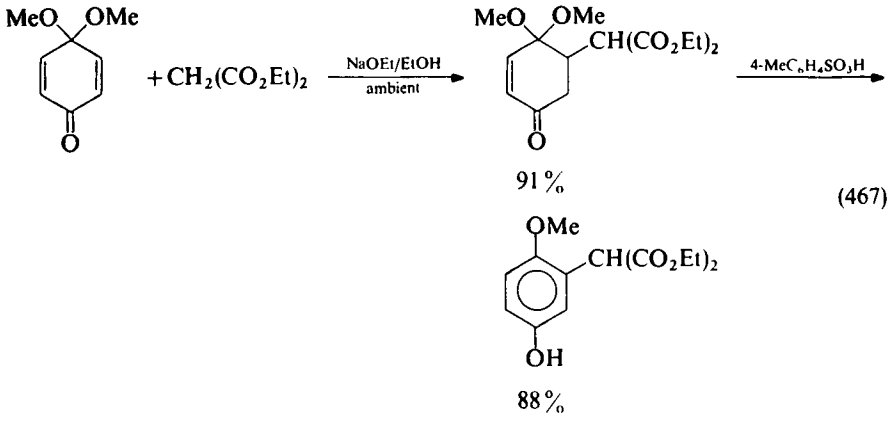
In the process of trying to prepare a dihydropyran system Rieck and Grunwell found a novel synthesis of anthraquinones (equation 466)[692]. The yield needs to be optimized and the generality of the reaction established.



(466)

33%

Parker has given a good introduction to the application of quinone monoacetals to quinonoid active methylene chemistry[693]. She and Kang obtained very good yields of both the initial adduct and the aromatic monoether with diethyl malonate (equation 467).



(467)

Similar results are obtained with a naphthoquinone acetal and ethyl cyanopropionate. However, with keto esters most of the products are bicyclic bridged compounds which can be converted by acid to benzofurans (equation 468). The yields are generally adequate.

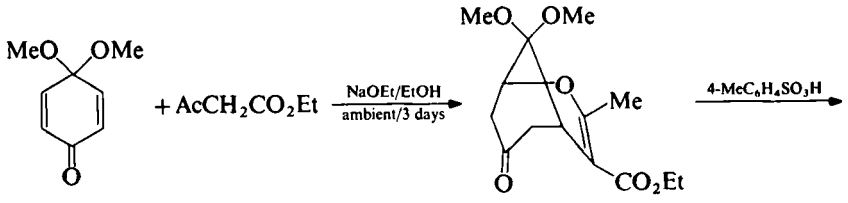
Chan and Brownbridge have added the 2,5-bis(trimethylsiloxy)furan (**155**) to the acetals of 1,4-benzo- and 1,4-naphthoquinone (equations 469, 470)[694]. The nature of the isolated adducts can certainly be understood on the basis of oxidation potentials. The final products appear to be mixtures of cyclic and open tautomers (equation 471). Semmelhack and his coworkers[695], using butyl lithium and nickel tetracarbonyl, were able to acylate naphthoquinone acetal (equation 472) and to trap the presumed enolate as well (**156**, equation 473). This chemistry has been used in the synthesis of two natural products with significant antibiotic activity.

VIII. THE SUBSTITUTION CHEMISTRY OF QUINONES

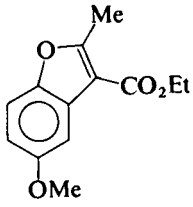
A. Nitrogen Substitution

1. Kinetics and mechanisms

In contrast to the general trend, the chemistry of nucleophilic substitution in quinones has produced little in the way of truly new knowledge or technique during the past decade

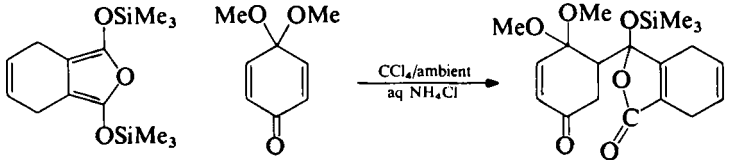


69%



42%

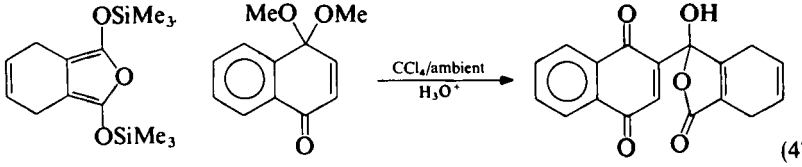
(468)



(155)

49%

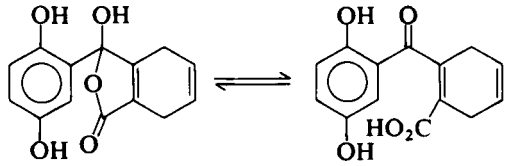
(469)



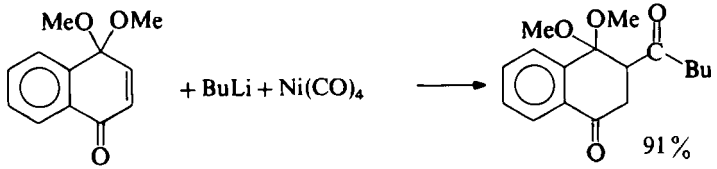
(155)

51%

(470)

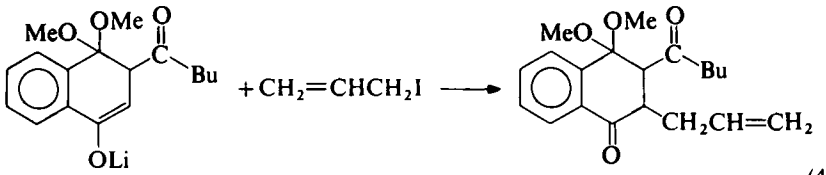


(471)



91%

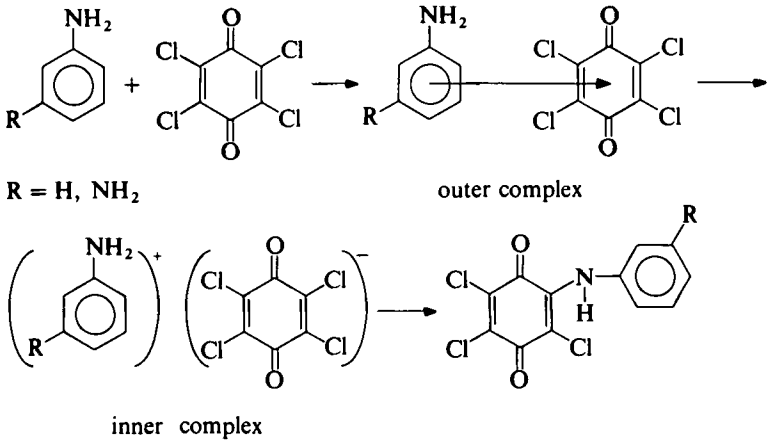
(472)



(156) 85% (473)

and a half. An important exception is apparent with carbanions (see Section VII). Kinetic studies have concentrated exclusively on the charge transfer intermediate with chloranil although anilines[696], tertiary amines[697] and primary amines[698] have been included.

A detailed study of the behavior of substituted anilines allowed the recognition of several distinct classes of mechanistic pathways[696]. Diphenylamine and *N,N,N',N'*-tetramethyl-*p*-phenylenediamine form such stable charge transfer complexes with chloranil that no further reaction takes place. Aniline and *m*-phenylenediamine form substitution products after passing through both an outer and an inner complex (equation 474). Finally, *o*-

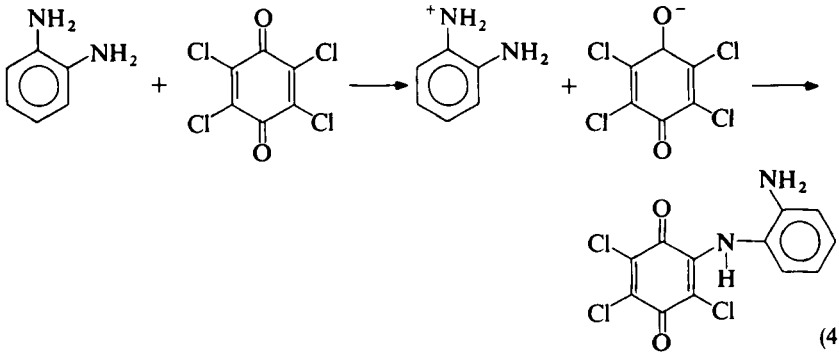


(474)

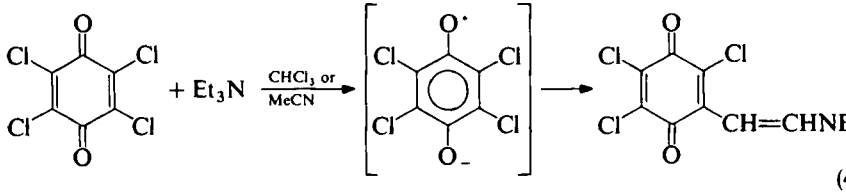
phenylenediamine proceeds to product through the outer complex and an ionic species (equation 475). The differences are discussed on the basis of electron density of the amino substituent.

Shah and Murthy have reinvestigated the interaction of triethylamine with chloranil (equation 476) in a variety of solvents[697]. They confirm the earlier suggestion of a radical anion intermediate and find this species to be unreactive with more highly branched alkyl groups. The chemistry of this system changes in hydroxylic solvents but the products were not identified.

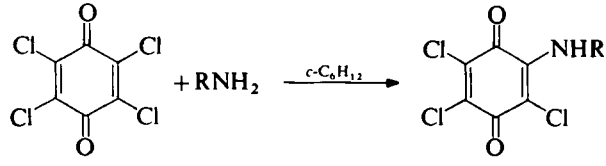
Similar evidence for a charge transfer intermediate was presented for the reaction of primary amines with chloranil (equation 477)[698]. This is found in the fast reaction forming monosubstitution product **157**, but there is no evidence for an analogous complex in the slow formation of disubstituted product (**158**). The rates depend on the electron donor strengths of structurally similar amines except in those cases in which the alkyl groups are significantly different. The rates also increase with solvent polarity while activation energies decrease. Clearly there must be charge separation in the transition state leading to product.



(475)

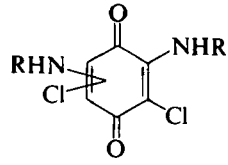


(476)



(157)

(477)



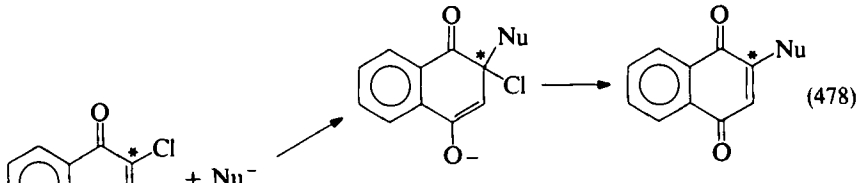
(158)

R = *s*-Bu, *i*-Bu, *i*-Pr, allyl, *c*-C_6H_{12}

Cameron and his colleagues have established the regiospecificity in the reaction 2-^{13}C-2-chloro-1,4-naphthoquinone with a variety of nucleophiles[699]. In principle two different paths might be followed by reaction at the halogenated or *ipso* carbon (equation 478) or at the vicinal carbon (equation 479). They found that the amines, being neither hard nor soft nucleophiles, show a striking solvent dependence (equation 480).

A product and kinetic study of reactions between various heterocyclic secondary amines and sodium 1,2-naphthoquinone-4-sulfonate has been carried out (equation 481)[700]. The products obtained from reaction with pyrrole are unique in this series since they involve carbon–carbon bond formation (equation 482). The authors attribute this outcome to the low electron density of nitrogen in the quasi-aromatic ring. The product with 1,2,4-triazole is also unexpected (equation 483).

The second-order rates were determined polarographically and the pH-rate profile showed a maximum at pH 10. This suggests a typical nucleophilic substitution



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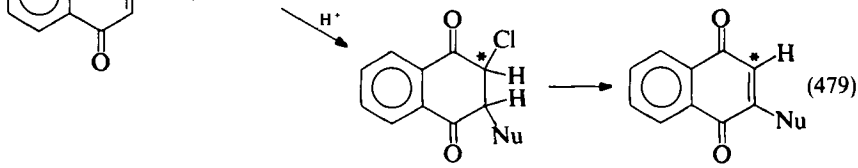
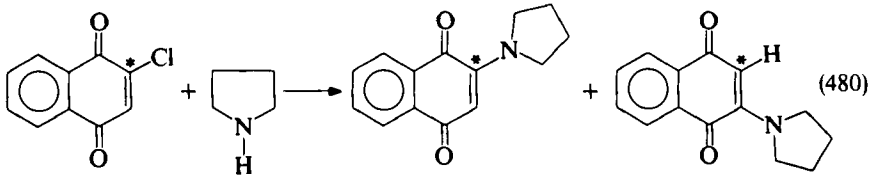
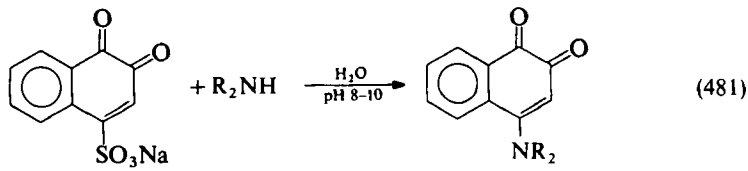


(479)



(480)

Solvent	%	%
MeCN	25	70
PhH	8	80
MeOH	84	10



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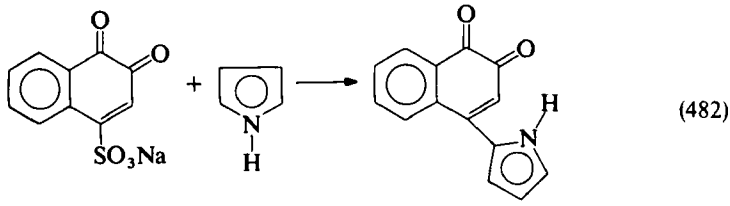
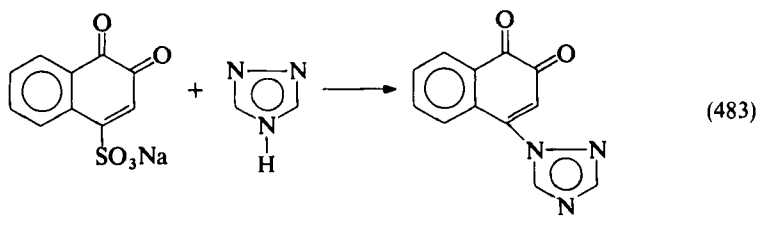
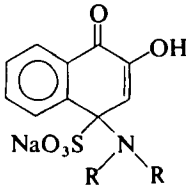


(482)

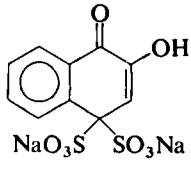


(483)

intermediate (**159**). The displaced sodium hydrogen sulfite reacts in a successive second-order reaction with another equivalent of quinone to give the 4,4-disulfonate **160**.



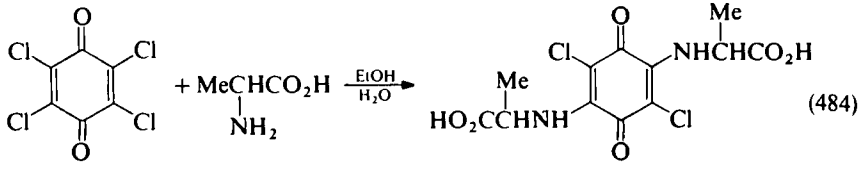
(**159**)



(**160**)

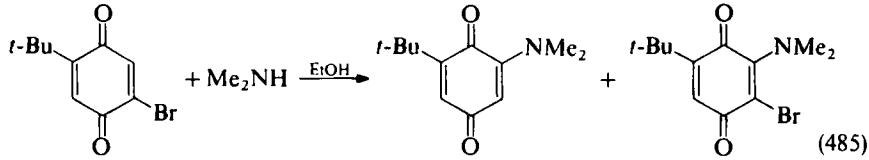
2. *Synthetic studies with mechanistic implications*

A reinvestigation of the reactions of amino acids with 1,4-benzoquinones reveals that earlier claims for charge transfer intermediates are unfounded[701]. It seems clear that all of the observed absorptions are explained by the formation of mono- and disubstitution products (equation 484).

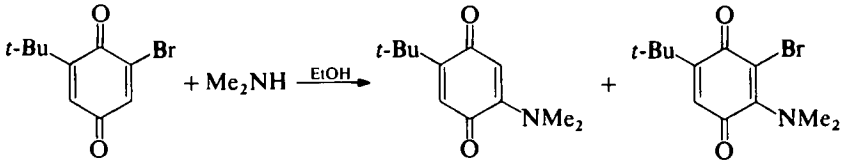


(484)

Hewgill and Mullings followed their important study of quinone–oxygen substitution reactions[702] with a parallel examination using dimethylamine[703]. Strong evidence is presented for the addition–elimination pathway (equations 485, 486). Unlike the charged



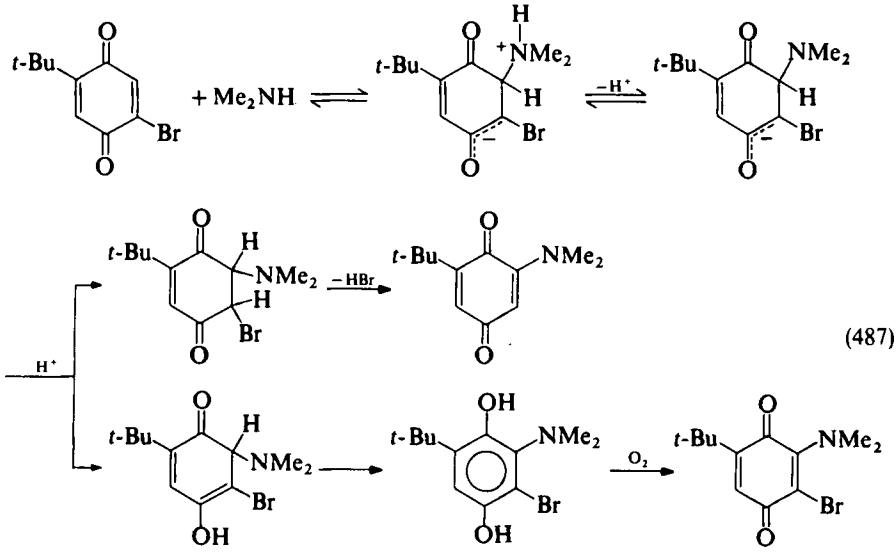
45 : 55 (485)



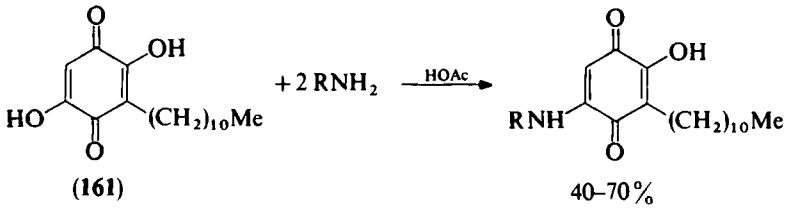
70 : 30 (486)

methoxide ion case these reactions show very little influence of the solvent on the product composition. The absence of a direct substitution product makes the following addition intermediates, common to both products, attractive (equation 487).

The displacement of hydroxy substituents from quinones by primary amines is much less usual. Joshi and Kamat studied the reactions of embelin (**161**) with a variety of primary



(487)

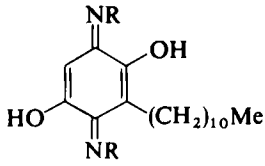


(161)

R = Me, Et, Pr, Bu, Bz, $PhCH_2CH_2$

40–70%

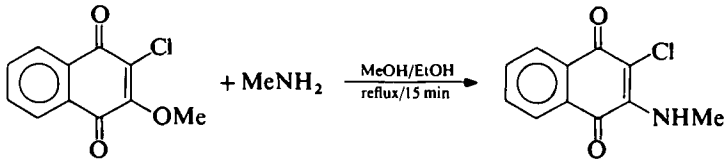
(488)



(162)

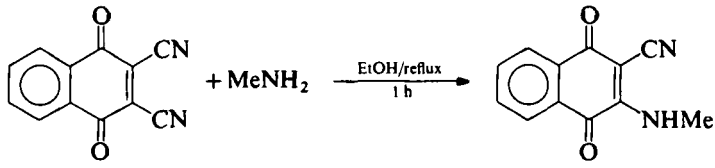
amines and found generally good yields of substitution at the 5-position (equation 488)[704]. A greater excess of methylamine leads to the bismethylimine (**162**) which appears to involve the ring nitrogen adduct as an intermediate.

Higher yields of 2-amino-1,4-naphthoquinones were obtained using methoxy as the leaving group (equation 489)[705]. The cyanide anion proved unreactive as a nucleophile but represents a good leaving group (equation 490). In this report, and subsequent papers,



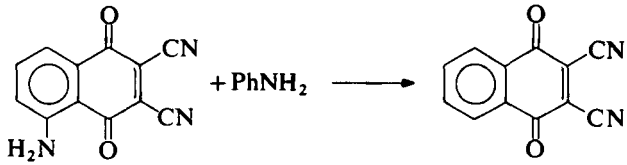
97%

(489)



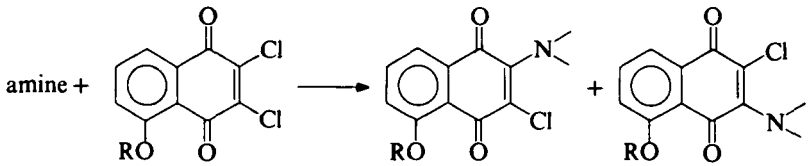
(490)

similar chemistry was extended to substituents in the aromatic ring[706, 707]. The one truly unexpected outcome of this chemistry is the reaction of aniline with 5-amino-2,3-dicyano-1,4-naphthoquinone (equation 491).



(491)

The halo atoms of 2,3-dichloro- or 2,3-dibromo-1,4-naphthoquinone continue to represent the major point of departure for many synthetic routes involving nucleophilic substitution. Parr and Reiss applied this method to the synthesis of enaminones for use in the Nenitzescu reaction[708]. Belitskaya and Kolesnikov studied the influence of oxygen substituents in the aromatic ring on such chemistry[709a]. Their results suggest that the selective replacement of each halogen is possible depending on the exact nature of the oxygen substituent at position five, but no truly comparable data are presented (equation 492). An earlier report by this same group had shown that aniline substitutes only at the 2-position with 5-hydroxy **163** and at the 3-position with the 5-acetoxy **163**[709b].



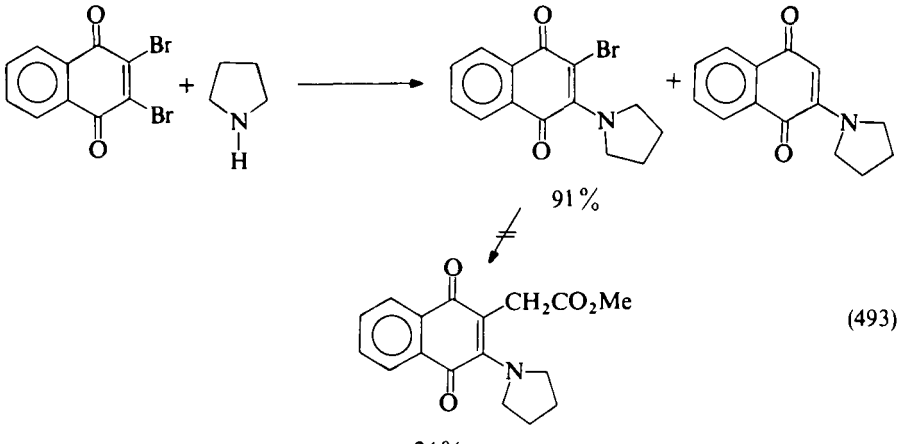
(492)

morpholine, R = H	77%	17%
aniline, R = Me	5%	89%

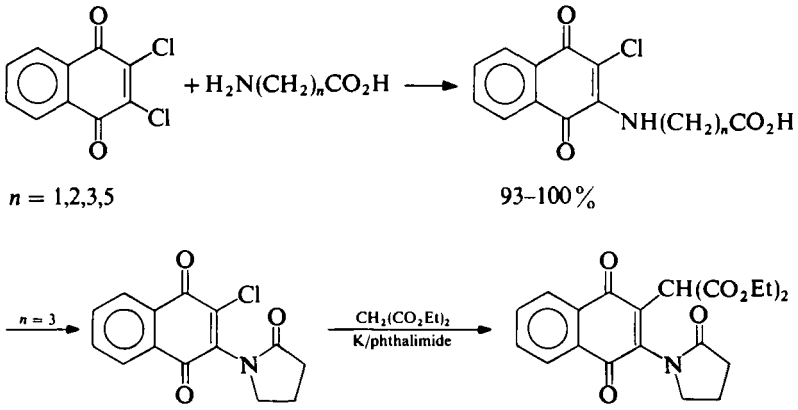
This chemistry has been applied and extended by workers interested in the synthesis of the mitomycin antibiotics. Rapoport and Falling tried a variety of routes involving the sequential displacement of the 2,3-bromines in 1,4-naphthoquinone, for example (equation 493)[710]. They found that the best route involved the proper balance of quinone and hydroquinone chemistry, but the specific quinonoid reactions they found add substantially to our appreciation of their possibilities.

Okamoto and Ohta made a similar approach to the same class of compounds (equation 494)[711]. The formation of the lactam and the successful active methylene reaction on it are both noteworthy. Unfortunately, no yields are given.

There has been little recent activity in the synthesis of ethylenimine substituted quinones. However, Driscoll and his coworkers have expanded the range of possibilities



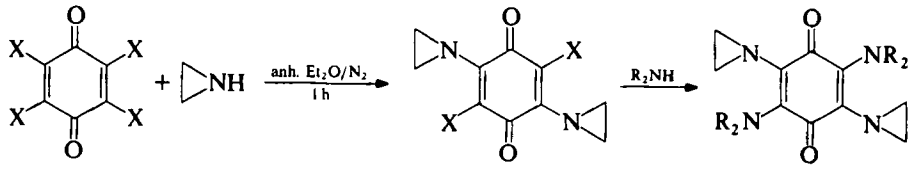
(493)



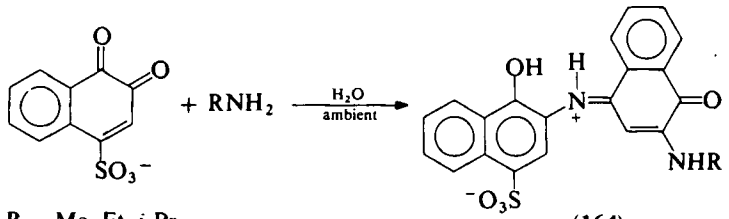
(494)

available[712,713]. Using either chloranil or fluoranil they were able to prepare a large variety of 2,5-diaziridinyl-3,6-diamino-1,4-benzoquinones (equation 495). The two substituents may be introduced in sequence permitting the preparation of unsymmetrical products. The yields are generally good regardless of the order of introduction. Methyl- and 2,2-dimethylaziridines undergo analogous reactions.

A limited number of studies involving 1,2-quinones have appeared. The displacement of the 4-sulfonate group from 1,2-naphthoquinone by primary amines leads to a complex dye mixture in which the principal component is **164** (equation 496)[714]. This structure was confirmed by independent synthesis.

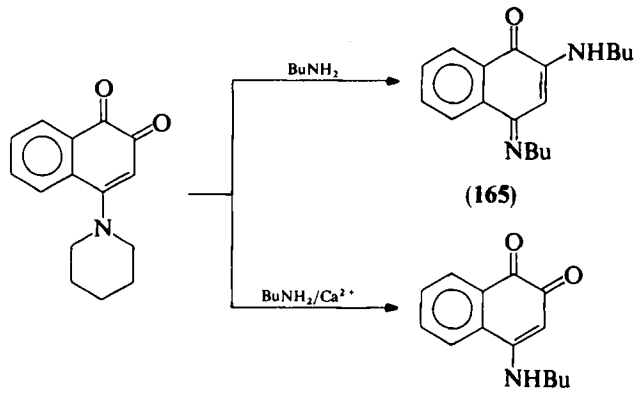


X = F, Cl
R = H, Me, Et, Pr, Bu, $HO(CH_2)_2$, morpholinyl, piperidyl, pyrrolidinyl (495)



R = Me, Et, *i*-Pr (**164**) (496)

In the transamination of 1,2-naphthoquinone[715], in the absence of a catalyst, such as a calcium ion, a 1,4-quinonoid monoimine (**165**) is formed. The catalyst, however, leads to the simple primary amine substitution product (**166**, equations 497, 498). The same



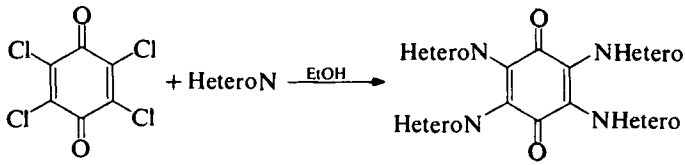
(497)

(**165**)

(498)

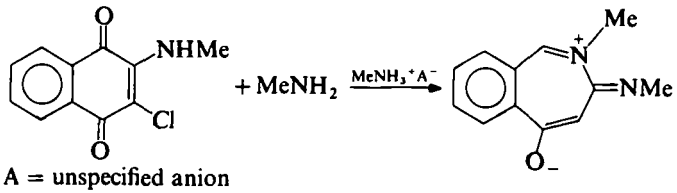
(**166**)

chemistry obtains with anilines if triethylamine is added. This method represents a valuable synthesis of compounds that are usually rather difficult to prepare, and it has been applied to several heterocyclic systems. Gauss and his colleagues have reported the complete substitution of chloranil and 2,3-dichloro-1,4-naphthoquinone by nitrogen aromatics (equation 499)[716]. The yields for these hindered compounds are surprisingly high.



HeteroN = pyrazolyl, imidazolyl, 1,2,4-triazolyl 66%, 83%, 72% (499)

A brief report of an entirely new carbon skeleton is noteworthy and should be developed (equation 500)[717].



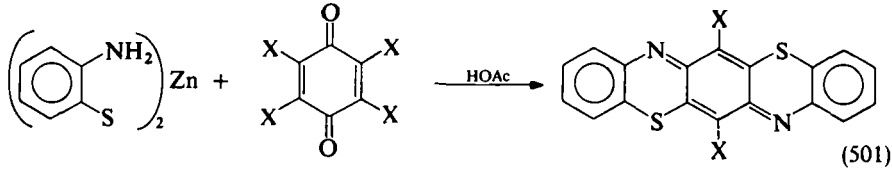
(500)

A = unspecified anion

3. *Heterocyclic syntheses*

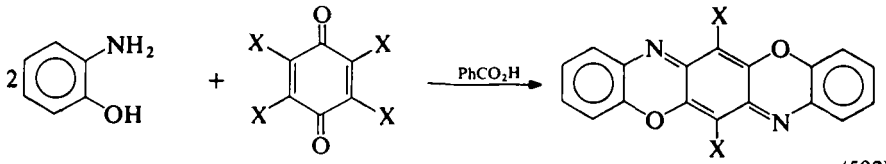
As was observed in the section on nitrogen addition chemistry the fastest growing area of quinone chemistry in the past decade and a half is the synthesis of heterocyclic compounds. This has been especially true with respect to substitution reactions. While much of the work has dealt with routine synthesis there are instances of exciting new chemical thought.

The two most heavily studied systems are the triphenodithiazines (**167**) and the triphenodioxazines (**168**). In both of these structural classes Mital and his collaborators have been exceedingly active[718]. The best chemical routes to these dyestuffs are quite similar (equations 501, 502). Considering the complexity of the products the yields of **168**



(501)

(167)

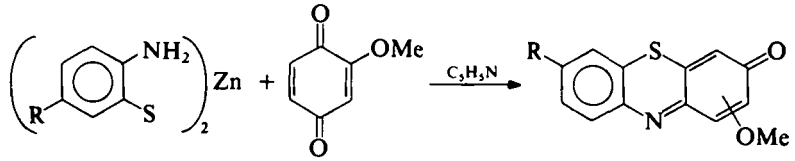


(502)

X = Cl, Br

(168)

are high (40–80%) but very low (10–13%) for **167**. Potentially useful intermediates can be isolated in good yield from both reactions with anhydrous ethanol as the solvent. This observation was developed further, and pyridine was found to be the preferred solvent (equation 503)[719].

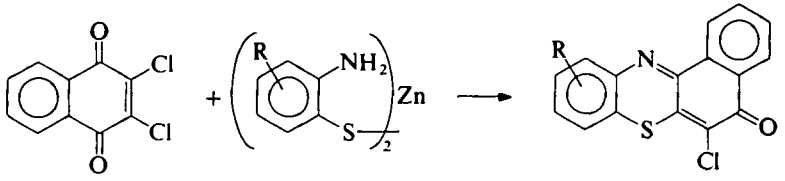


(503)

R = Cl, Br, Me, OMe, OEt

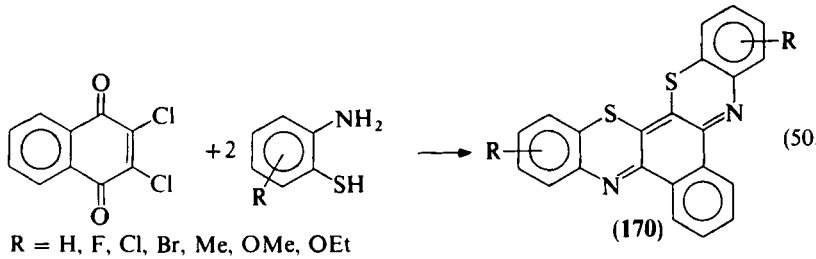
89–97%

With 2,3-dichloro-1,4-naphthoquinone Mital and Agrawal found that the monocyclization product (**169**, equation 504) alone is obtained using the zinc salt but that the free thiol leads to bis-product (**170**, equation 504)[720]. Yields are good to excellent in both instances.



(504)

(169)



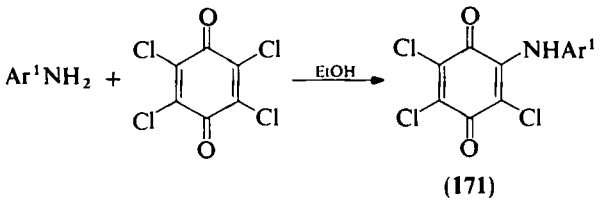
(505)

R = H, F, Cl, Br, Me, OMe, OEt

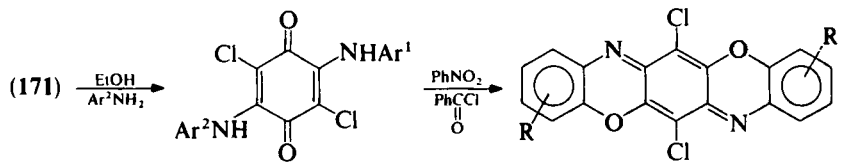
(170)

This chemistry has been applied to a large number of additional examples, and the resulting compounds studied extensively[721–734]. Other laboratories have followed Mital's lead and expanded the range of substituents and ring systems[735–743].

Similar advantage of the synthesis of the triphenodioxazines (**168**) is apparent in the work of Gupta and his colleagues (equation 506)[744–747]. Their approach has concentrated



(171) (506)

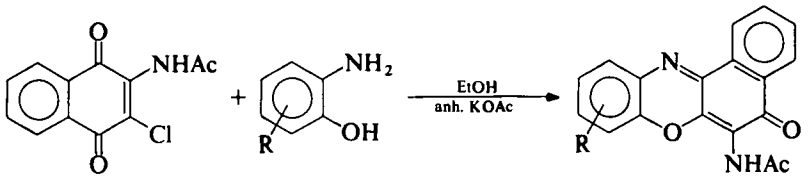


R = Cl, Br, Me, OMe, OEt

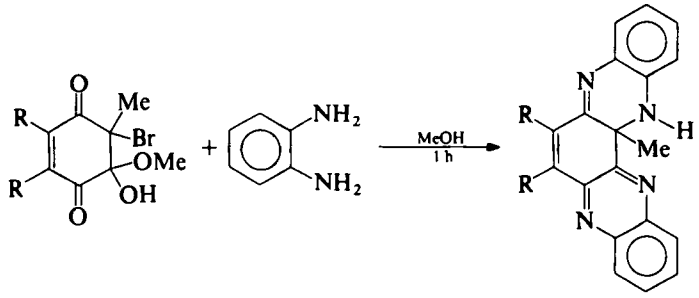
on the use of anilines and chloranil; also suggested by Mital[719]. By isolation of the monosubstituted product (**171**) they have been able to prepare unsymmetrical products in quite good yields.

Ueno and his coworkers have extended this chemistry to the 1,4-naphthoquinone series[748] again following the pioneering efforts of Mital (equation 507)[749].

The phenazines represent another series in which the quinones offer an attractive entry. Ried and Schaefer showed that the quinone–halogen addition products with which they had been working react with *o*-diamino aromatics in excellent yield (equation 508)[750]

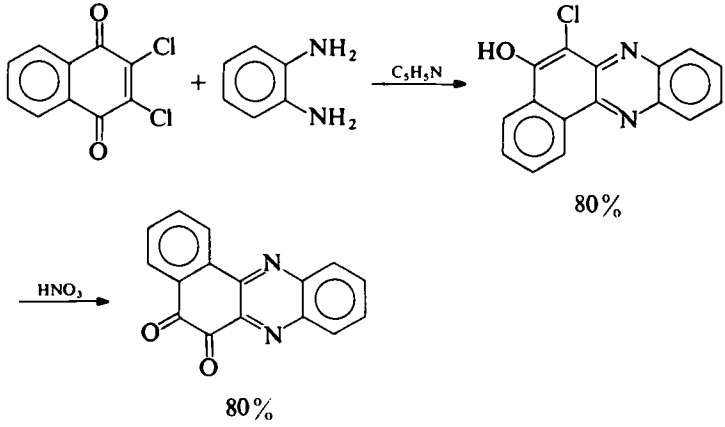


R = H, Cl, NO_2 57–80% (507)



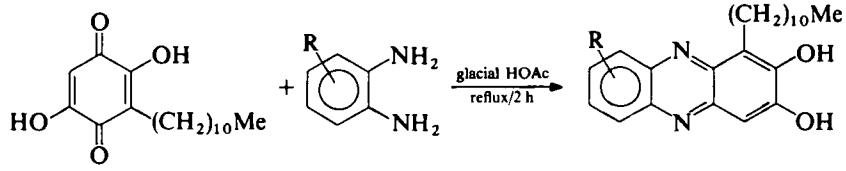
R = H, Me, –CH=CHCH=CH– 79%, 67% (508)

Here, too, Mital has made a contribution by showing that with pyridine as the solvent a facile conversion to the corresponding 1,2-quinone takes place (equation 509)[751]. Rao



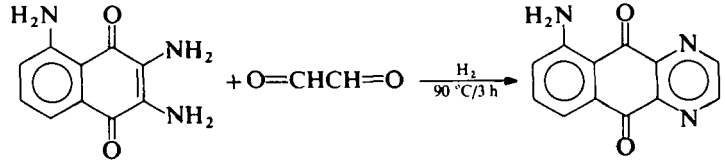
80% (509)

has shown that hydroxyl groups can be displaced by various 1,2-phenylenediamines (equation 510)[752].

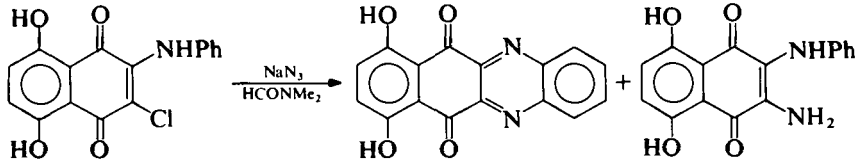


R = H, Me, Cl, Br, OMe, NH_2 (510)

Nakazumi and his coworkers have developed some novel approaches to these compounds. For example, they reversed the usual method using 2,3,5-triamino-1,4-naphthoquinone and glyoxal (equation 511)[753]. They have also employed a novel ring-closure reaction using an azide substitution (equation 512)[754]. The low yield may be



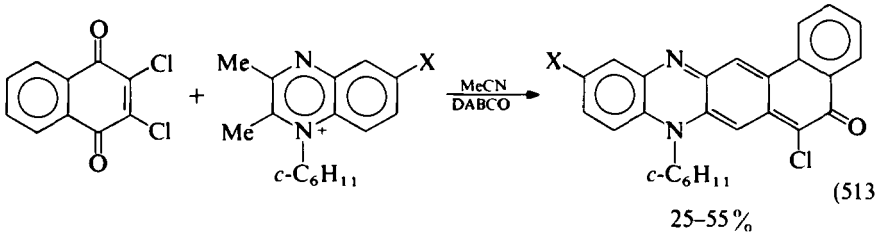
(511)



(512)

improved but the difficulty of other preparations for this compound or its nitrogen substitution products makes this an attractive route.

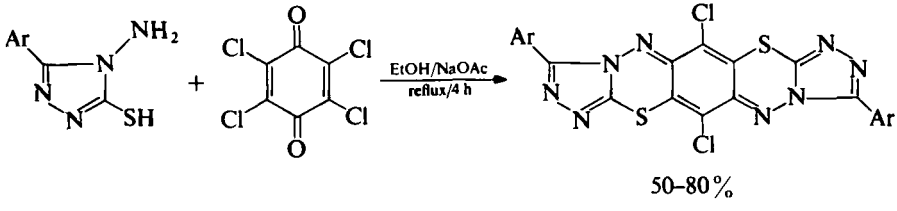
Still another slightly explored and potentially valuable synthesis has been presented by Schelz and Rotzler (equation 513)[755].



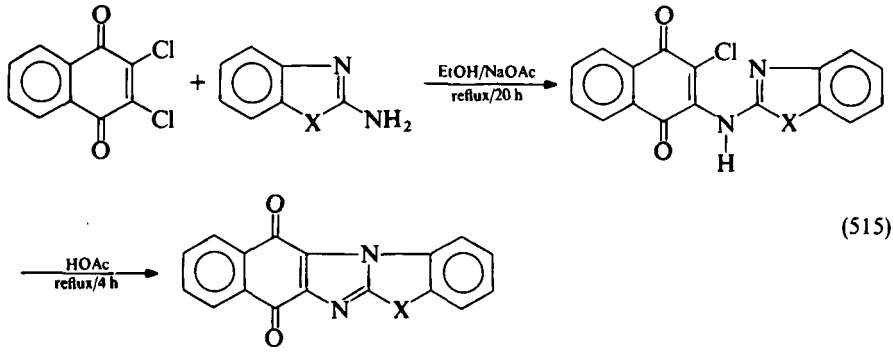
(513)

X = H, Me, F, Cl, Br, OMe, NHAc, CO_2Et, CF_3

Syntheses involving bridgehead nitrogen atoms have attracted quinone chemists. Two complementary approaches make use of substitution by thiols (equation 514)[756] or amino (equation 515)[757, 758] groups attached to heterocyclic rings which can then undergo ring



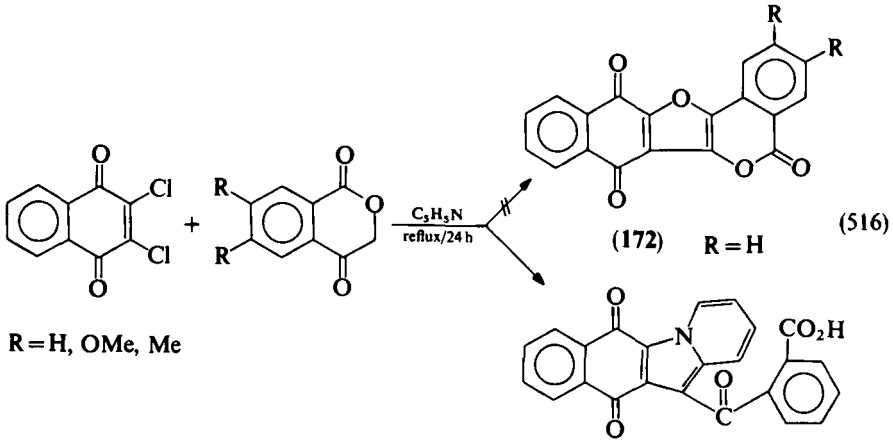
Ar = Ph, 4-BrC_6H_4, 4-ClC_6H_4, 3-$O_2NC_6H_4$; 3,4-$(HO)_2C_6H_3$ (514)



(515)

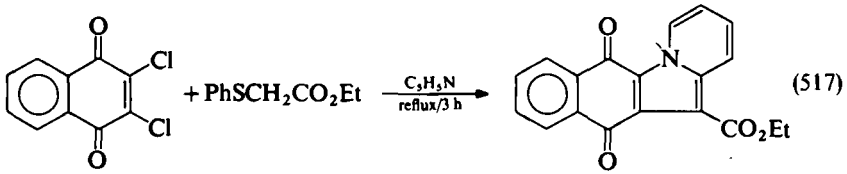
fusion. Vernin and his colleagues have applied the phase transfer technique to a wide range of these reactions with extraordinary results; yields are not lower than 60% and most are 75% or greater[759].

A number of other laboratories have extended the range of substitution patterns and ring systems available by this substitution–ring closure chemistry. Bhakta and Chattopadhyay corrected a structure (**172**) presented earlier and prepared a series of related compounds (equation 516)[760]. Tilak and his colleagues have made more extensive



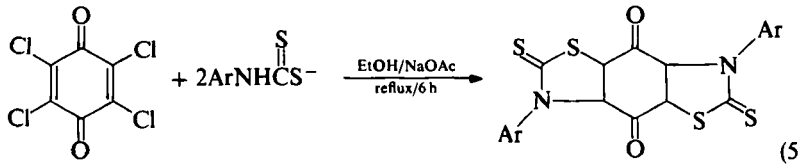
(516)

efforts along these lines using α-picoline, isoquinoline, and ethyl isonicotinate as well as pyridine[761,762]. When thiols or sulfides are employed the major product has often undergone sulfur expulsion (equation 517)[763].



(517)

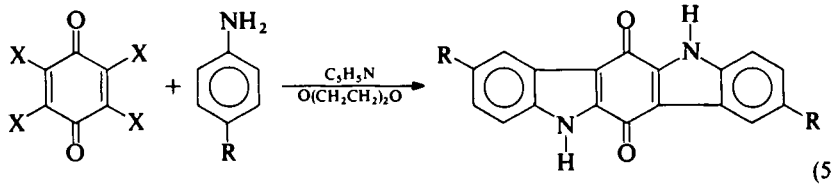
Soni and Saxena have published extensions and applications of several of these synthetic techniques[764-767], for example, the reaction of chloranil with substituted dithiocarbamates (equation 518)[765].



30–60%

(518)

Under the influence of pyridine alone or as a cosolvent anilines can react with bromanil or 2,5-dichloro-1,4-benzoquinone to produce fair to good yields of diindoloquinones (equation 519)[768].

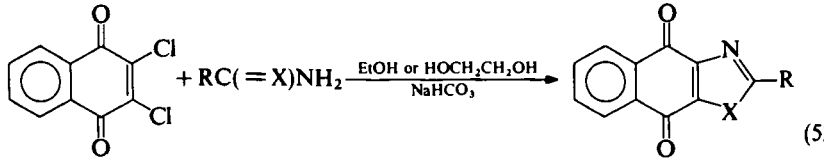


50–85%

(519)

X = H, Cl, Br; R = H, Me, MeO, OH, NH_2, Cl, CO_2H, NO_2

Hammam and his coworkers have added amides[769] and thioamides[770] to 2,3-dichloro-1,4-naphthoquinone to produce two related heterocyclic dione series in excellent yields (equation 520).

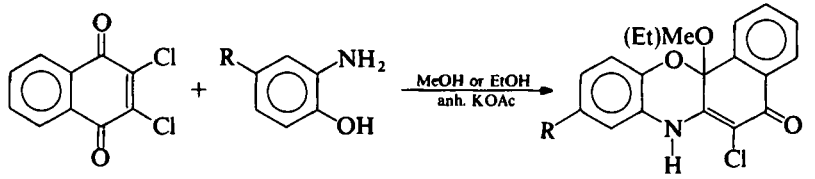


70–90%

(520)

X = O, S; R = Me, NH_2

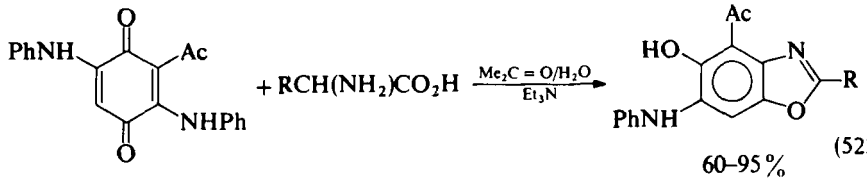
In an intense reinvestigation Schäfer and Agarwal have corrected earlier structural assignments in the reaction of 2,3-dichloro-1,4-naphthoquinone with 2-aminophenols (equation 521)[771-773]. In the process of these studies Schäfer and coworkers have developed useful methods for the synthesis of phenothiazinones[774] and acridine-



R = H, Me, Cl

(521)

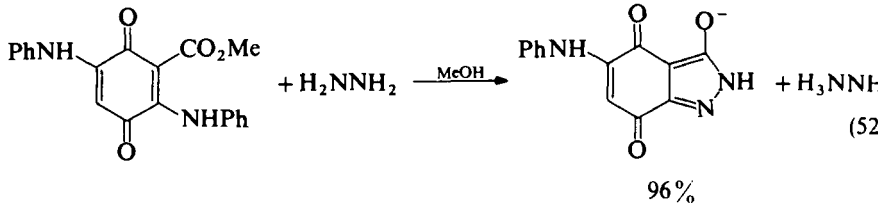
quinones[775]. They have studied the exchange of anilino substituents by amino acids and developed a fine method for the synthesis of 5-hydroxybenzoxazoles (equation 522)[776].



(522)

R = alkyl, Ph, Bz, PhCO, CH_2 = CH

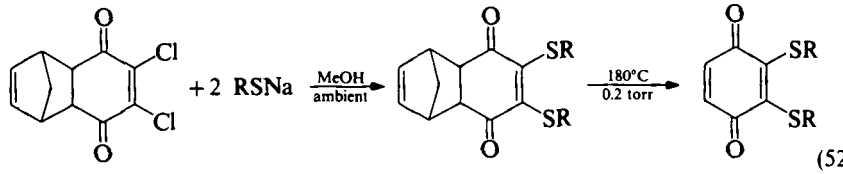
Kumar and Bhaduri also used 2-acyl-3,6-dianilino-1,4-benzoquinones in syntheses of indazolequinones and benzisoxazoles[777]. Schäfer and his colleagues have made similar synthetic efforts in connection with their studies of tautomerism of phenylazohydroquinones and hydrazinoquinones (equation 523)[778,779].



(523)

B. Other Substitution Reactions

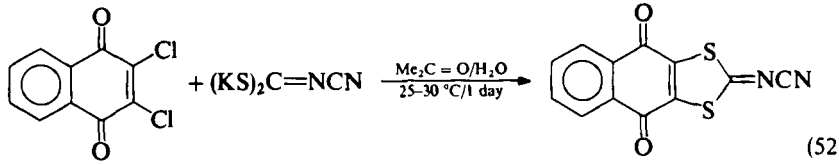
Interest in the synthetic applications of thiol substitution of quinones has continued to produce useful modifications of the well studied standard reactions. For example, in an effort to prepare 2,3-dialkylthio-1,4-benzoquinones Wladislaw and his collaborators employed the reversible Diels–Alder addition of cyclopentadiene (equation 524)[780].



(524)

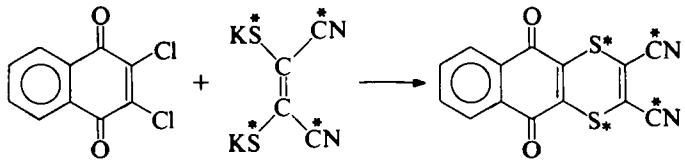
R = Me, Et, Bu 87%, 41%, 35% 88%, 77%, 80%

A dithio heterocyclic quinone is obtained in 90% yield from the reaction of potassium cyanodithioimidocarbonate with 2,3-dichloro-1,4-naphthoquinone (equation 525)[781].



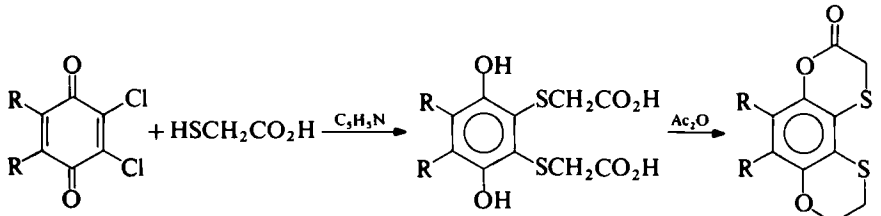
(525)

Somewhat similar chemistry has been used to introduce ^{14}C- and/or ^{35}S-labelled atoms in 2,3-dicyano-1,4-dithia-9,10-anthraquinone (equation 526)[782].



(526)

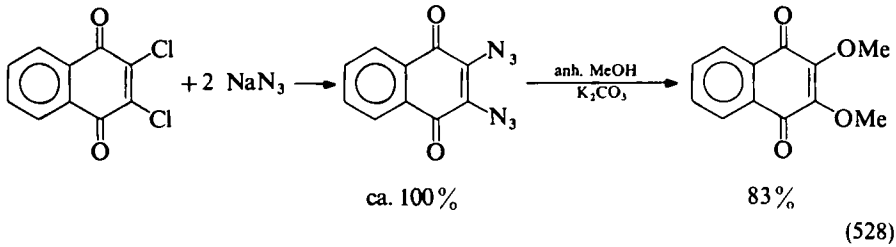
Oediger and Joop have made a series of polyfunctional quinonoid compounds beginning with the substitution of 2,3-dihaloquinones by mercaptoacetic acid (equation 527)[783]. The readily formed bislactones react with secondary or other strongly basic amines to provide good yields of these interesting molecules.



R = Me, -CH=CHCH=CH-, -N=CHCH=CH-

(527)

So many natural products are oxygenated quinones that it is surprising how little attention has been paid to their synthesis by nucleophilic substitution. Brassard has examined several aspects of this question[784]. He and Huot verified that the substitution of chloranil by methanol gives mixtures which are easily separable and provides useful amounts of several compounds. A significant improvement in the yield of 2,3-dimethoxy-1,4-naphthoquinone was obtained by an indirect approach (equation 528). In agreement

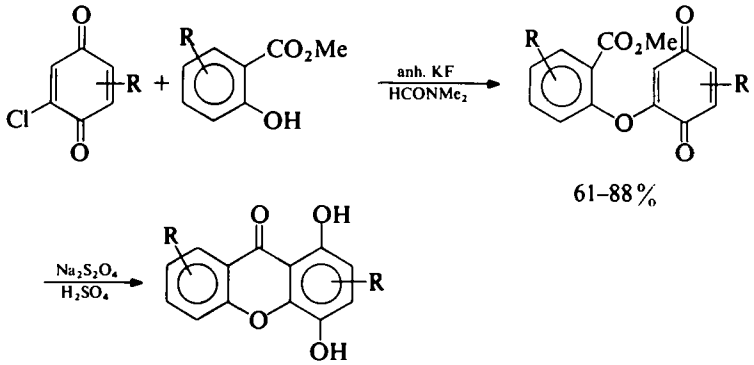


(528)

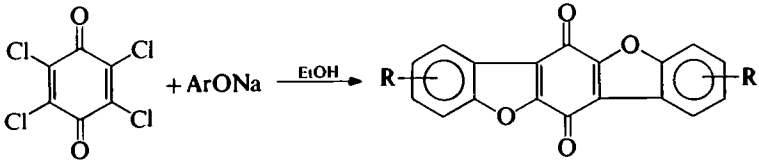
with other studies they found that the methanolysis of dichloronaphthazarin is not a useful preparative method; the corresponding diether works well as a substrate.

The substitution of chlorine by phenoxide has been shown to be a highly regiospecific method for the preparation of the 1,4-dihydroxyxanthones (**173**, equation 529)[785]. 2-Chloro-6-methyl-1,4-benzoquinone gave a large number of products, but it is the only compound showing erratic behavior. In an attempt to obtain samples of benzo-bisbenzofuranquinones for comparison with some natural products chloranil was allowed to react with a sodium aryloxide–ethoxide mixture (equation 530)[786]. Incredibly some members of this extensive series actually produced useful amounts of the desired product!

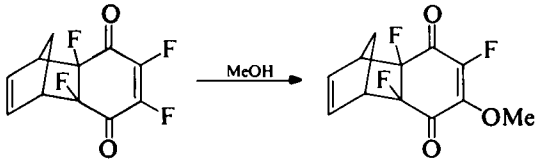
The great ease with which certain quinonoid halogen atoms can be replaced is illustrated by the attempt to recrystallize the Diels–Alder adduct of fluoranil and cyclopentadiene (equation 531)[787].



(529)

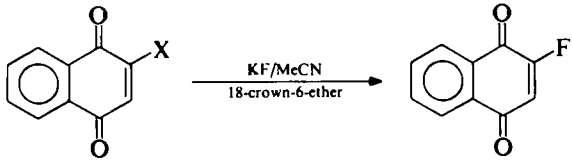


(530)



(531)

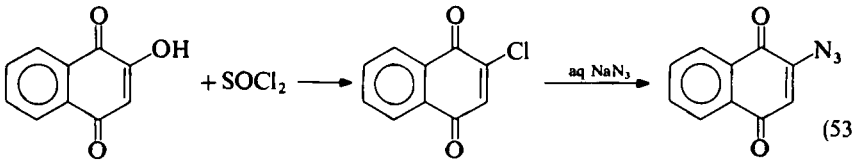
The introduction of a fluorine on a quinone ring has been a problem, but Cameron and his colleagues have offered some help in the naphthoquinone series (equation 532)[788]. This



(532)

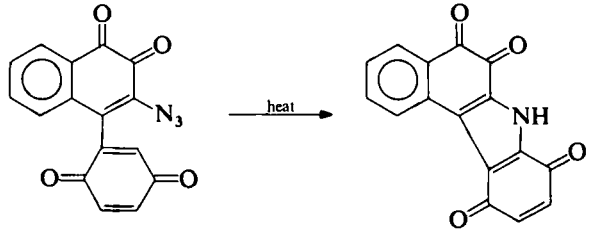
chemistry is not successful with benzoquinones, as was noted earlier[789]. However, Feiring and Sheppard were able to obtain some substitution of 2-chloro-1,4-benzoquinone using silver fluoride.

Buckle and his coworkers used thionyl chloride to chlorinate a 2-hydroxy-1,4-naphthoquinone which was then converted to the corresponding azido derivative (equation 533)[790]. Moore and his collaborators have often introduced the azido group by nucleophilic substitution in their extensive studies of such quinones. Most of these reports



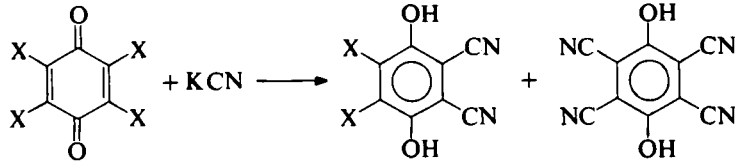
76% 75% (533)

are beyond the scope of the present review but provide excellent background for determining optimum substitution conditions[791–793]. Moore and Lee do report chemistry of immediate interest in showing that with an adjacent alkenyl group cyclization takes place giving an indolequinone (equation 534)[794]. The reaction involving two quinonoid rings leads to an entirely new class of fused ring systems.



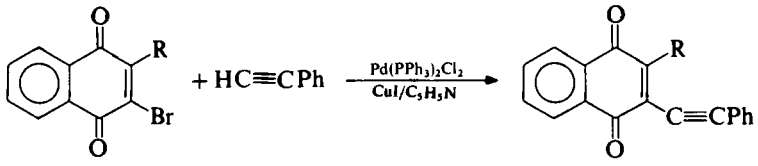
88% (534)

Another closely related anion is cyanide. Friedrich and Bucsis have examined the nucleophilic substitution of various halogenated 1,4-benzoquinones by cyanide and found modest yields of the corresponding 2,3-dicyanohydroquinone and much smaller amounts of tetracyanohydroquinone (equation 535)[795].



X = Cl, Br 33%, 32% 7%, 5% (535)

A final example of nucleophilic substitution at quinonoid carbon is represented by the introduction of acetylenic groups with a palladium complex catalyst (equation 536)[796].



R = Me_2N, morpholinyl, pyrrolidinyl, piperidinyl 40–80% (536)

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CHAPTER 12

Electrochemistry of quinones

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I. INTRODUCTION

Quinone/hydroquinone (Q/QH_2) couples have been widely used in electrochemical studies because they are readily available, easily handled under ordinary experimental conditions, and often exhibit 'well-behaved' electrochemistry. In addition they provide

good models for biological redox processes, many of which involve quinone couples of varying degrees of complexity. The simplest quinone couple, *p*-benzoquinone/*p*-benzohydroquinone or BQ/BQH_2, is perhaps the most thoroughly studied organic or inorganic redox couple. As a result, the subject of 'quinone electrochemistry' covers many quite diverse electrochemical investigations.

Electrochemistry itself is an eclectic science that draws on and has applications in many disciplines ranging into solid state physics, molecular biology, electrical engineering, synthetic organic chemistry and others. A review of quinone electrochemistry, consequently, touches on recent developments in many areas, as well as current thinking in fundamental electrochemistry. The thread of quinonoid redox chemistry in the recent literature outlines and underscores the chemistry in electrochemical science.

A major theme that emerges from this review of the last 15 years is that surface chemistry is of prime importance to the understanding of electrode reactions. While this is evident in many of the contributions surveyed below, the important work of Hubbard and coworkers stands out (Section IV.A.1). Furthermore, understanding of the surface of solid electrodes, in particular the quinonoid nature of carbon electrodes, has played a critical role in the design of electrodes at the molecular level. The applications to electrocatalysis from the laboratories of Kuwana and Wrighton can be cited in this regard (Section IV.B.1). Quinones have also played a prominent role in the fabrication of more complex electrode interfaces such as the polymer modified electrodes described in Section IV.B.2.

Much progress in the understanding of the electrode kinetics of simple quinone couples has been made in the last decade. The contributions of Laviron (Section IV.A.2) for aqueous and Rüssel and Jaenicke (Section III.A) for non-aqueous solutions have rationalized several confusing and conflicting aspects of the older literature. These contributions, and those of others, have substantially lessened the distinctions between aqueous and non-aqueous quinone electrochemistry.

Nonetheless, this review, which covers the period from ca. 1973 to the end of 1985, divides the literature (more or less) into non-aqueous and aqueous studies, much in the same format as that in the previous volume of this series[1]. The reader interested in a more complete survey of quinone electrochemistry, with more extensive older references and explanatory material, should consult both review chapters. This is especially true for the sections on electron transfer kinetics (III.A), proton donor effects (III.B), metal ion effects (III.C), electrode kinetics in aqueous solutions (IV.A.2) and coupled chemical reactions in aqueous solutions (IV.C).

The following abbreviations have been employed: BQ, *p*-benzoquinone; NQ, 1,4-naphthoquinone; AQ, 9,10-anthraquinone; DQ, 2,3,5,6-tetramethyl-1,4-benzoquinone (duroquinone). The corresponding hydroquinones are indicated by BQH_2, NQH_2, AQH_2 and DQH_2. The term Q/QH_2 will refer to a generic quinone couple with a formal standard potential $E^{o\prime}$. The half-wave potential, $E_{1/2}$, of quinone couples is usually a good approximation of $E^{o\prime}$ since the diffusion coefficients of quinone–hydroquinone pairs are approximately equal. Also the following common abbreviations for non-aqueous solvents are used: DMF, *N*,*N*-dimethylformamide; DMSO, dimethyl sulfoxide; HMPA, hexamethylphosphoramide; PC, propylene carbonate; THF, tetrahydrofuran.

II. HALF-WAVE POTENTIALS

A. Aqueous Solutions

Since quinone–hydroquinone couples often are electrochemically reversible, the half-wave potentials carry thermodynamic or quasi-thermodynamic information. Of particular importance in aqueous solutions is the pH dependence of $E_{1/2}$ which reflects the pK_a values for the acid–base dissociation equilibria of the species that interconnect Q and QH_2 in the

classical 3×3 nine-membered scheme[2]. In this scheme the quinone (Q) and the hydroquinone (QH_2) species are related by an array of electron and proton transfer steps. Simple $E_{1/2}$ measurements by polarographic or voltammetric techniques permit the construction of the Pourbaix diagram which shows the regions in which various members of the square scheme are the predominant solution species at different potentials. These $E^{o\prime}$–pH diagrams appear frequently in the older potentiometric literature[3,4], but not in the more modern polarographic or voltammetric literature where the data are more easily obtained. The review of Evans[5] contains several examples and a listing of $E^{o\prime}$ values for Q/QH_2 couples from Clark's monograph[3]. A useful compilation of mediator $E^{o\prime}$ values, including those of many quinone species, has also been published[6].

Bailey and colleagues[7] have recently constructed the pH–$E_{1/2}$ diagram for the *p*-benzoquinone–hydroquinone couple using data from a variety of sources, a slightly simplified and modified version of which is shown in Figure 1. This diagram has been drawn with the ideas of Laviron[8-10] in mind, as well as the measurements of Parker[11] in strongly acidic media (Section III.B). In Figure 1 the solid lines represent the equilibrium values for the borderlines between the areas in which the various members of the nine-membered scheme (seven out of the nine are included in this Figure) are the principal species in aqueous solution. As is well known, the BQ/BQH_2 couple is a two-electron, two-proton couple over a wide pH range, ca. -5 to 10. The dashed lines in the Pourbaix diagram represent the reversible formal potentials for the first and second steps of the BQ reduction, E_{r1} and E_{r2} in Laviron's nomenclature[9]. The relative position of these borderlines shows that the semiquinone intermediates are unstable with respect to disproportionation for pH < ca. 10.

There are several open questions concerning both the acidic and basic regions of Figure 1. The pK_a value for the BQH^+ species used by Bailey and coworkers[7] is probably too

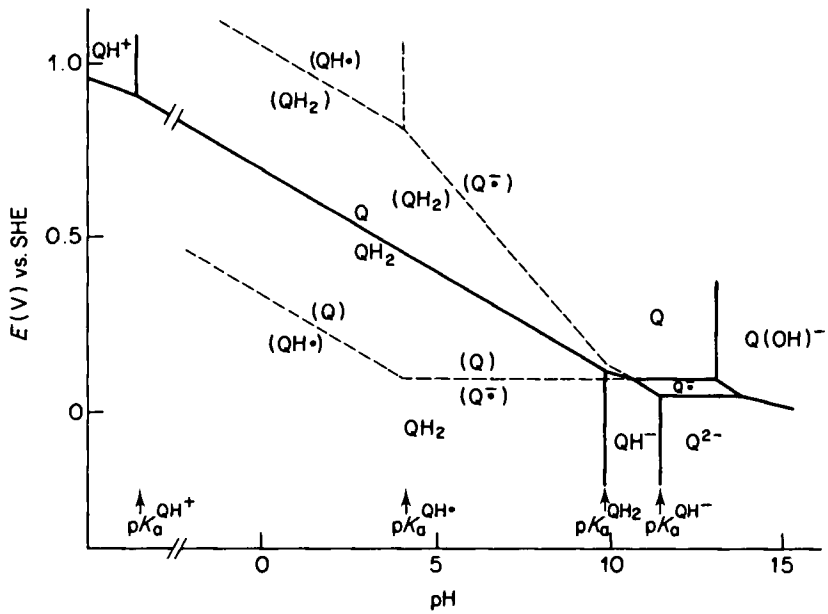


FIGURE 1. Predominance area diagram for the *p*-benzoquinone–hydroquinone couple, adopted from Bailey and coworkers, Ref. 7; SHE, standard hydrogen electrode

large. The value passed down in the literature is for protonated duroquinone, a much weaker acid than BQH^+. Laviron[10] uses the more reasonable value of -7 for the pK_a of BQH^+. It is possible to extend the diagram to the left using the $E^{o'}$ values recently reported by Parker[11] for the $BQH_2^{2+}/BQH_2^{+\cdot}/BQH_2$ couples in highly acidic non-aqueous media, although this hasn't been done here owing to uncertainties in solvent effects and liquid junction potential differences. In the basic region the borderlines are not completely consistent with the $E^{o'}$ values for the $BQ/BQ^{-\cdot}/BQ^{2-}$ couples in non-aqueous solvents, which are ca. 0.5 V more negative than indicated in Figure 1 for aqueous solutions. This region is difficult to study experimentally for several reasons, including the air sensitivity of the anionic species and the reversible addition of hydroxide to BQ that occurs at pH 13[7]. This latter reaction forms the $BQ(OH)^-$ species which complicates the Pourbaix diagram in the basic region. (It is worth noting that an OH^- adduct of AQ has recently been reported in non-aqueous solvents[12].) In the pH range, $4.2 < pH < 8.7$, the $BQO^-/BQ(OH)H_2$ couple exhibits a 90 mV pH dependence corresponding to a two-electron, three proton overall process[13]. A further example of the complex chemistry of quinone species in basic media is an ESR study showing that alkyl substituted quinone radical anions decay to secondary radicals including the anion radical of 2,3,5-trihydroxytoluene and diquinone radicals in aqueous KOH[14]. On the other hand, for quinones which are stable above pK_{a2} for the respective QH_2 species such as 9,10-anthraquinone-2-sulfonate or 9,10-phenanthraquinone-3-sulfonate[13], the Pourbaix diagrams feature a simple $Q^{0/1-/2-}$ 'EE' region at high pH values.

Pourbaix diagrams have been constructed for 9,10-anthraquinone and several substituted anthraquinones (1-amino-, 1-chloro-, 1,5-dihydroxy-, 1,4-dimethyl-, 2-sulfonate, and 2,6-disulfonate) using $E_{1/2}$ values obtained in a thin-layer electrochemical cell at pyrolytic graphite working electrodes[15]. While the $E_{1/2}$ values obtained in this fashion may contain contributions from adsorption terms, the accuracy possible is sufficient to yield much useful information. Furthermore, it is likely that the $E_{1/2}$ values are measured for quinone couples in solution at electrodes covered with adsorbed electroinactive species, in which case adsorption contributions may be minimal. This simple methodology was also applied to the Q/QH_2 couples derived from *p*-chloranil, *p*-chloranilinic acid, *o*-chloranil and *p*-fluoranil[16]. The latter species hydrolyzes in aqueous solutions limiting the pH range over which meaningful values can be obtained. Acid dissociation pK_a values for 1,4-dichlorotetrahydroxybenzene in solution and adsorbed on graphite electrodes have been reported for the pH range 0–10[17]. $E_{1/2}$ vs. pH diagrams have been constructed for several catechols in the pH range, 0–8[18]. The full $E_{1/2}$–pH diagram for the biologically important ubiquinone (UQ) molecule has been determined using the graphite electrode thin-layer cell technique[19]. Above pH 10 the leuco form of UQ must be considered since the pK_a for its formation, $UQ + H_2O = UQOH^- + H^+$, is 10.7. These measurements have been expanded to include other ubiquinones: CoQ_6, CoQ_9 and CoQ_{10} with isoprenoid side chains of varying length[20]. The effect of adsorbed phospholipid layers on the $E_{1/2}$ vs. pH diagrams has been determined in this study as well.

B. Non-aqueous Solutions

In non-aqueous solvents quinones are reduced in successive one-electron steps to form the radical anion and dianion in the absence of added acids.

$$Q \underset{E_1^\circ}{\overset{e^-}{\rightleftharpoons}} Q^{-\cdot} \underset{E_2^\circ}{\overset{e^-}{\rightleftharpoons}} Q^{2-} \qquad (1)$$

Under ordinary voltammetric conditions, the half-wave potentials for the two waves that result are excellent estimates of the formal potentials ($E^{o'}$s) for the two couples of equation 1. Several studies have been directed at the question of solvent effects on these $E^{o'}$ values.

Jaworski and coworkers[21] in an extensive study of BQ, NQ, AQ and 9,10-phenanthrenequinone in eight solvents (pyridine, acetone, HMPA, DMF, *N*,*N*-dimethylacetamide, acetonitrile, DMSO and PC) found a linear correlation with the solvent acceptor numbers of Gutmann[22]. (The $E_{1/2}$ values were also found to correlate with the spin density at oxygen of the semiquinone radical anions.) Solvent effects on $\Delta E_{1/2}$ ($= E_1^{o\prime} - E_2^{o\prime}$) have also been correlated with the Gutmann numbers[23] and with the solvent acidity as measured by the solvent autoionization constant or the potential difference when strong acid ($HClO_4$) or strong base (NEt_4OH) is added to the solvent[24].

In an even more extensive study than that of Jaworski and coworkers[21], Wilford and Archer[25] measured the $E_{1/2}$ values of BQ in 15 solvents and looked for correlations with 18 different solvent parameters. They found the best linear fit with Swain's A + B function[26] for solvents ranging from THF to water. Others have also reported poor correlations with Gutmann's donor numbers[27]. The A + B function is a measure of solvent polarity where A is the anion-solvating tendency and B is the cation-solvating tendency.

The temperature dependence of the $E_{1/2}$ values for BQ, NQ, AQ, and 5,8-dihydroxy-1,4-naphthoquinone has been determined in DMF and propionitrile by Nagaoka and Okazaki[28]. The temperature shift is most pronounced for BQ, which is ascribed to increased solvation of the radical anion being most important for the smallest quinone. The smallest temperature dependence was found for 5,8-dihydroxy-1,4-naphthoquinone where internal hydrogen bonding is possible. Finally, careful electromotive force measurements of the quinhydrone electrode in acetonitrile–water mixtures have been reported[29].

C. Substituent Effects

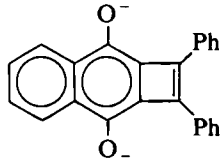
In the last 12 years substituent effects on $E_{1/2}$ values have been correlated with a variety of parameters, including the Hammett sigma substituent constants, as developed by Zuman in his classic monograph[30]. Studies of this type have included a series of more than 30 1,4-naphthoquinone derivatives substituted with arylamino groups where intermolecular charge transfer complexes are possible[31–33]. For these compounds a Hammett–Zuman substitutent effect treatment adequately described the results without invoking donor–acceptor complexes. Other correlations of this type have been noted for several ureido- and guanidino-substituted naphthoquinones[34], as well as anthraquinones[35], 6,11-dihydroxy-5,12-naphthacenequinones[36], 2*H*-benzo[*f*]isoindole-4,9-quinones[37] and several anthraquinones[38]. In the latter series solvent-dependent positive deviations from the Hammett–Zuman equation were seen when intramolecular hydrogen bonding was operative. Solvent effects have been noted on the Hammett–Streitwieser reaction constant, which increases with the Lewis acidity of the solvent[39].

Half-wave potentials have been reported for 20 quinones in 75% aqueous dioxane[40], several furanquinones in acetonitrile[41], a variety of anthraquinones in DMF[42,43] and fluoro- and trifluoromethylbenzohydroquinone[44]. In the latter case the strong electron-withdrawing nature of the $-CF_3$ group leads to a +73 mV increase in the $E_{1/2}$ value.

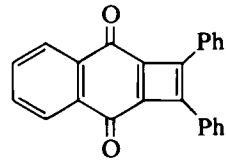
SCF molecular orbital calculations carried out on 36 quinones showed good correlation with $E_{1/2}$ and spectral data[45]. Correlations with electronic absorption energies have been observed[46,47] and $E_{1/2}$ values and charge transfer transition energies used to estimate electron affinities for NQ and derivatives[48] in the usual fashion[49]. Substituent effects on infrared frequencies have been noted[50,51]. In the work of Clark and Evans, a flow cell was used to obtain the IR spectra of the radical anions and dianions of several quinones at 0.001 M concentration levels[51].

Ring strain phenomena have been observed to influence the $E_{1/2}$ values of certain naphthoquinones[52]. The naphthoquinone with a tetramethylene bridge fused to the 2,3 bond is more difficult to reduce than the derivative with a fused four-membered ring by ca.

0.16 V. The former has an $E_{1/2}$ close to that of 2,3-dimethylnaphthoquinone, while the latter is reduced at almost the same potential as the parent unsubstituted compound. The results were interpreted using a hybridization model within the Huckel framework. In a related study, Breslow and coworkers used naphthoquinone as a probe to assess the energies of ring systems fused to the 2,3 bond in structures like **1** where oxidation of the dianion leads to an unstable, possibly antiaromatic, ring system[53]. With the aid of fast-

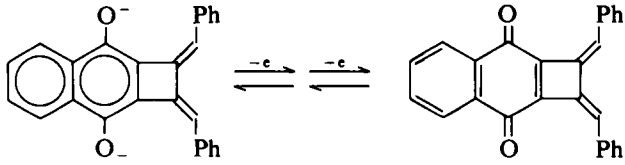


(1)



(2)

sweep cyclic voltammetry, evidence was obtained for successive one-electron oxidation (EE behavior) of dianion species like **1** to highly unstable quinones with 'antiaromatic' structures like that of **2**. The $E_{1/2}$ for the $Q^{1-/2-}$ couple is 0.60 V more positive than that of the unsubstituted naphthoquinone. In order to correct for inductive and strain effects of the above type, the dianion **3**, which can be oxidized (see equation 2) to a relatively stable quinone, **4**, was synthesized and found to exhibit classical EE behavior with $E_{1/2}$ values



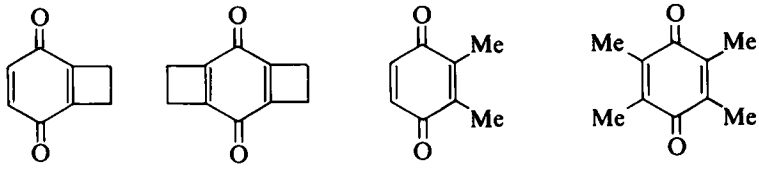
(2)

(3) (4)

intermediate between **1** and the dianion of naphthoquinone. After careful analysis, the authors conclude that cyclobutadiene is destabilized by at least 12–16 kcal mol^{-1}, and is clearly antiaromatic.

Breslow and coworkers have also reported the electrochemical reduction of several 'cyclobutadienoquinones'[54]. For these molecules it is found that fusion of two antiaromatic ring systems stabilizes the reduced dianion state. In another study the EE behavior of several tetradehydrol[18]annulenediones was established indicating that they can be considered as quinones of an aromatic system[55]. The application of electrochemistry to questions of this type has been reviewed[56].

Ring strain effects of the type noted by Rieke and coworkers[52] (see above) have also been reported by Iyoda and Oda[57,58] for BQ and 5,8-dihydroxy-1,4-naphthoquinone with fused four-membered ring substituents. For the series, **5–8**, potential shifts of 0.00, −0.03, −0.16 and −0.30 V vs. $E_{1/2}$ for *p*-benzoquinone were observed.

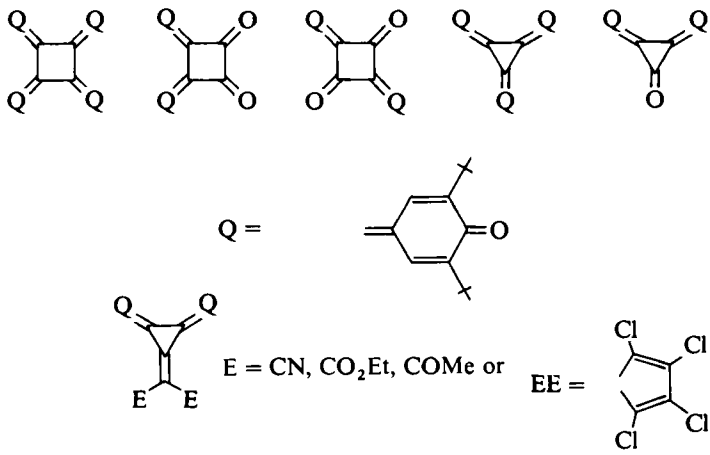


(5) (6) (7) (8)

D. Quinone Analogs

Half-wave potentials have been measured and used to establish quinonoid character for a variety of interesting molecules. These include two acepleiadylenediones[59], *p*-tropoquinone[60], 1,2,5-benzotropoquinone[61,62], and the croconate dianion and related dicyanomethylene derivatives[63]. $E_{1/2}$ values and ESR spectra have been reported for several di- and tri-quinones[64–67]. The ESR spectra of the electrochemically generated radical anions of triptycene bis- and tris(quinones) indicated diradical formation and the absence of intramolecular interactions[66].

The most fascinating quinone analogs of recent years are the polyquinocycloalkanes synthesized by West and his students[68–75]. These molecules have structures of the following type:



They exhibit EE quinone-like electrochemistry with $E_{1/2}$ values mostly well positive of *p*-benzoquinone. As is to be expected for the strong electron-withdrawing groups in West's molecules, the $E_{1/2}$ values approach those of DDQ (dichlorodicyano-*p*-benzoquinone) in several cases. In one example, where EE is a 10-(1,1-dicyanomethylidene)anthrylidene-9-ylidene electron-withdrawing group, the first and second reduction waves overlap, resulting in a two-electron voltammetric wave[74]. Reversible conformational changes (see Section III.D below) occurring during the reduction are suggested to account for this behavior.

III. ELECTROCHEMISTRY IN NON-AQUEOUS SOLVENTS

A. Electron Transfer Kinetics

Heterogeneous electrode kinetics of simple quinone couples in non-aqueous solvents has been a lively topic in recent years. There have been some real and some apparent discrepancies in the measured values for the rate constant k_f° of the $BQ^{0/-}$ couple in non-aqueous solvents such as acetonitrile or *N*,*N*-dimethylformamide. Electrode material, solvent, electrolyte, nature of the quinone couple, adsorption of impurities or reactants, and temperature can all influence an heterogeneous rate constant. In retrospect, the solvent and electrolyte have much more significant influences on the k° values than was initially suspected.

Rosanske and Evans[76] measured k_f° values for $BQ^{0/-}$, $AQ^{0/-}$, $NQ^{0/-}$ and the 3,5-di-*t*-butyl-*o*-quinone couple in 0.3 M NEt_4ClO_4/acetonitrile or DMF at Hg, Au and Pt

electrodes. They measured apparent rate constants in the range, 0.1–1.3 $cm\,s^{-1}$, considerably larger values than reported previously by Capon and Parsons[77]. The latter workers reported k_f^o values for $BQ^{0/-}$ in DMF/NEt_4ClO_4 of ca. 0.005 $cm\,s^{-1}$ at six metal electrodes (Pt, Pd, Rh, Ir, Au, Hg). The values of Capon and Parsons were approximately independent of electrode material and of the same order of magnitude as those measured for the BQ/BQH_2 couple in aqueous media[78,79]. Others have measured kinetics for fast quinone couples in non-aqueous solvents[80–83]. The paper of Howell and Wightman is especially noteworthy. Employing microelectrodes, they obtained exceptionally good cyclic voltammetric data at sweep rates up to 10^4 $V\,s^{-1}$ for the $BQ^{0/-}$, $NQ^{0/-}$ and $AQ^{0/-}$ couples in acetonitrile/NEt_4ClO_4 at Pt and Au surfaces. They found a significant dependence on molecular size: $k_f^o = 0.39 \pm 0.10$, 0.73 ± 0.12, 1.78 ± 0.35 $cm\,s^{-1}$, respectively, for the above couples. (The 1.8 $cm\,s^{-1}$ apparent rate constant for the AQ couple, measured using the widely employed theory of Nicholson[84], is very fast by current experimental standards.) Samuelsson and Sharp[81] also reported a similar, but not so dramatic, molecular size dependence.

It appears that in polar aprotic solvents the electrode material does not affect the quinone electron transfer rates markedly. This statement should be taken with a grain of salt since double layer corrections are seldom taken into account. However, in some cases[85], but not all[82], surface layer modification can decrease the rates considerably. Activation enthalpy values have been measured in DMF/NBu_4ClO_4 as a function of electrode material[28]. At glassy carbon, Pt and Au electrodes, values of 3.1 ± 0.5, 3.3 ± 1.0, and 5.0 ± 0.7 $kcal\,mol^{-1}$ were obtained for the $BQ^{0/-}$ couple.

Much of the confusion in this area has been removed by the excellent work of Rüssel and Jaenicke[23,27,86–88]. Upon careful measurement of the k_f^o values for $BQ^{0/-}$ in nine non-aqueous solvents containing three different tetraalkylammonium perchlorate electrolytes, they found that the values varied by 3–4 orders of magnitude. The activation energies, ΔG^*, were a non-linear function of the solvent polarity and increased with the size of the NR_4^+ cation. The results have been interpreted in terms of the Marcus theory, equation 3, where λ_i and λ_o are the inner and outer sphere reorganization energies that accompany an electron transfer reaction, and the ideas of Fawcett[89,90] on the variation of the location of the electron exchange site at an electrode surface with the size of the counter ion. (In the simplified form of equation 3, the potential drop across the diffuse double layer has been neglected.) For polar solvents Marcus theory describes the results with ΔG^* increasing with solvent polarity, and k^o decreasing, since the outer sphere reorganizational energy, λ_o, is directly proportional to solvent polarity. In opposition to theory, however, ΔG^* increases in non-polar solvents like chloroform and slow electron transfer rates are observed. Ion association in the non-polar solvents is a possible cause of this behavior. As a result the largest rate constants are observed in solvents of intermediate polarity, e.g. cyclohexanone, and for supporting electrolyte cations with the smallest ionic radii. This behavior is shown in Figure 2[87], in which the solid lines were calculated using a three-centered model for the quinone and the ionic radii of the tetraalkylammonium ions to estimate distance parameters in the calculation of ΔG^*. While the rate constant data are only partially explained by this treatment, the trends evident in Figure 2 rationalize much discordant data in previous literature. Earlier, Sharp also had noted marked solvent effects on the k_f^o for the tetracyanoquinodimethane couple[91].

$$k^o = A \exp\{-\Delta G^*/RT\} = A \exp\{-(\lambda_i + \lambda_o)/4RT\} \tag{3}$$

Rüssel and Jaenicke have extended their study of the quinone electron transfer kinetics to the $Q^{-/2-}$ couple[23]. Exchange rates for the second step are much slower than the first, and a value of ca. 1.2 was determined for the ratio of the activation energies for the two processes in acetonitrile. Part of the decrease could be due to ion association since they find that the quinone dianions are complexed with NEt_4^+ and NBu_4^+, but not $NOct_4^+$ in

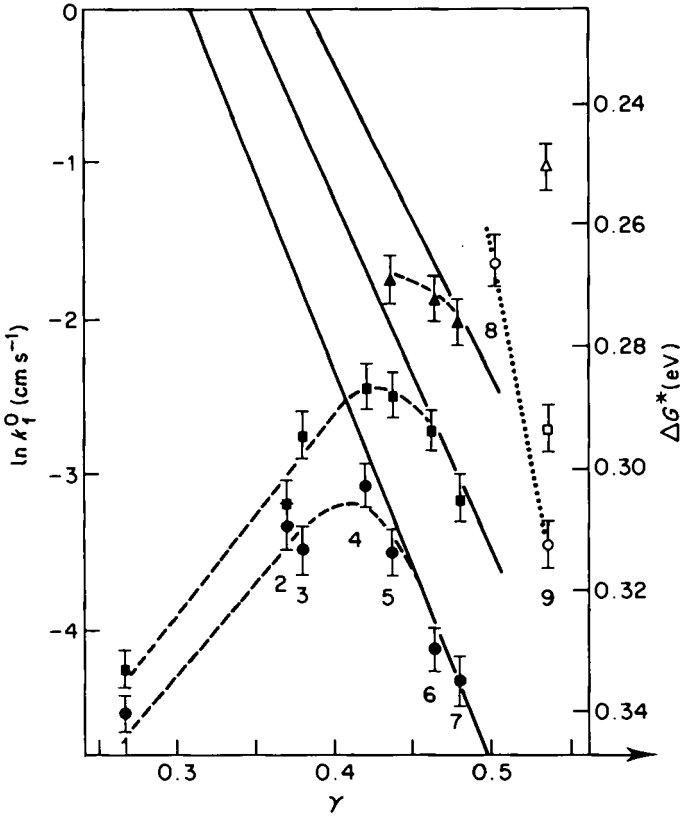


FIGURE 2. Apparent heterogeneous rate constant, ln k', (cm s^{-1}) and activation energy, ΔG^* (eV), at 298 K as a function of solvent polarity, γ. Parameter, supporting electrolyte (0.1 M): (▲, △) tetraethylammonium perchlorate; (■, □) tetra-*n*-butylammonium perchlorate; (●, ○) tetra-*n*-octylammonium perchlorate. Solvents: filled symbols: (1) $CHCl_3$, (2) THF, (3) CH_2Cl_2, (4) cyclohexanone, (5) DMSO, (6) DMF, (7) PC; open symbols: (8) propionitrile, (9) acetonitrile, solid lines: theoretical curves. *Reproduced by permission of Elsevier Science Publishers from Rüssel and Jaenicke, J. Electroanal. Chem.*, **180**, 205 (1984)

acetonitrile. In a very recent study of 13 quinone couples in DMF/NEt_4ClO_4, they found that $\Delta G_2^* - \Delta G_1^* = 0.78$ eV[88]. For the $BQ^{0/-/2-}$ couples in this system equation 3 describes the results with $k_1^\circ = 0.065$ cm s^{-1} ($\Delta G_1^* = 0.292$ eV), $k_2^\circ = 0.00083$ cm s^{-1} ($\Delta G_2^* = 0.404$ eV), and $A = 6040$ cm s^{-1}.

B. Proton Donor and Lewis Acid Effects

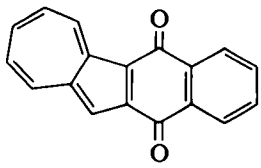
The effect of acids on the electrochemistry of quinones in non-aqueous solvents continues to be documented in the literature. Protonation of Q to form the QH^+ species, or of $Q^{-\cdot}$ to form $QH^\cdot$, opens mechanistic pathways for the quinone electrode reactions and gives rise to new voltammetric waves. Prewaves have been observed in the camphorquinone–benzoic acid system[92]; polarography of AQ-phenol has been reported[93]; protonation and disproportionation of quinone radical anions in formic acid[94]

and in $MeOH/NEt_4ClO_4$[95], have been proposed; the decay of haloquinone radical anions in ethanol and acetone has been studied[96]; protonation of $AQ^{-\cdot}$ or $BQ^{-\cdot}$ radical anions in 1,2-dimethoxyethane by AQH_2 or BQH_2 gives rise to the following overall electrode process[97], while formation of a Q–QH_2 donor–acceptor complex has been reported for

$$Q + QH_2 + 2e^- = 2QH^- \tag{4}$$

acenazulenedione, **9**, in acetonitrile/NEt_4ClO_4[98]. Proton donors disrupt charge transfer complexes between NQ and 2,4,6-trinitrobenzene with the result that H^+EE electrochemical behavior is observed[99]. Polarograms of alizarin (1,2-dihydroxyanthraquinone) and alizarin-S display two waves in MeOH/LiCl, which coalesce, either into one wave at more positive potential in the presence of benzoic acid, or into one wave at more negative potential in the presence of NEt_4OH[100]. An interesting observation is that surface protonation by carboxylate functionalities of oxidized carbon fiber electrodes gives rise to quinone prewaves in $MeOH/LiClO_4$ solutions[101]. Electrochemical oxidation of NQH_2 in acetonitrile or acetic acid/acetic anhydride mixtures has been suggested as a means of generating non-aqueous acid titrant solutions[102].

The absorption spectra of electrochemically generated $BQ^{-\cdot}$, $BQH^{\cdot}$ and BQH^- species in DMSO have recently been published[103]. A broad band at 670 nm and one at 410 nm are assigned to the $BQH^{\cdot}$ species. The $BQ^{-\cdot}$ radical anion was found to be stable in neutral water solutions as previously reported[104].



(9)

In an interesting approach, Keita and coworkers[105] studied protonation of AQ radical anions at *n*- and *p*-type silicon semiconductor electrodes in acetonitrile/acetic acid solutions. True ECE pathways are followed, since the radical anions are formed via photoinjection of electrons into the conduction band, and the protonated radicals are reduced by hole injection into the conduction band.

Increasing the basic character of the quinone by means of appropriate substituents clarifies the mechanistic pathways in the presence of proton donors considerably. Bessard and coworkers[106] examined the effect of proton donors on the voltammetry of 2,6-dimethoxy-*p*-benzoquinone, 3,3′,5,5′-tetramethoxy-*p*-biphenoquinone, and related species in acetonitrile and nitromethane in the presence of $HClO_4$. The protonated forms of these quinones are stable permitting measurement of the absorption spectra and careful characterization of the QH^+ reduction processes. The QH^+/QH_2 reduction waves are generally quasi-reversible and appear at potentials more than 1 V positive of the $Q/Q^{-\cdot}$ waves in neutral medium. Similar large potential shifts were found for the reduction of ubiquinone in acetonitrile with and without added $HClO_4$[107]. In the presence of 0.01 M $HClO_4$, the tetramethoxy-*p*-biphenoquinone couple displays a *reversible* two-electron voltammetric wave[106]. This study nicely demonstrates that the reversibility of quinone couples is strongly dependent on the nature of the substituents and the acidity of the medium.

The long-standing observation that radical cations form under acidic conditions can be rationalized by the following coproportionation reaction[106], equation 5:

$$QH^+ + QH_2 + H^+ = 2QH_2^{+\cdot} \tag{5}$$

Hammerich and Parker[111] have observed this reaction in $CH_2Cl_2/HFSO_3$ solution at $-50°C$ and suggest that the reaction proceeds via the QH_2^{2+} species. They estimate that the $E^{o'}$ value for the $QH_2^{2+}/QH_2^{+\cdot}$ couple is 1.8 V vs. SCE in this medium. The $QH_2^{+\cdot}/QH_2$ couple is reversible in CH_2Cl_2 in the presence of strong acids such as methylsulfonic or fluorosulfonic acid with an $E^{o'}$ of 1.3 V vs. SCE. These measurements fill in the upper part of the square scheme of Jacq[2].

The square scheme is also operative in molten salt media where the Lewis acidity can be varied permitting the observation of novel acid–base species. Cheek and Osteryoung have examined the electrochemical and spectroscopic behavior of AQ and chloranil in a room temperature molten salt mixture of $AlCl_3$ and *n*-butylpyridinium chloride[108, 109]. At high mole fractions of $AlCl_3$, Lewis adducts of the type $AQ(AlCl_3)_2$ are observed. Voltammetric reduction waves are assigned to different complexes suggesting that, in contrast to protonation steps in more common solvents, the acid–base equilibria are sluggish in these media. For chloranil, which has previously been studied in an $AlCl_3/NaCl$ melt at 175°C[110], HF solution[111] and HF/SbF_5[112], complexation by up to six (!) $AlCl_3$ molecules is observed[109]. Presumably the complexation sites are the two carbonyl groups and the four chloride substituents on the chloranil ring.

The electrochemistry of catechol, 3,5-di-*t*-butylcatechol, tetrachlorocatechol and tetrafluorocatechol has been examined in several non-aqueous solvents where proton donor effects of water have been noted[113]. The respective quinones all present typical EE voltammetric behavior except for 3,5-di-*t*-butyl-*o*-quinone where the second reduction wave is broadened and decreased in peak height. Water-catalyzed disproportionation of the radical anion (equations 6 and 7),

$$Q^{-\cdot} + H_2O = QH^{\cdot} + OH^- \tag{6}$$

$$QH^{\cdot} + Q^{-\cdot} = Q + QH^- \tag{7}$$

and reduction of residual water by the substituted catechol dianion (equation 8),

$$Q^{2-} + H_2O = 1/2\,H_2 + OH^- + Q^{-\cdot} \tag{8}$$

are invoked to explain the results. Extensive voltammetric data in the form of half-wave potentials and $E^{o'}$ data for the *reduction* of the catechols (QH_2 species) are given.

Protonation of the radical anion of 1,8-dihydroxy-AQ (DAQ) by benzoic acid in *N*,*N*-dimethylformamide has been examined using stopped-flow methods by Wightman and colleagues[114] in a careful study marked by attention to detail. For a 1:1 to 50:1 molar excess of benzoic acid to $DAQ^{-\cdot}$, only the following reaction (equation 9), is observed.

$$2\,DAQ^{-\cdot} + PhCOOH = HDAQ^- + DAQ + PhCOO^- \tag{9}$$

The $DAQH_2$ molecule, which is partially ionized even in the presence of $HClO_4$, is a very strong acid and is not formed. For the above protonation, the kinetic analysis indicates that neither a classical ECE nor a simple disproportionation mechanism can explain the results. The authors make a strong case that a heterogeneous acid–base dimer intermediate, $\{DAQ\text{---}PhCOOH\}^{-\cdot}$, plays the key role in the reduction process. Protonation of the closely related quinizarin radical anion (1,4-dihydroxy-9,10-anthraquinone) by benzoic acid in *N*,*N*-dimethylformamide has also been studied[115]. At a 5:1 ratio of benzoic acid to quinone the $AQH_2(OH)_2$ species was reported to be formed.

Hydroxy-substituted anthraquinones are strong enough acids to protonate the superoxide species[116]. As a consequence, the radical anions of these species can react with trace amounts of O_2 in non-aqueous solvents even though the $E_{1/2}$ values are positive of the $E_{1/2}$ for the $O_2/O_2^{-\cdot}$ couple since the process can be driven by the proton transfer step.

C. Metal Ion Effects

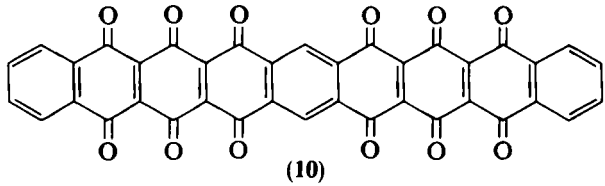
It is convenient to separate effects of metal ions that can form ion associates with quinone anions from proton donor effects, although the fundamental interactions are closely related. Furthermore, the observed electrochemical responses are similar: voltammetric or polarographic waves shift to more positive potentials as the reduced species are complexed by the metal ions added to the solution in accord with the Nernst equation[117]. The magnitude of the effect is dependent on the nature of the quinone species, the charge and size of the metal or counter ion, and the solvent. In recent years several researchers have placed these phenomena on sound experimental footing.

Fujinaga and coworkers[118] looked at 21 compounds, 15 of them quinones, in DMF in the presence of K^+, Na^+ and four alkaline earth dications. They found the following order of increasing strength for the $Q^{\cdot-}\text{---}M^{n+}$ ion pair: *para*-quinones = α-diketones < aromatic ketones < *ortho*-quinones. This group has also examined the dependence of the ion association formation constant on the size of the quinone anion for various Li^+, $Q^{\cdot-}$ pairs[119]. For *para*-quinones in DMF, formation constants for both ion pairs and ion triples ($QLi_2^{+\cdot}$) were found to correlate with the Fuoss equation[120], which is a simple electrostatic model that treats the ions as spherical charges in a dielectric medium. The dependence of the quinone $E_{1/2}$ values on the ionic radius of the cation of the supporting electrolyte was also noted by Kalinowski[121]. The variation of the $E_{1/2}$ values with the ionic potential of the cation in a linear fashion is an indication that the ion pairs are of the contact type and not solvent separated[121]. This is the situation for the alkali metal ion pairs formed with the radical anion of 1,2-naphthoquinone in DMSO[122]. Triple ions are also seen in this system. Similar conclusions were reached in an ESR study[123]. Ion association of the 1,2-naphthoquinone radical anion has also been studied by ESR, absorption spectrometry and electrochemistry in acetonitrile[124]. *Ortho*-quinones were also reported to be most strongly ion paired by Kalinowski and Tenderende-Guminska[125], who studied BQ, NQ, AQ, 1,2-naphthoquinone, 9,10-phenanthrenequinone and acenaphthenequinone. These authors also varied the solvent and suggested a correlation with Gutmann's donor numbers.

Solvent effects on the formation constant of the $BQ^{\cdot-}Li^+$ ion pair in acetonitrile, PC, DMF, *N*,*N*-dimethylacetamide, DMSO and *N*,*N*-diethylformamide, relative to HMPA where the $BQ^{\cdot-}$ anion is free, have been reported[126]. The term, $\log K_f$, where K_f is the formation constant of the ion pair, was found to be linear in Gutmann's donor numbers: $\log K_f = -0.155(DN) + 5.994$. The reasonable implication is that as the Lewis base character of the solvent increases, the ion pairing becomes weaker. The dependence of the $E_{1/2}$ values on the solvent basicity had been noted earlier[127].

The ion association of tetraalkylammonium ions with the dianion of benzoquinone has been observed[23] where it plays a role in governing the rate of electron transfer (see Section II.A). In the presence of $NOct_4^+$ counter ions, the quinone dianion is free, but it is associated for smaller cations.

Ion association has also been reported in recent years for $AQ^{\cdot-}$ with dications[128] and alkali metal ions in *N*,*N*-dimethylformamide[129], and for the $BQ^{\cdot-}$ anion with Li^+ in acetonitrile[130]. Reduction of *o*-chloranil in acetonitrile/$NaClO_4$ solution, which results in a deep blue adsorbed $Na^+Q^{\cdot-}$ film, has been suggested as an electrochromic system[131]. The polyquinone **10**, nonylbenzohexaquinone, takes up six Li^+ cations per molecule, one



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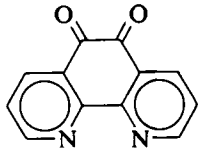
for each quinone function, upon reduction in one-to-one PC-dimethoxyethane/$LiClO_4$[132].

The voltammetric behavior of catechol complexes of several divalent and trivalent metal ions has been surveyed[113, 133]. For these systems, where both metal center and $Q/Q^{-\cdot}$ ligand center electron transfer reactions occur, the cyclic voltammetric behavior is complex. The paper by Sawyer and coworkers[133] reviews the inorganic literature in this area. In this context, it can be mentioned that zero valent transition metal complexes of quinones exist and their reduction potentials are occasionally reported[134, 135]. These species are more pertinent to the electrochemical behavior of quinones strongly adsorbed on metal electrodes (see Section IV.A) than quinone ion pairs in solution.

The electrochemistry of an interesting quinonoid compound containing the bipyridyl structure **11** has been examined and compared to that of **12**[136, 137]. Compound **11** binds Ni^{2+}, Co^{2+} and Zn^{2+}, but not Ca^{2+}, Mg^{2+}, Mn^{2+} and Pb^{2+}.



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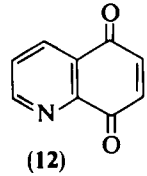

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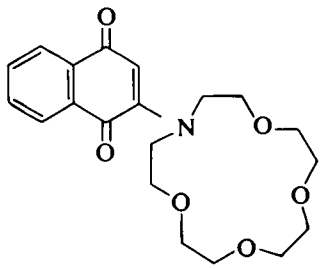
Bifunctional molecular species containing redox and specific complexing groups of a crown ether type have significant implications in biological electron transport and other energy conversion mechanisms. Several quinones have been incorporated into molecules of this type. Bock and colleagues[138] prepared compound **13** and found that upon reduction by metal in THF, the metal ion is bound via a contact ion pair in the solvate cage of azacoronandnaphthoquinone radical anion. Addition of excess free crown generates the ESR spectrum of the electrochemically produced radical anion.



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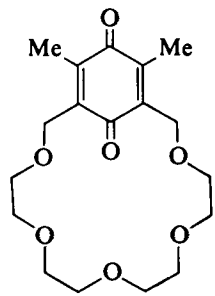
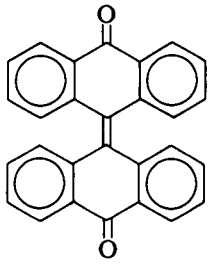


(14)

A related molecule, **14**, was synthesized by Sugihara and coworkers[139]. The electrochemistry of this molecule was examined by Wolf and Cooper[140], who found that the $E_{1/2}$ shifts in the presence of Li^+, Na^+ and K^+ were larger than for simple $BQ/BQ^{-\cdot}$ couples *and in the opposite order of that expected for ion association.* Thus in this molecule the selectivity of the crown ether moiety for the potassium ion is coupled to the electron transfer reaction of the quinone. Related quinone crowns that exhibit enhanced Li^+ binding have been reported recently[141].

D. Conformational Effects

The elegant work of Evans and his students[142, 143] on the electrochemistry of bianthrone, **15**, can be viewed in the context of quinone electrochemistry. Bianthrone,



(15)

which exists in a doubly folded butterfly conformation, conformation A, at room temperature, undergoes an irreversible two-electron voltammetric reduction to a dianion, which exists in a twisted conformation (B). This conformational change can be viewed as a result of the decrease in the double bond character in the *exo*-bond upon reduction to the dianion which allows the anthracene rings to adopt the twisted form. Oxidation of the twisted dianion (B^{2-}) proceeds by an EE pathway at fast sweep rates (equation 10) to form

$$\begin{array}{ccccc} A & \overset{e^-}{\rightleftharpoons} & A^{-\cdot} & & \\ \Updownarrow & & \Updownarrow & & \\ B & \overset{e^-}{\rightleftharpoons} & B^{-\cdot} & \overset{e^-}{\rightleftharpoons} & B^{2-} \end{array} \qquad (10)$$

the unstable B conformation of bianthrone. The system was nicely studied using double potential step spectroelectrochemical and cyclic voltammetric techniques and rate constants determined for the transformation of $A^{-\cdot}$ to $B^{-\cdot}$ and B to A. Reduction of bianthrone is suggested to occur by the sequence, $A \rightleftharpoons A^{-\cdot} \rightarrow B^{-\cdot} \rightleftharpoons B^{2-}$, although other pathways cannot be ruled out. Remarkably, the same conformational square scheme is operative and on the anodic side when bianthrone and related molecules are oxidized[144]. The $[\text{bianthrone}]^{2+/+/0/-/2-}$ system, spanning five oxidation states, thus affords one of the most dramatic examples of conformational effects on electrochemistry in the literature.

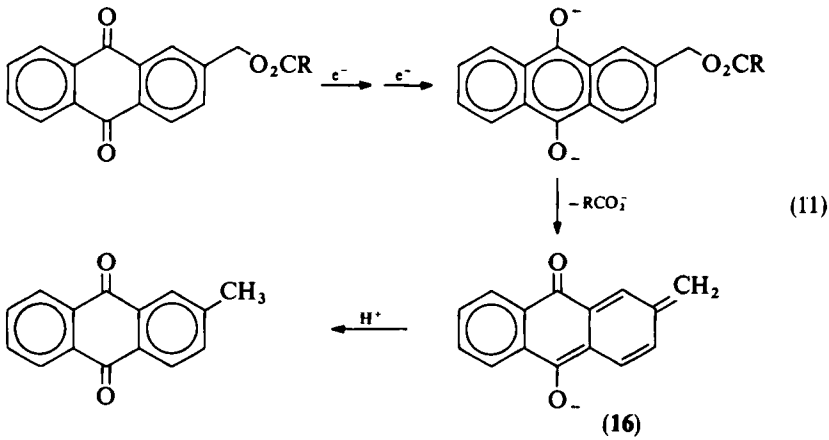
Parker and coworkers have also made significant contributions in this area[145, 146]. They measured the rate constant for the twist to butterfly conformational change using Parker's derivative cyclic voltammetry technique and report an activation energy of 15.3 kcal mol^{-1} for the B to A process[146].

Evans and coworkers have extended their examination of the bianthrone reduction process using homogeneous mediator catalysts[147, 148]. By selection of mediator couples (they actually used quinones such as duroquinone) with $E^{o\prime}$ values between the equilibrium $E^{0\prime}$ for the A/B^{2-} couple and the irreversible two-electron reduction of A, the reduction process can be carried out by the reduced mediator (i.e. $DQ^{-\cdot}$) in a thin reaction layer next to the electrode surface. Armed with the theory of Saveant[149, 150], rate constants can be determined for the coupled chemical reactions. For fast reactions such as the $A^{-\cdot}$ to $B^{-\cdot}$ conformational change, there are experimental advantages to this 'electrocatalytic' approach since the concentration of electrogenerated mediator can be controlled both by the $E^{0\prime}$ of the mediator couple and the applied potential. Evans and Naixian[147] employed six $Q/Q^{-\cdot}$ couples as mediators for the process and found the expected qualitative dependence on their $E_{1/2}$ values.

Finally, thin-layer coulometry (at 100°C in DMF) has been carried out to obtain the equilibrium potential for the A/B^{2-} couple of 1,1-dimethylbianthrone[151]. With the readily determined $E_{1/2}$ values for the $B^{0/-/2-}$ steps, this permits determination of the equilibrium constant for the $A \rightleftharpoons B$ conformational change: a value of 8×10^{-6} was found.

E. Coupled Chemical Reactions

Miller and colleagues[152] have documented the reductive cleavage of several 2-hydroxymethyl ester derivatives of AQ in DMF:



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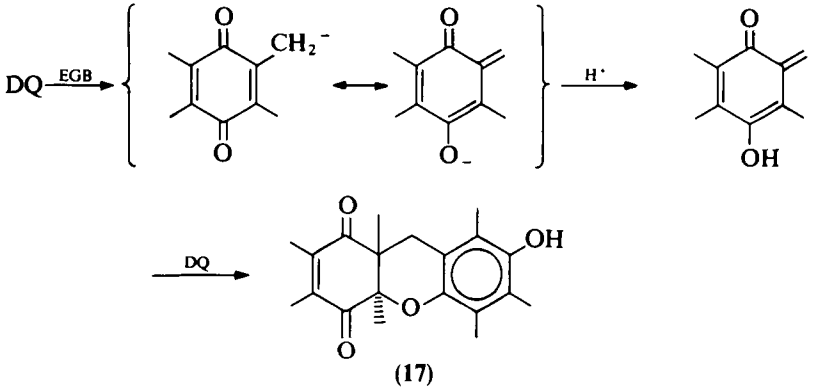
(16)

The reduction process was postulated to proceed via the quinone methide, **16**, shown in equation 11. A similar process has been found to occur for the reduction of the anthracycline drug, daunomycin, when it is reduced to the quinone dianion in DMF[115, 153]. Elimination of a sugar residue gives a quinone methide intermediate which was characterized by spectroelectrochemistry. Quite similar pathways were suggested by Plambeck and coworkers for the reduction of daunomycin in pH 7.1 phosphate buffers[154, 155]; this is discussed in Section IV.C.

The mechanism and stereochemistry of the reductive alkylation of AQ and acenaphthenequinone in DMF/NBu_4I has been examined[156]. Misra and Yadav also reported the reductive alkylation of AQ[157]. Reductive silylation of quinones takes place in the presence of *t*-butyldimethylsilyl chloride[158]. The synthesis of a diquinone bridged by a $-CH_2CH_2-$ group and its reductive cyclization via an internal radical coupling reaction has been reported[67]. In an interesting study, Rieke and coworkers[159] studied the electrocatalytic dimerization of duroquinone in DMF/NBu_4ClO_4 leading to the cyclyzed dimeric product, compound 17. Since this process (equation 12), can be initiated by the radical anion of duroquinone itself acting as an electrogenerated base (EGB), overall *n*-values less than 0.1 electron per duroquinone were observed.

The anthraquinone dianion will initiate styrene polymerization[160].

On the anodic side, oxidation of 1,4-dimethoxybenzene in wet acetonitrile leads to diquinones via radical cation coupling reactions and elimination of MeOH[65]. Good yields have been obtained for the electrosyntheses of vitamin K_3 by four-electron oxidation of a partially saturated precursor in 9:1 acetonitrile/*t*-butyl alcohol/$LiClO_4$[161] and for tetrafluorobenzoquinone and perfluorohydrocarbons in trifluoroacetic acid/trifluoroacetic anhydride media[162]. Anodic pyridination of several hydroquinones in pyridine–water has been reported[163], in agreement with previous work[164].



(12)

(17)

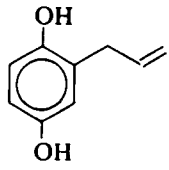
IV. ELECTROCHEMISTRY IN AQUEOUS SOLUTIONS

A. Electrochemistry at Solid Electrodes

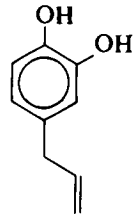
1. Adsorbed Q–QH_2 layers

While there have been several significant contributions to our understanding of electrochemical kinetics of quinone couples at solid electrodes in recent years, the monumental contributions of Hubbard and coworkers dominate the literature of the 1975–1986 period. Using the sophisticated high-vacuum techniques of surface science, the simple methodology of thin-layer electrochemistry and penetrating insight into the nature of electrode reactions, Hubbard's group has revealed the atomic and molecular nature of electrode processes at new levels of detail. Quinone/hydroquinone couples have figured predominantly in this work, to an extent that it is difficult to review Hubbard's contributions in this area in reasonable space. Fortunately, Hubbard has reviewed his work in part[165, 166], but his research is on-going, making an up-to-date survey difficult at this time.

In an important 1973 paper[167], Lane and Hubbard first pointed out that adsorbed hydroquinones and catechols oxidize irreversibly at platinum in 1 M $HClO_4$, while the quinone couple in solution remains reversible at the surface covered with the adsorbed layer. Compounds **18** and **19** were among the molecules studied by Lane and Hubbard



(18)



(19)

with the expectation that adsorption would take place via the unsaturated sidearm and that surface orientation effects could be seen in the electrochemical response. They were on the right track as remarkable surface orientation effects are found for edge-on vs. flat configurations of the quinonoid and aromatic rings (see below). The ideas of Lane and

Hubbard also presage the great activity of the last decade on chemically modified electrodes.

The simple thin-layer electrochemical technique for measurement of adsorption of Q/QH_2 and related species from aqueous solutions (typically 1 M strong acid or acidic buffers) has been described by Soriaga and Hubbard[168]. A polished polycrystalline Pt(111)–Pt(100) electrode, cleaned between runs by electrochemical cycling in $HClO_4$, was employed in a thin-layer cell of ca. 4×10^{-6} litre volume. Thin-layer voltammograms of the initial filling of the cell show a symmetrical cyclic voltammogram for the Q/QH_2 couple in solution at potentials negative of a massive irreversible oxidation of the adsorbed layer (Figure 3). When the potential range is restricted to leave the adsorbed layer intact, subsequent fillings of the thin-layer cell give rise to markedly increased peak heights and areas for the reversible Q/QH_2 wave. This occurs because the bulk concentration of the hydroquinone is not decreased in the second or subsequent fillings of the cell by adsorption on the already saturated surface. For the initial filling of the thin-layer cell, the amount of substrate left in solution is given by $VC = VC^0 - A\Gamma$, where V is the volume, C is the solution concentration, C^0 is the initial concentration, A is the electrode area, and Γ is the surface coverage (mol cm^{-2}). The charge under the reversible wave is given by equation 13,

$$Q_1 - Q_b = nF(VC^0 - A\Gamma) \tag{13}$$

and upon repeating the scan after refilling the cell, by equation 14:

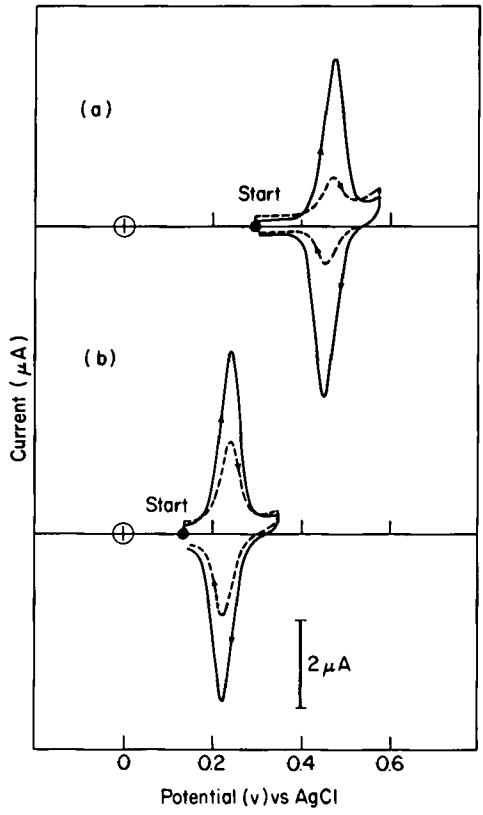
$$Q - Q_b = nFVC^0 \tag{14}$$

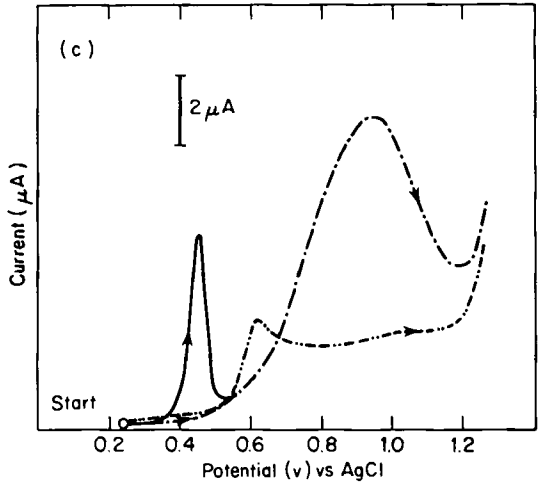
In these equations Q_1 is the measured charge after the initial filling of the cell, Q is the charge after subsequent fillings, and Q_b is the background charge. Only slightly more refined applications of Faraday's law to this thin-layer coulometry experiment allow variation of Q_b and Q upon successive fillings of the cell to be taken into account[169, 170]. Solving equations 13 and 14 for Γ gives $\Gamma = (Q - Q_1)/nFA$. In terms of area per molecule (σ in A^2) this translates into $10^{16}/N_A\Gamma$, where N_A is Avogadro's number. Surface cleanliness is favoured in thin-layer cells by the large surface to volume ratios that can be achieved, and in the hands of Hubbard and coworkers, a high degree of absolute accuracy in surface electroanalysis has been realized.

Initial application of the technique to 40 quinone or hydroquinone species present in solution at the 10^{-4} M concentration level revealed that most were adsorbed in a flat orientation on the platinum surface[168]. For example, hydroquinone was found to have a surface coverage of 51.6 ± 1.4 A^2, in good agreement with calculations for a flat orientation based on molecular models using covalent and van der Waals radii of Pauling. (Benzoquinone gave the same value, 52.7 ± 1.4 A^2; it is likely that BQH_2 adsorbs on the platinum surface in the quinone form via an oxidative process[171].) Accordingly, the flat (η^6), edgewise (η^2 bonding to the 2,3 bond), and endwise (η^1 bonding to the oxygen) orientations have calculated coverages, respectively, of 53.8, 28.6 and 21.8 A^2. Optical monitoring of the QH_2 absorbance in a long optical path length thin-layer spectroelectrochemical cell gives the same result[172].

As stated by Soriaga and Hubbard, the orientation of an adsorbed molecule is potentially a function of the molecular structure of the adsorbate, electrolyte, solute concentration, solvent, electrode potential, temperature, pH, electrode material, surface structure, co-absorbates and perhaps other factors. These thin-layer measurements confirm, for example, the above expectations for compounds **18** and **19** which have surface coverages significantly less than the values calculated for η^6 orientations. Other deviations from flat orientations were observed for alkyl-substituted ring systems where tilted η^2 orientations were suggested as possibilities[168, 173].

The existence of different orientations of the adsorbed molecules gives rise to 'packing density plateaus' in the adsorption isotherms that correspond to specific orien-


(a)
Start
(b)
Start
2 μA
Current (μA)
0
0.2
0.4
0.6
Potential (v) vs AgCl


(c)
2 μA
Start
Current (μA)
0.2
0.4
0.6
0.8
1.0
1.2
Potential (v) vs AgCl

tations[169, 171]. For example, BQH_2 undergoes a transition from the flat to the edgewise orientation between 1×10^{-4} and 3×10^{-4} M. Chirality was found to influence the absorbate orientation in the case of L-DOPA (L-3-(3,4-dihydroxyphenyl)alanine) and a racemic mixture of D,L-DOPA. At concentrations where the edgewise orientation predominates, the pure enantiomer packs more densely than the racemic mixture[174]. Surface coverage isotherms depicting this behavior for the adsorption of 26 Q or QH_2 molecules on platinum are shown in Figure 4.

The temperature dependence of the surface coverages reveals additional features of the molecular surface[175]. For Q/QH_2 species with unsubstituted rings that tend to absorb in the flat configuration, the transitions become sharper at low temperature (e.g. 5 °C), and at higher temperatures additional surface rearrangements are suggested by the isotherms. For molecules that are attached to the platinum surface by a functional group other than a benzene ring (e.g. 2,5-dihydroxythiophenol or 2,3-dihydroxypyridine), the packing densities tend to be independent of temperature.

The ability to determine the molecular orientation of the adsorbed quinone couples allowed Hubbard to make a fascinating observation. The massive irreversible oxidation of the adsorbed layers is dependent on the surface orientation[176]. For flat configurations, essentially complete oxidation of the aromatic rings takes place in strong acid media yielding *n*-values up to more than 40 (!) electrons per molecule in some cases. Oxidation of the edgewise orientation requires fewer electrons, but the oxidation is still a multi-electron process. As a result, there is a distinct and striking correlation between the *n*-values and the surface coverages in the isotherms. The *n*-values for the oxidation of the edgewise orientation (e.g. for oxidation of adsorbed NQH_2) are strongly temperature dependent[177]. Kinetic barriers to reorientation of adsorbed layers from the flat to the edgewise orientation have been noted[165].

The latter observation is one of the reasons advanced for the fact that these effects have not been noted in previous studies of the electro-oxidation of aromatic compounds. Common practice is to immerse the electrode under study in a blank solution, and increase the concentration of adsorbate by successive addition of aliquots of a standard solution. This procedure can trap the surface in the Pt–η^6 adsorption configuration. The thin-layer cell area/volume ratio advantage mentioned above is another significant feature of the Hubbard methodology. Adsorbed impurities can influence the packing densities in subtle ways and obscure the transitions between flat, edgewise and other orientations. As emphasized by Hubbard and coworkers[170], this is a fundamental error in the technique of hydrogen codeposition that many have used to measure adsorption isotherms on solid electrodes. Another feature of the Hubbard approach is that relatively smooth electrode surfaces are used. For surface roughness factors above ca. 5, the concentration-dependent packing factor transition for adsorbed BQH_2 disappears, presumably due to suppression of the vertical adsorption mode[178]. This explains why these effects are not observed by other techniques, e.g. radiotracer methods, where platinized platinum electrodes are used.

The effect of the platinum electrode potential on surface coverage has also been studied[179]. The surface coverage shows little variation with potential in the double-layer region, but decreases considerably at positive potentials where coadsorption of oxygen can take place and at more negative potentials where hydrogen adsorbs. Once an adsorbed

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FIGURE 3. Thin-layer current–potential curves for (A) hydroquinone, (B) durohydroquinone and (C) hydroquinone at a polycrystalline platinum electrode: (– – –) first filling; (——) presaturated surface; (·—·—) presaturated surface rinsed to remove dissolved reactant; (– –·– –) clean surface. The solutions contained initially 0.15 mM reactant and 1 M $HClO_4$ (thin-layer volume, V, 4.08 μl; platinum electrode area, A, 1.18 cm^2; rate of potential sweep, r, 2.00 $mV\,s^{-1}$; solution temperature, T, 296 ± 1 K). *Reprinted with permission from Soriaga and Hubbard*, J. Am. Chem. Soc., **104**, *2735(1982)*

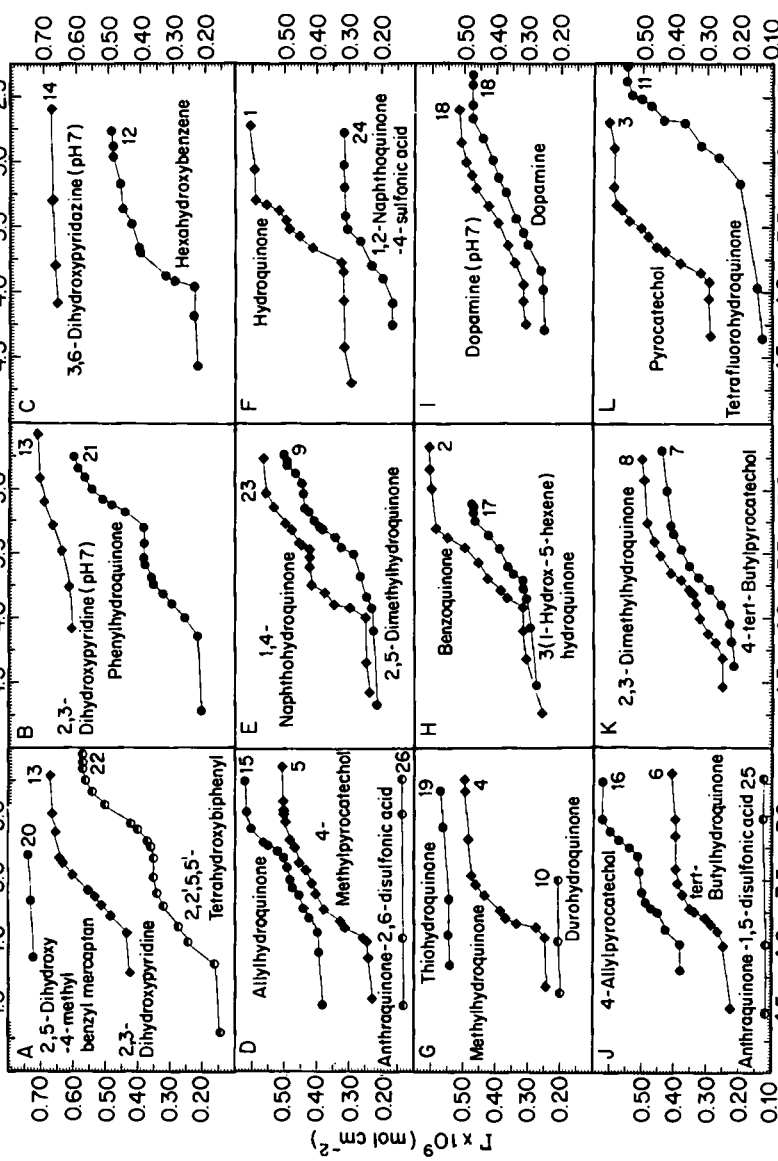


FIGURE 4. Surface coverages, expressed as Γ (mol cm^{-2}), as a function of solute concentration for the adsorption of 26 quinonoid compounds on atomically smooth platinum electrodes from 1 M $HClO_4$[171]. *Reproduced by permission of Elsevier Science Publishers from Soriaga* et al., J. Electroanal. Chem., **142**, *317 (1982)*

layer is formed, the coverage is relatively insensitive to the electrode potential within the range where faradaic processes do not occur.

The Q/QH_2 adsorption is markedly dependent on the presence of halide ions[180-182]. Treatment of the platinum electrodes with 5×10^{-4} M NaI, for example, totally prevented the adsorption of BQH_2. Treatment with 2×10^{-3} M NaBr severely attenuated the η^6 adsorption at low BQH_2 concentrations, but not the η^2 edgewise adsorption at higher concentration. Chloride ions had only a moderate influence on the adsorption isotherms. Other electrolytes such as $H\bar{C}lO_4$, $NaClO_4$, $CsClO_4$, H_2SO_4, H_3PO_4, $NaPF_6$, or NaF had little effect on packing density, oxidation *n*-values, or orientation. Other examples of these phenomena have occasionally been reported; for example, adsorbed BQH_2 is displaced from gold electrodes at pH 10.5 by sulfite ions[183].

Exchange and insertion reactions in coadsorbate layers have been examined recently by Hubbard and coworkers[184,185] in a very pretty fashion. For NQH_2 and 2,2',5,5'-tetrahydroxybiphenyl, for example, which oxidize (in the non-adsorbed form) at well separated potentials, it is possible to measure the competitive coverage of both adsorbates by the thin-layer technique[185]. Ordering effects are seen in the adsorbed layers which are attributed to hydrogen-bonding interactions between adsorbates. Small mole fractions of one component, e.g. Ar' in equations 15 and 16 below, were shown to introduce a significant degree of disorder in the adsorbed layer. For electrodes pretreated with BQH_2 (or with NQH_2), the surface reactions described in equations 15 and 16 were documented[184].

$$\eta^6\text{–Ar} + \text{Ar}'_{aq} \xrightarrow{C^o > 1\ \text{mM}} \eta^2\text{–Ar} + \eta^2\text{–Ar}' \tag{15}$$

$$\eta^2\text{–Ar} + \text{Ar}'_{aq} \xrightarrow{C^o > 1\ \text{mM}} \eta^2\text{–Ar} + \eta^2\text{–Ar}' + \text{Ar}_{aq} \tag{16}$$

The extent of molecular detail obtained with these simple experiments is indeed impressive.

Adsorption of quinones on other electrodes such as graphite from aqueous solutions has been known for some time[186-188]. Symmetrical, well behaved surface waves were obtained for the NQ, 9,10-phenanthrenequinone and 9,10-anthraquinone-2-sulfonate/hydroquinone couples adsorbed on the basal plane of pyrolytic graphite[186]. All three adsorbed quinones yielded voltammetric surface waves indicative of non-ideal, destabilizing interactions. Of the three, NQ, which was adsorbed at the highest coverage corresponding to the edgewise orientation based on the data of Soriaga and Hubbard[168], exhibited the most ideal behavior. Finally, the adsorption of 9,10-phenanthrenequinone and oxoapomorphine on carbon paste electrodes has been examined with a view toward analytical applications[189]. Baldwin has also reported the cyclic and differential pulse voltammetry of surface adsorbed adriamycin on carbon paste at pH 4.5[190,191]; sensitivity for determination of this drug in urine samples was 10^{-8} M, with a linear concentration range of 10^{-5} to 10^{-7} M for the latter technique.

2. *Electrode kinetic studies*

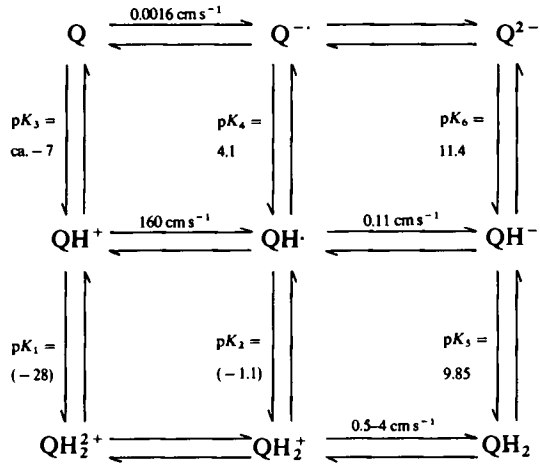
The kinetics of simple Q/QH_2 couples at solid electrodes is a difficult problem and many questions remain open in this area. Clearly, adsorption of the quinone species, electrolyte components and possible impurities in solution must be taken into account. In addition, the protonation and disproportionation reactions embodied in the square scheme cannot be ignored. Significant observations on this problem have been made by several groups in recent years. These should be put in context of previous work, which is briefly reviewed in Volume I of this series[1].

As is well known, experimentalists in electrode kinetics must deal with the difficulty of adsorption of impurities that might alter the rate of the reactions[192]. A particularly dramatic example of the effect of surface adsorbed layers on the rate of Q/QH_2 couples at Pt comes again from the laboratory of Hubbard and coworkers[193]. The BQ, NQ, DQ and *t*-butyl-*p*-benzoquinone couples were examined at pH 4 where a minimum exists in the exchange rate of the BQ/BQH_2 couple. This pH range is just below the transition from the HeHe to the eHeH mechanism in the classical study of Vetter[78]. (This notation specifies the sequence in which protons and electrons are transferred in the reduction of Q to QH_2.) For this system addition of CN^- ion retards the rate of the quinone couples to total irreversibility as measured by the anodic to cathodic peak potential separation in the thin-layer cyclic voltammograms. For sulfonated BQ/BQH_2 couple, the indication is that not only does the rate decrease, but that the rate-determining step changes and the mechanism becomes eeHH[194]. Furthermore, the BQ/BQH_2 rate at pH 4 can be enhanced to near reversibility by the presence of adsorbed iodine. As emphasized by Hubbard and colleagues, these results show that the kinetics can be manipulated at will by the addition or removal of surface adsorbed components.

More interestingly, with the above thin-layer electrochemical methodology of Hubbard to control the surface layer structure available, new questions can be addressed that should give further insight into the Q/QH_2 kinetics. For example, significantly different rates are observed for the BQ/BQH_2 couple at pyridine-coated platinum electrodes when pyridine is adsorbed via the nitrogen (Pt–η^1 bonding) or via a C(4)–C(5) ring bond (Pt–η^2 bonding). The peak potential separations are 151 mV and 68 mV, respectively, under the same experimental conditions[193].

Others have observed the effect of adsorbed species on the kinetics of the BQ/BQH_2 couple in recent years using more classical techniques. Schmid and Holmes in a careful study found that the apparent rate constant was decreased exponentially with surface coverage of benzo[*f*]quinoline at low coverages[195]. The kinetics at oxygen covered rhodium electrodes has been reported[196], where the rate was found to be faster at the unblocked electrodes. Sulfite has been found to inhibit BQH_2 oxidation on gold at pH 8.1[197]. In some cases rate enhancements have been reported: Lacaze and coworkers[198] made the interesting observation that a specific polymer film, poly(2-hydroxymethyl-1,4-phenylene) oxide, coated on a platinum electrode increased the rate of BQ/BQH_2 to reversibility in $HClO_4$ solutions. Underpotential deposition of Bi, Tl and Pb on platinum was also found to improve the reversibility of this system[199]; however, deposition of Tl on silver single crystals had no effect on the BQ/BQH_2 electrochemistry[200].

Laviron has developed theoretical treatments of electrode kinetics that take into account fast protonation steps coupled to one- and two-electron processes in the context of the square scheme (Scheme 1). In an important paper[10], he has rationalized several puzzling aspects of the literature by means of theory which assumes that the coupled proton transfer reactions are at equilibrium. In this view, breaks in the Tafel slopes in Vetter's experimental results at low pH on the cathodic segment and at high pH on the anodic segment are due, respectively, to rate control by the second and the first electron transfer steps. In the square scheme reproduced, the apparent electron transfer rate constants that Laviron cites, and the pK_a values of the protonated species, are indicated. (The value of -28 for the pK_a of QH_2^{2+} is estimated from the data of Hammerich and Parker[146].) It is significant that this treatment predicts the minimum in the rate of the BQ/BQH_2 couple that is observed in the region of pH 4. The view that the protonation steps are fast for Q/QH_2 couples is supported by other studies, e.g. that of Albery and coworkers[201] discussed below. In passing it can be mentioned that the Tafel plots for the methylbenzoquinone couple[202] are nearly identical to those for BQ/BQH_2 in the pH 0–3.14 range; accordingly, they are also consistent with Laviron's analysis. Also, very recently Laviron's theoretical treatment has been nicely used to sort out the mechanistic details of several catechol/quinone couples at carbon electrodes[203].



SCHEME 1

The extremely large rate constant given for the $QH^+/QH^{\cdot}$ couple, 160 cm s^{-1}, deserves comment. It is the correspondingly low value for the charge transfer resistance in this arm of the square scheme that allows the mechanism to follow the HeHe pathway at low pH. Whether or not rate constants of this magnitude are physically meaningful is uncertain. On the other hand, the value of 0.0016 cm s^{-1} for the apparent rate constant of the $Q/Q^{-\cdot}$ couple is not too far out of line with the values reported in non-aqueous solvents (see Section III.A). This is particularly true if one considers the results of Rüssel and Jaenicke[23, 27, 87] on the solvent and electrolyte dependence of k_1^0 *and* the picture of the Pt/solution interface that emerges from Hubbard's work. As realized by Laviron[10, 204], in aqueous buffers, electron transfer must occur through a compact adsorbed layer of quinone, which should decrease the observed rate constant. This unification of the literature is a satisfying aspect of Laviron's contribution.

As is often the case, however, the situation may be even more complex. In a more recent paper[205], theory has been developed that considers the three direct disproportionation reactions in the square scheme and the eight 'cross' disproportionation reactions, e.g. equation 17.

$$QH^{\cdot} + QH_2^{+\cdot} \rightleftharpoons QH^+ + QH_2 \tag{17}$$

As has been realized for some time, the second electron transfer step in ECE mechanisms often occurs via a solution redox reaction in the diffusion layer. Laviron's analysis[205], for example, indicates that at low pH (< -1), the HeHe pathway actually takes place via equation 17 above. Around pH 5, equation 18 takes place in the diffusion layer; and at higher pH,

$$QH^{\cdot} + Q^{-\cdot} \rightleftharpoons QH^- + Q \tag{18}$$

disproportionation of $Q^{-\cdot}$ is indicated. The important point here is that the overall rate is determined by a complex function of the pK_as, the individual apparent rate constants and the concentration ratios. In principle since quinone redox chemistry in solution may involve direct hydride transfer[206, 207], additional complexities may be operative.

Others have postulated rate-determining electron transfer steps between adsorbed states of quinone species coupled to equilibrium protonation reactions[188, 208, 209].

In an ingenious experiment, the electrochemistry of photochemically generated QH· radicals was studied at an optically transparent Pt electrode[201]. Owing to their favourable solubility, disulfonated anthraquinone couples were employed in the pH range 0–6. In the presence of both the quinone and hydroquinone forms, neutral QH· radicals could be generated in the diffusion layer by the sequence of equations 19 and 20,

$$AQ + h\nu \rightarrow AQ^* \tag{19}$$

$$AQ^* + AQH_2 \rightarrow 2\,AQH^{\cdot} \tag{20}$$

and their current–potential curves measured. Plots of E^* vs. pH, where E^* is the zero photocurrent potential, exhibited breaks corresponding to the transition between eHHe and eHeH mechanisms at pH = 3.2 and 3.9 for 9,10-anthraquinone-2,6-disulfonate and -1,5-disulfonate, respectively. At pH 1.12, where the mechanism is eHHe, a reasonable value of 0.0015 cm s^{-1} was obtained for $k_1^?$. In an analogous experiment, the pH dependence of the photocurrent at a *p*-type GaP semiconductor indicated a pK_a-like transitions for BQ solutions at pH 5.5[210]. It was suggested that the initial step involves electron transfer from the conduction band of the photocathode and protonation to form BQH, followed by protonation and charge transfer by hole injection into the valence band, i.e. a HeHe or eHHe mechanism.

Coulostatic techniques have been applied to the 9,10-phenanthrenequinone couple adsorbed on graphite electrodes in 1 M $HClO_4$[188]. The analysis indicated that the rate-determining step is the electron transfer for the $QH^+/QH^{\cdot}$ couple, presumably in the adsorbed state, and that the proton transfers are fast. (It can be noted that the slow process may involve adsorption–desorption steps bracketing electron transfer to a solvated species.) On the other hand, for noradrenaline in 1 M H_2SO_4 at carbon paste and glassy carbon electrodes the rate-determining step in the two-electron oxidation was reported to be the deprotonation of the radical cation[211].

B. Electrochemsitry of Modified Electrodes

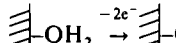
1. Covalently bonded surface quinones

In the last decade, modified electrodes have been the focus of attention in many electrochemical laboratories. The authoritative reviews of Royce W. Murray[212, 213] should be consulted for details. Quinone couples have occupied an important position in the efforts to modify electrode surfaces with electroactive groups owing to their well behaved and characterized electrochemical response, and to their possible chemical specificity. The promises of the proponents of modified electrodes, which have often involved combination of these properties, have been realized in part in several examples involving surface quinone functionalities.

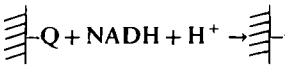
The distinction between this section and the above (IV.A.1) on adsorbed Q/QH_2 layers is obviously diffuse. Qualitatively, one can imagine increasing levels of interaction with the electrode surface as follows: physical adsorption < chemical adsorption < covalent bonding. The latter includes the situation where the quinone functionality is part of the surface structure of the electrode itself, which can be the case for ordinary carbon materials. The electrochemical responses for the above modes of confinement at the electrode/solution interface can be quite similar.

Tse and Kuwana[214] demonstrated electrocatalysis of dihydronicotinamide adenosine diphosphate (NADH) oxidation at pyrolytic graphite electrodes modified by covalently

attached *ortho*-quinones (3,4-dihydroxybenzylamine or dopamine), via equations 21 and 22.



$$\equiv\!\!\equiv\!\!-QH_2 \xrightarrow{-2e^-} \equiv\!\!\equiv\!\!-Q + 2H^+ \tag{21}$$



$$\equiv\!\!\equiv\!\!-Q + NADH + H^+ \rightarrow \equiv\!\!\equiv\!\!-QH_2 + NAD^+ \tag{22}$$

In this manner, oxidation of the NADH substrate takes place near the reversible potential of the Q/QH_2 couple, ca. 0.2 V more negative than the irreversible oxidation of NADH under the same conditions (pH 7, phosphate buffer, 0.05 V s^{-1} sweep rate) at a bare electrode. This paper is an important conceptual and experimental advance that drew on previous work of Kuwana's group, and that of others. Previously, they had reported that surface quinone functions could electrocatalyze ascorbate oxidation[215] and the above catechol derivatives were found to enter into a homogeneous electrocatalytic cycle with NADH. The next step was therefore to attach the catechol directly to the electrode surface.

Tse and Kuwana[214] achieved electroactive surface coverages of the attached quinone of 0.13 nmol cm^{-2} (130 A^2 per site) by the following procedure. Radiofrequency plasma oxidation of the surface of a pyrolytic graphite electrode[216] produced surface carboxylic groups; this surface was then treated with the amine using dicyclohexylcarbodiimide as a coupling agent[217] to form $\equiv\!\!-C(O)NHCH_2QH_2$ surface groups. In later work[218], coupling to surface acid chloride groups has been exploited to attach 2-*N*-methylanthraquinone groups to glassy carbon surfaces at a slightly higher coverage.

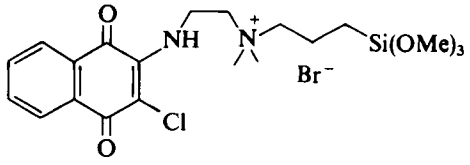
Other attempts to attach quinones to surfaces have been less successful[219, 220]. In one report[220] a possible orientation effect of the Lane and Hubbard type[167] was indicated. It must be mentioned that repeated cycling of the Tse and Kuwana electrodes leads to decreased electrocatalytic activity, presumably due to fouling by the products of the NADH oxidation, which limits their utility[221].

Other approaches to the construction of an electrocatalytic interface have been based on the above scheme. Graphite electrodes modified with a high surface coverage (ca. 20 A^2 per molecule) adsorbed layer of 4-[2-(2-naphthyl)vinyl]catechol exhibit catalytic activity for NADH oxidation[222], as do carbon paste electrodes containing dissolved *ortho*-quinones in the pasting material[223]. Electrodes modified with polymers containing electroactive pendant hydroquinone groups also show electrocatalysis of NADH oxidation in the manner of Tse and Kuwana[214]. It is difficult to evaluate the relative merits of these approaches, and the use of homogeneous couples, to electrocatalysis on the basis of the existing literature.

There is some indication that the behavior of certain redox couples at carbon electrodes is related to Q/QH_2 groups on the graphite surface. As mentioned above[215], the oxidation of ascorbic acid was illustrated using surface Q/QH_2 groups; hydrogen reduction of the carbon used to prepare carbon paste electrodes increases the irreversibility of the BQ/BQH_2 couple[225]; and glassy carbon modified with carbon black shows electrocatalysis for NADH oxidation, presumably via surface Q/QH_2 groups[226]. Very fast surface exchange rates have been recently reported for quinone groups on oxidized carbon electrodes[227]. In this study it was shown that the electrode kinetics of quinone and phenazine couples in solution were markedly influenced by the oxidation state of the carbon electrodes. It can be speculated that interactions of this type may be responsible for the differences between the electrochemistry of adsorbed quinone layers on graphite and platinum electrodes.

The presence of electroactive quinone functions on carbon electrodes has been known for some time[228-231]. The paper of Hallum and Drushel, for example, accounts for the polarography of carbon black suspensions in DMF by means of reduction of surface quinone functions to $Q^{-\cdot}$ and QH^{-}[229]. Some of the initial experiments on the chemical modification of glassy carbon and graphite electrodes were conceived with hydroquinone-like surface groups in mind[232], and 1,2-naphthoquinone groups were invoked to explain the ESCA spectra and electrochemistry of pyrolytic graphite[216]. The paper of Schreurs and coworkers[227] is especially interesting. They detected surface quinone functions using phase-sensitive AC voltammetry and were able to identify 1,2-naphthoquinone and 9,10-phenanthenequinone surface groups. Poorly defined waves for $Q/QH^{-}/QH_2$ couples were seen at -0.05 V, -0.16 V and -0.5 V vs SCE in pH 7 phosphate buffer. In a convincing experiment the quinone waves were replaced by phenazine surface waves after the electrodes were refluxed in alcohol solutions of *o*-phenylenediamine. This result has been confirmed by Kuwana and his colleagues who also presented ESCA evidence that the quinone groups represent only a minor fraction of the surface oxygen functionality[233,234].

Another example of electrocatalysis with quinone modified electrodes is that of Wrighton and coworkers on the production of hydrogen peroxide in aqueous solutions[235,236]. These workers attached a naphthoquinone group to tungsten, platinum, and *p*-WS_2 electrodes by means of the derivative **20** possessing a surface active $Si(OMe)_3$ group. The resulting electrodes showed dramatic enhancement of the two-electron



(20)

reduction wave of O_2 at the potential of the attached quinone couple, indicating that a scheme analogous to that of Tse and Kuwana[214] was operative. The solution reaction of oxygen with electrogenerated hydroquinone had been studied earlier[237]. Greater than 90% coulomb efficiency was reported for the generation of H_2O_2 at the quinone-modified electrode. Using the *p*-WS_2 photocathode modified with the surface quinone, O_2 reduction was seen at potentials 0.6 V more positive than the formal potential of the O_2/H_2O_2 couple upon illumination with visible light. In a novel extension of this approach, silica and alumina particles were derivatized using **20**, and oxygen reduction carried out via electrogeneration of mediators at more conventional working electrodes[236]. This approach retains the advantages of electrocatalysis using homogeneous mediators and the ability to separate the particles containing the catalytic sites from the electrolysis solution. Up to 0.1 M H_2O_2 in 0.1 M KCl was produced in this system.

The catalytic reduction of oxygen by AQ/AQH_2 couples has also been reported at *p*-type semiconductor electrodes, *p*-Si and *p*-WSe by Keita and Nadjo[238], who found high efficiencies for both the photochemical and electrochemical reduction, the latter at glassy carbon electrodes. On the other hand, low efficiency was reported for the formation of H_2O_2 at *p*-Si photocathode using 2-*t*-butyl-9,10-anthraquinone in acetonitrile[237].

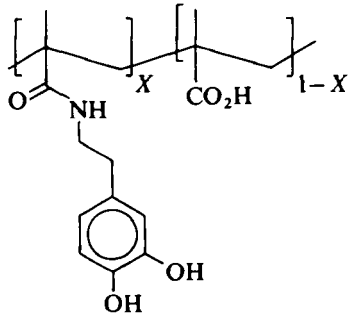
Others have seen electrocatalysis for the two-electron reduction of oxygen to hydrogen peroxide at quinone modified electrodes. These include the crystalline chloranil or 2,6-diamino-9,10-anthraquinone electrodes studied by Roullier and colleagues[239] and several of the quinone polymer modified electrodes described in the next section.

2. *Polymeric quinone films*

One strategy for the fabrication of chemically specific interfaces is to coat electrode surfaces with thin films of redox polymers containing electroactive groups, either pendant to, or as part of the polymer backbone. The electrochemistry of several polymeric quinones has been studied in this manner in the last few years[240-244]. Electrocatalytic activity has been exhibited in some cases, e.g. for the reduction of O_2 at electrodes modified by a polymer containing pendant AQ groups attached to an ethenimine backbone[242], reduction of O_2 in H_2SO_4 at a poly(NQ) surface[245] and the NADH oxidation at surfaces containing dopamine groups attached to poly(methyl methacryloylate) mentioned above[224].

In solution, electroactive polymers can exhibit electrochemistry characteristic of the redox groups incorporated into the polymer structure. In the limiting case of negligible interaction between the groups, reversible voltammetric responses are observed for polymers containing repeating units derived from reversible monomer couples[246], although diffusion currents will be attenuated on account of the smaller diffusion coefficients of macromolecular species. This is the situation for anthraquinone-substituted polymers of known molecular weight in DMF solution[247]. For this system, log(peak current) was a linear function of the molecular weight in accord with the Mark–Houwink equation.

When electroactive polymers are coated on electrodes, however, charge transport through the polymer film may be controlled by electron hopping steps between redox sites, ion migration, polymer motions, or combinations of these phenomena. Accordingly, polymers containing reversible quinone functionalities may exhibit only limited electroactivity, or be entirely inactive when coated as a film on a substrate electrode. This is demonstrated by the catechol polymer of Degrand and Miller[224], a copolymer of methacrylic acid and methacrylamide with pendant catechol groups, **21** ($x = 0.41$), for which only a few equivalent monolayers are electroactive unless small mediator molecules are present that can penetrate the polymer network and shuttle electrons between redox sites[248,249]. The catalytic efficiency of these electrodes is dependent on electrode loading, increasing for thin films and then decreasing for thick films[224].



(21)

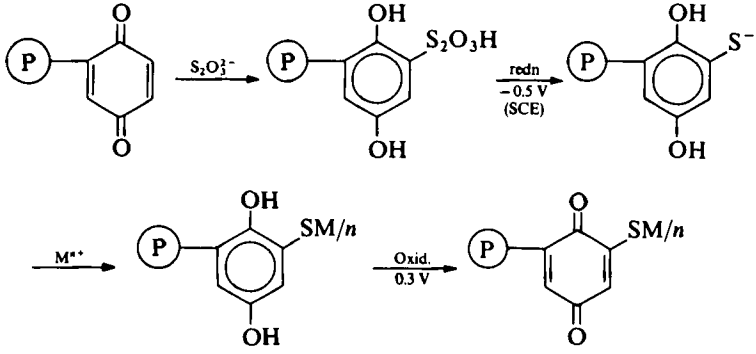
The need for a good solvent to impart polymer chain flexibility, and thereby facilitate charge transport, was emphasized by Degrand and Miller[241]. This has repeatedly been noted by researchers studying electroactive polymer quinone films[248,250,251]. Also, solution pH will dramatically alter the extent of electroactivity of quinone polymer films[241,250,252,253]. It is likely that these pH effects are due to the complex nature of the Q/QH_2 redox reactions that are required to transport charge through the films (see the

above discussion of Laviron's analysis[10, 205] of the BQ/BQH_2 kinetics in Section IV.A.2). In the related example of a tetracyanoquinodimethane polymer film[253], the pH dependence of the charge transport process was correlated with pK values of the reduced redox sites.

Substrate surface effects have been noted[245, 252, 254]. Roughening the surface or anodization can increase the charge capacity of adsorbed polymeric quinones[252] and greater electroactivity is sometimes seen on carbon substrates than on platinum[245].

DuBois and coworkers[245] have reported that oxidation of 5-hydroxy-1,4-naphthoquinone in MeOH/NaOH leads to insoluble electroactive poly(quinone) films that display good electrochemistry when transferred to other solutions. This is significant since *in situ* electropolymerization is a very attractive method for preparation of electroactive polymer films in their conducting forms, which has been widely exploited since Diaz and coworkers first reported the electrosynthesis of metallic-like polypyrrole films[255]. Importantly, the film obtained from 5-hydroxy-2-methyl-1,4-naphthoquinone is stable in H_2SO_4 and alkaline solutions[245].

Examples of chemical and electrochemical modification of polymer electrodes have appeared in recent years. Arai and coworkers[256] have described an elegant synthetic procedure, Scheme 2, for the conversion of a polymeric quinone surface film to a mercaptohydroquinone polymer. The resulting surface shows selectivity for metal ions and serves as a potentiometric sensor for Ag^+, Hg^{2+}, Cu^{2+}, Cd^{2+} and Pb^{2+} at the 10^{-3}–10^{-5} M level. Interestingly, the polymer film quinone couple remains electroactive at ca. 0.3 V vs. SCE after formation of the metal ion complexes. Polymer films of this type should find applications in electroanalysis following the ideas of Abruna[257].



SCHEME 2

3. *Electrochemistry at other modified electrodes*

BQH_2 oxidation in neutral solution has been carried out at Nafion polymer film electrodes loaded with $Ru(bipyridyl)_3^{2+}$ ions[258]. Decreased overpotentials for the oxidation of catechol derivatives were observed at glassy carbon electrodes containing micron size alumina particles on the surface[259]. The alumina particles probably function in part as getter materials for removal of surface contaminants. Catechol phosphate is oxidized under diffusion control at enzyme electrodes prepared by attaching alkaline phosphatase covalently to a carbon surface[260]. The cyanuric acid method of Bourdillon[261] was employed for the surface modification.

The reaction of BQH_2 at a AgX 'electrode'

$$2AgX + BQH_2 \rightarrow 2Ag + BQ + 2HX \quad (23)$$

consisting of a photographic film disk (equation 23), was monitored by the reduction of BQ at a ring in a ring–disk electrode assembly[262].

4. Composite electrodes

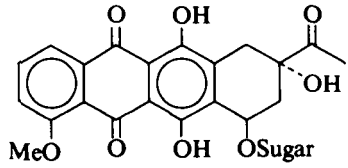
Several reports have appeared describing electrodes containing Q/QH_2 couples, pasted or bonded with conducting materials, and used as working electrodes in voltammetric or electrolysis experiments. Typical of these, which are termed 'composite electrodes' in this review, are the Alt electrodes[263–266]. These are constructed from quinone–graphite mixtures (ca. 1 : 1 wt ratio) pressed between graphite felt disks. In aqueous electrolyte solutions very large, and often quite sharp, voltammetric peaks are observed. Sizeable coulombic charges are measured indicating that a significant number of equivalent monolayers of quinone molecules are electrolyzed in a voltammetric sweep. Since insoluble quinone couples are generally employed, the electrolyzed layers remain intact upon electrochemical cycling. In some cases, double peaks are observed which have been attributed to the formation of quinhydrone, or possibly semiquinone, intermediates. These and related electrodes have usually been touted as positive electrodes for battery applications[266, 267].

Other quinone composite electrodes have been fabricated that exhibit similar behavior. These include electrodes containing various quinones and carbon black[267–270], 2,3-dichloro-5,6-dicyanobenzoquinone bonded with poly(styrene)[271], poly(aminoquinone) and graphite[272] and hydroquinone–phenol–formaldehyde resins mixed with acetylene black and Teflon and compacted on a Ni mesh[273]. The latter two electrodes could also be classified as polymer electrodes.

The above composite electrodes containing insoluble monomeric quinones are closely related to the crystal deposit electrodes studied by Laviron and coworkers[239, 274]. Similar voltammetric responses are observed, which are attributed to strong interactions between adsorbate molecules for the better defined crystalline electrodes. The voltammograms are characterized by marked hysteresis between the anodic and cathodic waves, which is independent of the sweep rate. It is suggested that the electrode process involves dissolution, electron transfer to the quinone presumably in some partially solvated state and then recrystallization[274].

C. Coupled Chemical Reactions

An interesting literature has developed concerning the electrochemistry of antitumor antibiotics (**22**) and related anthracycline derivatives. Usually mercury working electrodes are employed for these studies, and often pronounced adsorption effects are evident in the published voltammograms. At the dropping mercury electrode in pH 7.1 phosphate buffer,



(22)

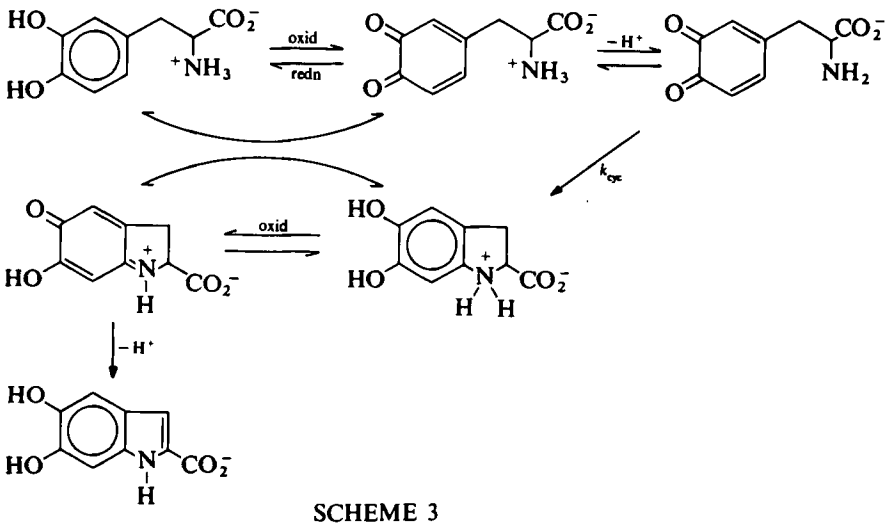
loss of the sugar residue occurs upon reduction to the hydroquinone form[154,155]. The mechanism of the glycoside elimination has been studied further under similar conditions by Malatesta and coworkers[275], who found that the reaction was under stereochemical control. Glycoside bonds that have small dihedral angles with respect to the π-orbitals of the AQ ring system undergo rapid cleavage. The mechanism of this follow-up reaction has also been studied in DMF[115,153], as mentioned in Section III.E.

The surface nature of adriamycin electrochemistry at mercury in acetate buffer has been examined by Kano and colleagues[276,277], who analyzed the cyclic voltammograms in terms of a surface disproportionation reaction of the semiquinone form. Extensive adsorption on the mercury surface was indicated, corresponding to a maximum coverage of ca. 150 A^2 per molecule ascribed to a flat configuration. The pH dependence of the surface wave permitted evaluation of the pK_as for the dissociation of a hydroxyl group for the adsorbed quinone, semiquinone and hydroquinone forms; the values obtained, respectively, were 8.53 ± 0.09, 6.93 ± 0.08 and 6.83 ± 0.09. Wave shape changes were noted when the electrode was set at potentials negative of the $E_{1/2}$ value, which may be related to the loss of the sugar residue.

Anthracycline drugs such as adriamycin bond strongly to DNA molecules[278]. This property and the surface electrochemical behavior of the drugs permit electrochemical DNA binding studies to be carried out by measuring the decrease of the quinone reduction wave in the presence of DNA[279,280].

Mitomycin B and C, heterocyclic quinone antibiotics containing an aziridine ring, have been studied in aqueous solution at 37.5°C. The opening of the aziridine ring in the reduced form to generate a new Q/QH_2 couple was followed by cyclic voltammetry[281,282]. The air oxidation of vitamin K_5, 4-amino-2-methyl-1-naphthol hydrochloride, to H_2O_2 and 2-methylnaphthoquinone has been studied in aqueous buffers by polarography[283]. Ubiquinone-10 solubilized in sodium dodecyl sulfate micelles gives diffusion controlled polarographic waves which permits an estimate of the radii of the micelles to be made[284].

Young and coworkers have published several papers on the intramolecular cyclization of electrogenerated *ortho*-quinones derived from dopamine and related molecules[285-287]. These catechol amines oxidize in aqueous acidic buffers at carbon paste electrodes via an ECC mechanism, where the second two-electron transfer takes place in the diffusion layer. Scheme 3, based on that proposed by Hawley and colleagues[288] in a pioneering paper,

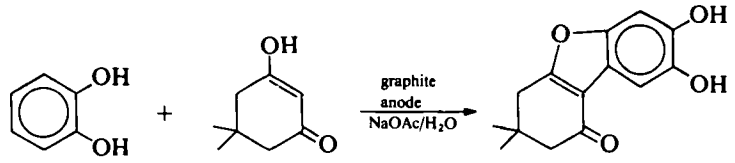


SCHEME 3

shows the pathway from DOPA to 5,6-dihydroxyindole[285]. Kinetic parameters of the cyclizations, which occur on the cyclic voltammetric time-scale, have been reported for several derivatives of DOPA[286, 287]. This intramolecular cyclization of dopaquinone has also been studied by Brun and Rosset[289] above pH 4 by voltammetric techniques. In $HClO_4$ media hydration of the *ortho*-quinones generated from DOPA, dopamine, adrenalin and pyrocatechol was observed. The reaction of the chloropromazine radical cation with several catechols, including dopamine, was studied using glancing angle incidence reflection techniques by Mayansky and McCreery[290]. The rate-determining step was found to be the initial electron transfer between the catechol and the radical cation.

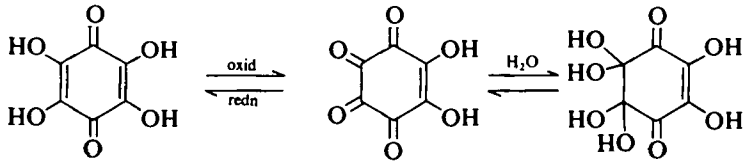
Electrochemically generated *ortho*-quinones will react with nucleophiles other than water purposely added to the electrolysis solution. Adams and his students[291] measured the rates of addition of various nucleophiles with the quinones derived from dopamine and 4-methylcatechol and discussed their relationship (or lack thereof) to metabolic pathways. Adams has previously reviewed the relevance of these electrochemical results to problems in pharmaceutical chemistry[292].

In some cases, e.g. the use of nucleophiles such as dimedone in equation 24[293], the electrode reactions can have synthetic utility. In the absence of nucleophiles, dimeric products can be formed in related electrode processes[294].



(24)

At pH 2 a two-electron, two-proton oxidation of tetrahydroxy-1,4-benzoquinone (equation 25), occurs on mercury electrodes to give rhodizonic acid, **23**, which exists as the dihydrate **24**[295]. At pH < 1, a four-electron reduction of rhodizonic acid is seen, which



(25)

(23) (24)

proceeds to hexahydroxybenzene[295]. Similar electrode reactions have been reported for 1,2,3,4-tetraoxonaphthalene[296].

Oxidation of BQH_2 in the presence of sulfite leads to the monosulfonated quinone in an ECE process[297]. For the 1,4-addition of thiols to the 3 position of 2-methyl-1,4-naphthoquinone in aqueous ethanolic buffers, good agreement was obtained between kinetic measurements using rotating disk and stopped-flow methods[298]. Berg and coworkers have continued their studies of β-hydroxyalkylaminobenzoquinone/quinol cyclization equilibria using classical Koutecky polarographic analysis and temperature-jump methods[299].

On platinum or silver cathodes, AQ is reduced to anthrone in concentrated H_2SO_4 with ca. 70% current efficiency[300].

V. PHOTOELECTROCHEMISTRY OF QUINONES

Quinone couples have often been employed in experimental schemes in which electromagnetic radiation is coupled to the flow of electrical current in electrochemical cells. For the sake of completeness several recent studies of this type will be mentioned here. However, photoelectrochemistry, which is a diverse area of increasing activity, will not be treated in any depth in this section. The reader will note that several examples of photoelectrochemical effects were discussed above when there was direct relevance to the conventional electrochemistry of quinones.

Quinones can function as electron acceptors, and hydroquinones as electron donors (or positive hole acceptors), in photochemical reactions where separation of charge occurs. One or both of these steps is generally involved when photocurrents are observed at semiconductor or dye modified electrodes in the classical manner of Tributsch and Gerischer[301]. The coupling of BQH_2 oxidation to the photon flux for ZnO–dye and ZnO–chlorophyll electrodes was demonstrated several years ago[302,303], and photochemical oxidation of BQH_2 has been exploited at chlorophyll monolayer SnO_2 electrodes[304]. Honda and coworkers have also shown the photoelectrochemical oxidation of BQH_2 at *n*-CdS(single crystal)/rhodamine B dye sensitized disk electrodes[305,306]. In these studies, the disk was illuminated from the backside and the quinone product was detected at a gold ring electrode. Polycrystalline TiO_2 photoanodes have been employed for the oxidation of BQH_2 and several other substrates with relatively high current efficiency[307].

The use of quinones as electron acceptors in conjunction with chlorophyll (Chl) modified electrodes has been a popular subject in part due to the relevance to photosynthesis where naturally occurring quinones function as acceptor molecules. Takahashi and colleagues have employed this strategy in several studies in which chlorophyll–quinone modified electrodes were prepared with water insoluble quinones that are miscible with chlorophyll[308–310]. Upon illumination of these electrodes, the following photoelectrochemical process can take place (equation 26–28)[310],

$$\mathrm{Chl} \xrightarrow{h\nu} \mathrm{Chl}^* \xrightarrow{Q} \mathrm{Chl}^+ + Q^{-\cdot} \tag{26}$$

$$n\mathrm{Chl}^+ + R \rightarrow n\,\mathrm{Chl} + Ox \tag{27}$$

$$Q^{-\cdot} \rightleftharpoons Q + e^- \tag{28}$$

where Ox and R are components of a redox couple present in solution. For different quinones, or different redox couples, these chlorophyll electrodes can also function as photocathodes[308], as was found earlier for an aqueous Pt(Chl)//quinhydrone(Pt) divided cell[311]. Related to these studies, are the pyranthrone electrodes of Ahuja and coworkers[312], for which both anodic and cathodic photocurrents were observed. An interesting application of these concepts is that of Janzen and Bolton[313] who constructed monolayer assemblies of chlorophyll-A and quinone acceptors sandwiched between Hg and Al electrodes. Upon illumination, electron ejection to the Al electrode took place.

Quinone reduction has been coupled to solvent oxidation, namely methanol conversion to formaldehyde, at illuminated rutile catalysts[314]. Quinone couples in non-aqueous solvents have been used extensively by Bard and coworkers to map the limits of the band gap in a variety of semiconductor materials[315–319].

A description has appeared of a rechargeable solar cell based on the uphill generation of 9,10-anthrahydroquinone-2,6-disulfonate driven by the oxidation of iodide at a semiconductor photoanode (*n*-WSe_2 or *n*-MoS_2) in an electrochemical cell[320,321]. For light of 632 nm wavelength, conversion efficiencies of ca. 10% were achieved. Coupling to the O_2 reduction to hydrogen peroxide was also shown in this study.

Several quinones have been used to scavenge photoemitted electrons from mercury electrodes in aqueous and non-aqueous solvents[322].

The known photochemistry of the excited state of AQ has been coupled to electrode reactions, e.g. in the work of Bobbitt and Willis, where increased selectivity for photosynthetic reactions is possible by the controlled-potential generation of the ground state precursor[323]. The photochemical oxidation of 2-propanol to acetone has long been known. Fujihira and colleagues[218,324] achieved photoassisted electrolysis of this process using glassy carbon electrodes modified with covalently attached anthraquinone groups. The quantum efficiency was low, however, presumably due to quenching of the excited state of AQ by the electrode. Studies in this area should be aided by the recently reported solution of the diffusion equation boundary value problem for the photogeneration of AQH_2 in a chronoamperometry mode[325].

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CHAPTER 13

Recent advances in the photochemistry of quinones

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I. INTRODUCTION

In recent years the photochemistry of quinones has been a subject of extensive investigations. As a result, a large number of papers have appeared describing novel aspects of quinone photochemistry. Our knowledge of the mechanism of photochemical reactions of quinones has expanded rapidly. Particularly, charge transfer or electron transfer interactions of photoexcited quinones with other substrates have been widely recognized as the important primary process in numerous photoreactions such as reduction, cycloaddition, substitution and decomposition. The advances in nanosecond and picosecond time-resolved spectroscopy and magnetic resonance techniques, particularly those of CIDEP and CIDNP, have enabled a much more systematic study to be undertaken and have led to a much more precise description of the reaction mechanism.

Because of the availability of excellent reviews on the photochemistry of quinones covering the literature prior to 1973[1-4], this chapter will focus mainly on the recent developments in the photochemistry of quinones. Recent developments are now summarized annually in *The Chemical Society Specialist Periodical Reports on Photochemistry*, volumes 1–16 (1968–1984)[5]. Additionally, two reviews appeared in 1974[6] and 1977[7], mainly dealing with voluminous contributions reported in the USSR.

Representative quinones are expressed by the abbreviations summarized below, and the abbreviations Q, $Q^{-\cdot}$, $QH^{\cdot}$ and QH_2 are used to indicate, respectively, the quinone, the semiquinone anion radical, the neutral semiquinone radical, and the hydroquinone.

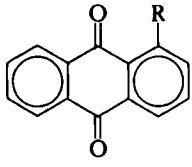
Quinone	Abbreviation
1,4-benzoquinone	BQ
tetramethyl-1,4-benzoquinone	DQ
tetrachloro-1,4-benzoquinone	CQ
1,4-naphthoquinone	NQ
2-methyl-1,4-naphthoquinone	MQ
9,10-anthraquinone	AQ
9,10-phenanthraquinone	PQ
plastoquinone-*n*	PLQ-*n*
9,10-anthraquinone-2-sulfonate	ASQ
9,10-anthraquinone-2,6-disulfonate	ADSQ

II. SPECTRA AND EXCITED STATES

Recent advances in the main features of the absorption and emission spectra of quinones in relation to their photochemistry are discussed in this section.

Experimental and theoretical studies concerning the electronic structure and absorption and emission spectra of quinones continue to appear[8-23]. These spectroscopic studies have shown that at least two excited (n, π^*) states of B_{1g} and A_u symmetry lie within 250–300 cm^{-1} for both the singlet and triplet excited state of BQ. The pure electronic $S_0 \rightarrow T_1$ transition of NQ single crystals has been investigated in electric and magnetic fields[24]. Highly resolved phosphorescence spectra of AQ and AQ-d_8 in crystals and solution were reported[25-28]. Photoelectron spectra of BQ and NQ and their derivatives are extensively studied[29-32]. Highly structured fluorescence and fluorescence excitation spectra of **1** (R = NH_2) and **4** (R^1 = R^2 = OH) are measured in low-temperature Shpol'skii matrices[33,34].

In contrast to the lowest (n, π^*) triplet state of AQ and 2-chloroanthraquinone (**2**, R = Cl), 1-halogenoanthraquinones (**1**, R = F, Cl, Br) have a lowest triplet state of (π, π^*) character with short lifetimes[35]. The short lifetimes of the lowest triplet state and the small phosphorescence quantum yield of **1** (R = halogen) indicate the presence of a rapid radiationless decay process through the interaction of the carbonyl group with the 1-halogen atom[35]. The relative contributions of (n, π^*) character in the lowest triplet states of polyhalogenoanthraquinones are assessed on the basis of the magnitudes of their quenching rate constants by benzene molecule[36]. A new absorption with a rise time of 35 ps and decay time of 700 ps in the flash photolysis of **5** (R^1 = R^2 = Cl) is observed in toluene and is ascribed to the $T_2 \rightarrow T_n$ transition[37].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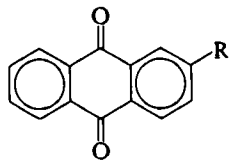
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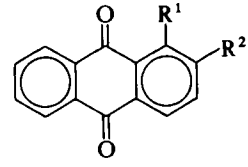
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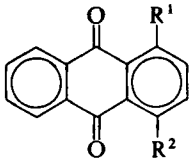
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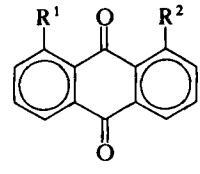
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In general, introduction of electron-donating substituents such as amino and hydroxy groups to AQ changes the electronic nature of the lowest excited state to the intramolecular CT state[38,39]. The photochemistry of amino- and hydroxy-substituted anthraquinone derivatives has been extensively studied because of their structural relationship to vat dyes, which can promote phototendering of textiles. Quantum yields for intersystem crossing (ϕ_{isc}) of amino-substituted anthraquinones are very low (Table 1). The decrease in ϕ_{isc} on substitution of amino and hydroxy groups must result from the change in the nature of the excited state involved and also from the increased singlet–triplet energy gap, which for amino-substituted anthraquinones ranges from 5000 cm^{-1} to 7000 cm^{-1}, compared with a value of 1600 cm^{-1} for AQ itself[45]. The quantum yields for

TABLE 1. Quantum yields for intersystem crossing of quinones

Quinone	Solvent	ϕ_{isc}	Ref.
AQ	Benzene	0.90	40
MQ	Water	0.66	41
DQ	Cyclohexane	1.0	42
	Ethanol	1.0	42
	Water	1.0	42
CQ[a]	DCE[b]	1.0	43
ASQ	Water	>0.9	44
ADSQ	Water	1.0	44
4 ($R^1 = R^2 = NH_2$)	Benzene	0.015	45
4 ($R^1 = NH_2$, R^2 = NHMe)	Benzene	0.02	45
4 ($R^1 = R^2$ = NHMe)	Benzene	0.015	45
4 ($R^1 = NH_2$, R^2 = NHPh)	Benzene	0.025	45
4 ($R^1 = NH_2$, R^2 = OH)	Benzene	0.01	45

[a] The rate of intersystem crossing from ^{1}(CQ)* to ^{3}(CQ)* is 3.0×10^{10} s^{-1} (Ref. 46).
[b] 1,2-Dichloroethane.

photodecomposition of these amino-substituted anthraquinones, particularly for oxidation of the amino group and photodealkylation of the alkylamino group, have been determined to be 10^{-4} or less[47,48], which suggests that the photodecomposition may be initiated through the triplet state. Thus one may attribute the light-stability of amino and hydroxy-anthraquinones largely to rapid deactivation within the singlet manifold[49b].

Fluorescence lifetimes, quantum yields, and solvent shifts of amino and hydroxy-anthraquinones were studied by several groups (Table 2). The wavelength of the fluorescence maximum is red-shifted in polar solvents, consistent with the notion of the

TABLE 2. Fluorescence parameters of anthraquinones

Anthraquinone	Solvent	ϕ_f[a]	λ_{max} (nm)[b]	τ_f (ns)[c]	Ref.
1-Amino	DMC[d]	0.24			50
	n-Hexane	0.07	530		49a
	Benzene	0.022	548		51
	Benzene	0.058		1.75	52
	Ethyl acetate	0.008	567		51
	Furan	0.07	558		49a
	2-Propanol	0.003	590		49a
	Ethanol	0.0082		0.46	52
	Ethanol-d_1	0.0498		3.03	52
	Acetonitrile	0.034	600	0.7	53
	Acetonitrile	0.01		0.66	52
2-Amino	Benzene	0.24			54
	Benzene	0.08	548		51
	Benzene	0.21		6.5	52
	n-Hexane	None	None		49a
	Ethyl acetate	0.024	563		51
	Furan	0.05	532		49a
	2-Propanol	$< 10^{-5}$	None		49a
	Ethanol	0.00059		0.054	52
	Ethanol-d_1	0.0014		0.109	52
	Acetonitrile	0.008		0.85	52
	Acetonitrile	0.019	620	0.7	53

TABLE 2. (*Continued.*)

Anthraquinone	Solvent	ϕ_f[a]	λ_{max} (nm)[b]	τ_f (ns)[c]	Ref.
1-Piperidino	*n*-Hexane	$< 10^{-5}$	None		49a
2-Piperidino	Cyclohexane	0.19			39b
	n-Hexane	0.27	510, 545		49a
	Benzene	0.085		7.7	52
	Furan	0.04	615		49a
	2-Propanol	10^{-5}	630		49a
	Ethanol	0.00012		0.040	52
	Ethanol-d_1	0.0006		0.068	52
	Acetonitrile	0.0012		0.3	52
1-Methylamino	*n*-Hexane	0.003	560		49a
	Benzene	0.0076		0.33	52
	Furan	0.04	615		49a
	2-Propanol	10^{-4}	612		49a
	Ethanol	0.0014		0.094	52
	Acetonitrile	0.0016		0.19	52
N-1-Chloroacetylamino	*n*-Hexane	$< 10^{-5}$	None		55
	Ethanol	0.0013	509		55
	2-Propanol	0.0011	515		55
1-Acetylamino	*n*-Hexane	10^{-5}	500		49a
	Benzene	0.017		0.41	52
	Ethyl acetate	0.0068	515		55
	Furan	0.02	505		49a
	2-Propanol	0.004	505		49a
	Ethanol	0.0041		0.066	52
	Acetonitrile	0.0082		0.32	52
1-Benzoylamino	*n*-Hexane	10^{-5}	505		49a
	Furan	0.005	510		49a
	2-Propanol	10^{-5}	528		49a
1,4-Diamino	Benzene	10^{-5}	612, 635		51
	n-Hexane	10^{-5}	610, 630		49a
	Furan	10^{-5}	612, 645		51
	Ethyl acetate	10^{-5}	614, 640		51
	2-Propanol	$< 10^{-5}$	None		51
	Acetonitrile	0.03	660	0.6	53
1,5-Diamino	Benzene	0.013	550		51
	Ethyl acetate	0.007	555		51
	2-Propanol	0.0047	575		51
1,2,3,4-Tetraamino	Benzene	0.004	672		51
	Ethyl acetate	0.0024	672		51
	2-Propanol	0.002	684		51
1-Amino-2-chloro	*n*-Hexane	0.021	540		55
	Toluene	0.018	550		55
	Ethyl acetate	0.016	563		55
	2-Propanol	0.0084	583		55
1-Amino-3-chloro	*n*-Hexane	0.017	528		55
	Toluene	0.015	540		55
	Ethanol	0.014	563		55
	2-Propanol	0.0077	585		55
2-Amino-3-chloro	Toluene	0.085	512		55
	Ethanol	0.018	545		55
	2-Propanol	0.0022	558		55

TABLE 2. (*Continued*)

Anthraquinone	Solvent	ϕ_f[a]	λ_{max} (nm)[b]	τ_f (ns)[c]	Ref.
1-Amino-2-carboxy	Ether	0.0024	562		55
	Ethyl acetate	0.015	572		55
	2-Propanol	0.004	590		55
1-Amino-3-carboxy	Ether	0.0078	558		55
	Ethanol	0.01	565		55
	2-Propanol	0.0035	585		55
2-Amino-3-carboxy	Ether	0.06	520		55
	Ethanol	0.05	535		55
	2-Propanol	0.0014	573		55
1-Anilino		None			49a
1-*N*-Methylanilino		None			49a
1,5-Dipiperidino		None			49a
1,4-Bis(methylamino)	*n*-Hexane	10^{-5}	665, 670		49a
	Furan	10^{-5}	670, 710		49a
	2-Propanol	$< 10^{-5}$	None		49a
2-Dimethylamino	*n*-Hexane	0.2	495, 535		49a
	Furan	0.04	590		49a
	2-Propanol	10^{-5}	610		49a
1-Amino-4-hydroxy	Acetonitrile	0.041	630	1.0	53
1-Amino-4-hydroxy-2-Methoxy	Acetonitrile	0.12	616	1.9	53
1,8-Diamino	Acetonitrile	0.032	596	0.8	53
1-Amino-2,4-dibromo	Acetonitrile	0.003	594		53
1,5-Bis-*N*-ethylanilino	Acetonitrile	0.013	630		53
1-Hydroxy	Acetonitrile	0.013	608	0.6	53
1,2-Dihydroxy	Acetonitrile	0.004	660		53
1,2-Dihydroxy-3-$CH_2N(COOH)_2$	Acetonitrile	0.003	660		53
1,4-Dihydroxy	Acetonitrile	0.126	575	2.8	53
1,8-Dihydroxy	Acetonitrile	0.017	585	0.8	53
1,2,5,8-Tetrahydroxy	Acetonitrile	0.025	590		53
1,2-Diethoxy	Acetonitrile	0.009	646		53
1-Methylamino-4-bromo	Benzene	0.0032		0.19	52
	Ethanol	0.00087		0.053	52
	Acetonitrile	0.0011		0.19	52
2-Bis(dibutylamino)	Benzene	0.15		9.8	52
	Ethanol	0.00021		0.076	52
	Acetonitrile	0.0053		0.68	52

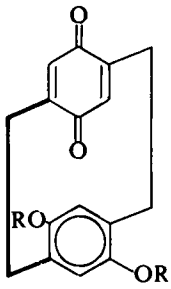
[a] Quantum yields for fluorescence.
[b] Fluorescence maxima.
[c] Fluorscence lifetimes.
[d] 1,4-Dimethylcyclohexane.

first singlet CT state. Of these, 2 (R = NH_2) is considerably much more sensitive to solvent polarity than the others. Amines quench the fluorescence by an electron transfer mechanism. Alcohols also quench the fluorescence but by a different mechanism involving

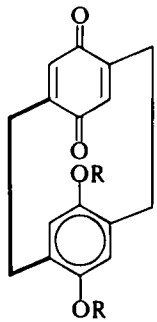
hydrogen bonding[39]. The almost no difference between the fluorescence lifetimes of **3** ($R^1 = R^2 = OH$) (0.25 ns) and **3** ($R^1 = R^2 = OEt$) (0.30 ns) is interpreted in terms of a radiationless decay by intramolecular electron transfer from the substituent to the carbonyl group rather than as being due to hydrogen bonding[56]. However, solvent isotope effects on the radiationless decay rate constant, $k_d(EtOH)/k_d(EtOD)$, 9.0 for **1** ($R = NH_2$), 2.1 for **2** ($R = NH_2$), and 1.7 for **2** (R = piperidino) are regarded as evidence for a radiationless deactivation of S_1 (CT) through intra- and intermolecular hydrogen bonding[52]. These fluorescence data as well as the intersystem crossing yields and the phosphorescence data are often used in the interpretation of light fastness properties of anthraquinone dyes in both polyester and nylon textiles.

Extensive pulse radiolysis studies have been used to characterize the spectra and the formation and decay kinetics of the radicals and their triplet states of quinones[57-61].

Charge transfer (CT) bands due to π complexes between quinones and electron-donating molecules are often observed[4, 43, 62, 63]. The comparison of the intramolecular CT absorptions of **6** and **7** shows very large differences; whereas a strong CT absorption is observed for **7** in the 350–600 nm region ($\lambda_{max} = 495$ nm, $\varepsilon = 1600$), **6** shows only a weak absorption ($\lambda_{max} = 515$ nm, $\varepsilon = 170$)[64, 65]. The differences in absorption due to the



(6, R = H)
(10, R = Me)



(7, R = H)
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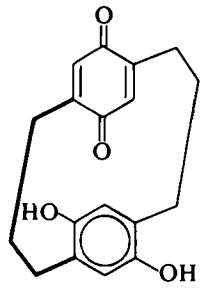

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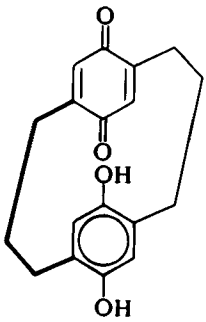

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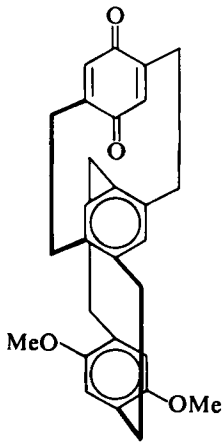

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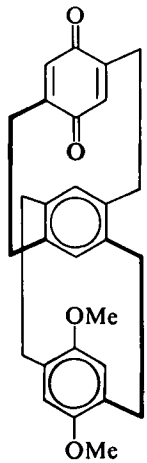
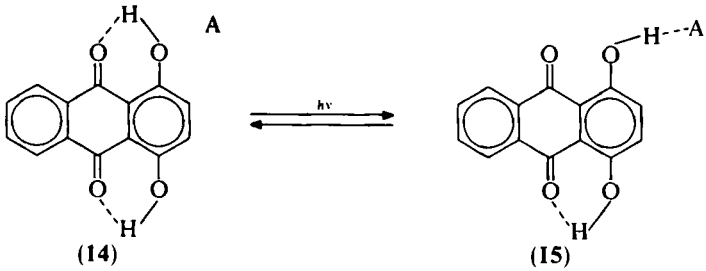


(13)

different donor–acceptor orientations are much more pronounced for the different connectivity pair **8**/**9**; whereas a strong CT absorption is observed for **9** (λ_{max} = 462 nm, ε = 3210), **8** shows only a weak absorption shoulder around 500 nm with ε = 105[66]. Similar orientation-dependent CT absorptions are also observed for **10** and **11**[65,66]. Intramolecular CT absorptions, which seem to be indirectly transmitted through the intercalated aromatic π system, are observed in triple-layered [2,2]paracyclophanes **12** and **13**; however, the orientation dependence of the CT absorptions is almost lost in these compounds: **12** (λ_{max} = 415 nm, ε = 2010), **13** (λ_{max} = 437 nm, ε = 2270)[66]. Quantum mechanical calculations indicate that the intramolecular CT interaction arises only from through-space interaction[67,68].

In relation to photochemical hole burning (PHB) phenomena, the photochemistry of **14** was studied in *n*-alkane (non-hydrogen bonding), polymethylmethacrylate (PMMA) (proton accepting), and ethanol and polyvinyl alcohol (PVA) (strong hydrogen bonding) matrices at low temperature. The PHB observation is moderate in PMMA and prominent in PVA matrices but only scarce in the *n*-alkane matrix[69]. Formation of a rotamer **15** in which the intramolecular hydrogen bond is broken and an intermolecular hydrogen bond is newly formed with a hydrogen bond accepting matrix molecule (A) is suggested for this PHB process[69] (equation 1).



(14) (15) (1)

TABLE 3. Triplet lifetimes (τ_t) of quinones

Quinone	Solvent	τ(s)	Ref.
BQ	Ethanol	< 0.01	70
	Ethanol/water (1:1)	< 0.01	70
	Water	< 0.01	70
	Water	0.5	71
TQ[a]	Ethanol	< 0.01	70
	Ethanol/water (1:1)	< 0.01	70
	Water	0.3	70
	Water	0.37	71
2,5-DMBQ[b]	Ethanol	< 0.01	70
	Ethanol/water (1:1)	0.03	70
	Water	0.32	70
	Water	0.87	71
2,3-DMBQ[c]	Ethanol	0.045	70
	Ethanol/water (1:1)	0.045	70
	Ethanol/benzene (1:1)	0.1	70
	Water	1.2	70
	Water	5.9	71

TABLE 3. (*Contd.*)

Quinone	Solvent	τ(s)	Ref.
TMBQ[d]	Ethanol	0.45	70
	Ethanol/water (1:1)	2.4	70
	Water	1.9	70
DQ	Benzene	25	72
	Benzene	10	70
	Benzene[k]	0.5	70
	Cyclohexane	21	42b
	Cyclohexane	8.3	70
	Cyclohexane[k]	0.25	70
	Liquid paraffin	29	70
	Ethanol	15	42b
	Ethanol	9	70
	Ethanol[k]	0.3	70
	Ethanol/water (1:1)	7.7	70
	Water	2.9	70
	Water	5.9	71
	Water	5.9	42b
	2-Propanol[k]	0.3	73
	2-Propanol	45	74
CQ	Cyclohexane	2.0	77
	DCE[l]	5.6	75
	Ethanol	1.2	77
	Butyronitrile	6.25	76
AQ	Benzene	0.11	44
	Benzene	0.125	61
	Benzene	0.13	36
TFAQ[e]	Benzene	0.20	36
PFAQ[f]	Benzene	0.17	36
TCAQ[g]	Benzene	3.0	36
ADSQ	Water	< 1	44
ASQ	Water	< 0.1	61
ASQ	Water	0.1	78
ASQ	Acetonitrile	12.5	78
MQ	Water	1.5	41
2-PAQ[h]	Benzene	20	61
1-AAQ[i]	Benzene	5	61
2-AAQ[j]	Benzene	5	61

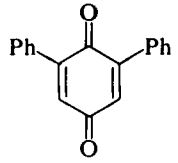
[a] TQ, 2-methyl-1,4-benzoquinone; [b] 2,5-DMBQ, 2,5-dimethyl-1,4-benzoquinone; [c] 2,3-DMBQ, 2,3-dimethyl-1,4-benzoquinone; [d] TMBQ, trimethyl-1,4-benzoquinone; [e] TFAQ, 1,2,3,4-tetrafluoro-9,10-anthraquinone; [f] PFAQ, perfluoro-9,10-anthraquinone; [g] TCAQ, 1,2,3,4-tetrachloro-9,10-anthraquinone; [h] 2-PAQ, 2-piperidino-9,10-anthraquinone; [i] 1-AAQ, 1-amino-9,10-anthraquinone; [j] 2-AAQ, 2-amino-9,10-anthraquinone; [k] air saturated; [l] DCE, 1,2-dichloroethane.

III. PHOTOREDUCTION

A. Electron Transfer

The excited states of quinones decay by numerous reactive and non-reactive pathways such as emission (fluorescence and phosphorescence), energy transfer, charge or electron transfer, hydrogen (H) abstraction, bimolecular dimerization and cycloaddition, unimolecular rearrangement, fragmentation and many others. Of these, photoreduction,

which can proceed via either electron transfer or H abstraction, is the major mode of photochemical reaction of quinones. When the triplet state of the quinone lies below the triplet state of the molecule being quenched, electronic energy transfer has been shown to occur in many cases. However, if charge transfer or electron transfer reaction is energetically feasible, such reaction is often favored over energy transfer. For instance, quenching of triplet *N*-methylindole by AQ, for which the quenching rate is $8 \times 10^9\ M^{-1}\ s^{-1}$ in benzene solution, does not give $^3(AQ)^*$ but produces triplet exciplex with greater charge transfer nature even though its energy is about 7.2 kcal mol^{-1} below that of triplet *N*-methylindole[79]. Photoreduction of quinones can occur by two mechanisms. One is the two-step mechanism of electron transfer followed by proton transfer via the ion-pair state. Another is the direct H-atom transfer in a non-relaxed encounter complex. Since most of the triplet quinones are strong electron and hydrogen acceptors, it is not easy to distinguish which mechanism is predominant in their H-abstraction reactions. The coexistence of the ion-pair formation and the rapid H-atom transfer in the non-relaxed encounter complexes has recently been claimed by nanosecond and picosecond absorption spectroscopy for the systems of 2,6-diphenylbenzoquinone (**16**)/diphenylamine[80] and CQ/durene[43], respectively. Since photoexcited quinones have



(16)

strong oxidizing power, their bimolecular quenching processes are, in general, more or less charge transfer in nature. Many evidences indicate that the quenching efficiency is determined by a charge transfer process from an electron donor to photoexcited quinone which will induce, or not, a chemical reaction, depending on the medium. The charge transfer interaction of excited quinone with electron donor produces an exciplex whose reactivity is sometimes quite different from that of the parent quinone in its excited state. For example, AQ/ammonia triplet exciplex abstracts a primary hydrogen from *t*-butanol or acetonitrile to give a cross adduct with much more efficiency and selectivity compared with AQ itself (see Section III.B)[81, 82].

The energy of the charge transfer or electron transfer state can be estimated by the excited energy of the quinone and electrochemical redox potentials[83]. Here, extensive data on the family are available[84, 85].

Reported results of the quenching rate constants of photoexcited quinones by electron donors and oxygen are summarized in Table 4.

TABLE 4. Quenching rate constants of photoexcited quinones by electron donors and oxygen

Quinone	Quencher	Solvent	$k_q(M^{-1}s^{-1}) \times 10^{-9}$	Ref.
$^3(DQ)^*$	$Fe(CN)_6^{4-}$	Water[a]	2.6×10^9	86
	Fe^{2+}	Water[a]	1.3	86
	Aniline	Water[a]	3	86

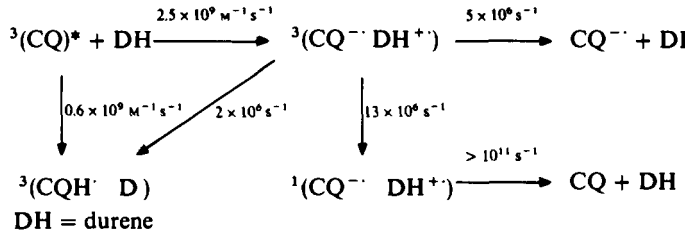
Table 4. (*Continued*)

Quinone	Quencher	Solvent	$k_q(M^{-1}s^{-1}) \times 10^{-9}$	Ref.
	TMB[b]	Water[a]	3.3	86
	CO_3^{2-}	Water[a]	7.3×10^{-2}	86
	Ethanol	Water[a]	2.8×10^{-5}	86
	Acetone	Acetone	5×10^{-5}	86
	Cl^-	Methanol[c]	1×10^{-2}	87
	Br^-	Methanol[c]	4	87
	I^-	Methanol[c]	9	87
	BA[d]	Methanol[c]	8×10^{-4}	87
	OH^-	Methanol[e]	1.5	87
	TPA[f]	Benzene	0.18	42a
	TPA	MeCN	10	42a
	DEA[g]	MeCN	9.4	42a
	TEA[h]	MeCN	6.0	42a
	TEA	Cyclohexane	2.0	42a
	DEA	Cyclohexane	8	42a
	c-ST[i]	Water[k]	1.5	88
	t-ST[j]	Water[k]	1.6	88
$^3(DQH^+)^*$	Cl^-	Methanol[l]	1	87
	BA	Methanol[l]	2.7×10^{-2}	87
$^3(CQ)^*$	Naphthalene	BN[m]	7	76
	AN[n]	DCE[o]	3.1×10^{-5}	89
	MMA[p]	DCE	5.1×10^{-3}	89
	MMA	MeCN	6.7×10^{-3}	89
$^3(16)^*$	TMPD[q]	Toluene	18	80a
	TMPD	DBP[r]	1.1	80a
	DPA	Toluene	7.9	80a
	DPA	DBP	5.1	80a
	TPA	Toluene	5.0	80a
	TPA	DBP	0.33	80a
$^3(AQ)^*$	NMI[s]	Benzene	10.7	79
$^3(MQ)^*$	MQ	Water	4.5	41
	Thymine	Water	2.7	41
	Uracil	Water	3.0	41
	MU[t]	Water	3.2	41
$^3(AQS)$	Cl^-	Water	0.5	78, 90
	N_3^-	Water	3.1	78, 90
	NO_2^-	Water	3.2	78, 90
	Br^-	Water	3.8	78, 90
	NSC^-	Water	3.9	78, 90
	I^-	Water	4.2	78, 90
$^3(BQ)^*$	O_2	Benzene	2.4	71
$^3(MQ)^*$	O_2	Water	1.2	41
$^3(DQ)^*$	O_2	Toluene	2.1	412
$^3(AQ)^*$	O_2	Benzene	1.5	61
^{3}(2-PAQ[u])*	O_2	Benzene	1.9	61

[a] Ethanol/water = 1:2; [b] TMB, 1,3,5-trimethoxybenzene; [c] pH = 7; [d] BA, benzyl alcohol; [e] pH = 10–12; [f] TPA, triphenylamine; [g] DEA, diethylamine; [h] TEA, triethylamine; [i] *c*-ST, *cis*-stilbene; [j] *t*-ST, *trans*-stilbene; [k] in the presence of sodium dodecylsulfate; [l] pH = −2; [m] BN, butyronitrile; [n] AN, acrylonitrile; [o] DCE, 1,2-dichloroethane; [p] MMA, methyl methacrylate; [q] TMPD, tetramethylphenylenediamine; [r] DBP, dibutyl phthalate; [s] NMI, *N*-methylindole; [t] MU, 6-methyluracil; [u] 2-PAQ, 2-piperidino-9,10-anthraquinone.

1. Aromatic hydrocarbons

The laser photolysis at the charge transfer band of CQ and durene in 1,2-dichloroethane does not give any transient absorption over the time range from picosecond to several microseconds. These findings suggest that the singlet excited state of the charge transfer complex decays so rapidly through internal conversion that its detection is not possible even by means of the picosecond laser photolysis. Excitation of uncomplexed CQ at 347 nm results in the formation of $^3(CQ)^*$, which is rapidly quenched by durene. Interestingly, the H-atom transfer leading to production of $CQH^{\cdot}$ is shown to proceed through two distinct mechanisms; a sequential electron and proton transfer and a more rapid direct H-atom transfer competing with the electron transfer process (Scheme 1)[43].



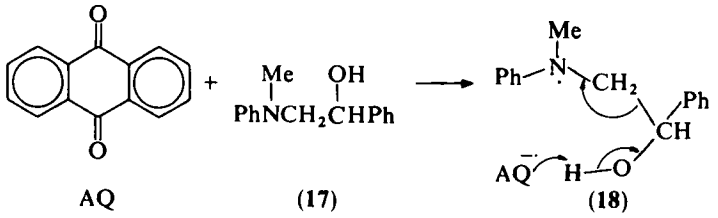
SCHEME 1

Excitation of CQ in butyronitrile at room temperature leads to a rapid production of $^3(CQ)^*$ which decays predominantly to $CQH^{\cdot}$ with $k_d = 1.6 \times 10^5\ M^{-1} s^{-1}$. Observation of a photo-induced current suggests simultaneous production of $CQ^{-\cdot}$, formed by electron transfer quenching of $^3(CQ)^*$ by the medium. Added naphthalene (NA) quenches $^3(CQ)^*$ with $k_q = 7.0 \times 10^9\ M^{-1} s^{-1}$; the cation radical of naphthalene is unambiguously identified as product of the electron transfer process[76]. This electron transfer process follows a Weller-type[83] quenching mechanism; the yields and lifetime of exciplex composed of CQ and NA are reduced in polar solvents as a result of ionic dissociation of the CQ/NA pair. The same CQ/NA pair has been investigated by picosecond spectroscopy in order to elucidate a more detailed mechanism of the electron transfer[46]. The intermediate non-relaxed exciplex, $^3(CQ^-NA^+)^{**}$, may be produced by interaction between the molecular components of the encounter complex, $^3(CQ \cdots NQ)$. This non-relaxed complex then may minimize its total energy by changing the relative positions of CQ and NA and also by solvent reorientations. Depending upon such factors as solvent polarity and relative oxidation and reduction potentials of CQ and NA, this non-relaxed intermediate may either form an exciplex, $^3(CQ^-, NA^+)^*$, or solvent-shared exciplex, $^3(CQ^- \cdots NA^+)^*$. However, the existence of a discrete encounter complex, unrelaxed exciplex, and/or exciplex is not revealed even in the picosecond time region[46].

Undoubtedly, most photochemical reactions of quinones proceed via the triplet state, since the intersystem crossing of the excited singlet of quinone is a rapid process. On the other hand, anthraquinones bearing amino and hydroxy groups have the lowest singlet (CT) state whose lifetimes are sometimes long enough for chemical reactions as well as fluorescence (Table 2). Electron transfer to these states occurs from electron-donating molecules whose oxidation potential lies between 0.35 V (*N*, *N*-diphenylethylenediamine) and 1.76 V (anisole)[56, 91]. Usually the quenching of the excited singlet quinone forms no detectable separate ions, contrary to the ion pair arising from the triplet excited state[56, 91].

2. *Amines*

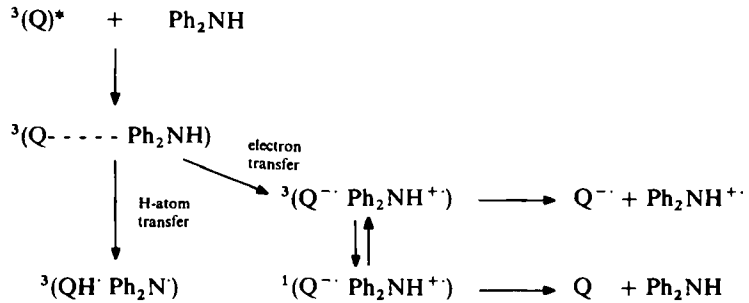
Electron transfer is the generally observed mode of reaction between a photoexcited quinone and an amine in polar solvents, while exciplex formation is frequently detected and precedes the photoreduction of quinones by amines in non-polar solvents. In either case, the rate constant for the quenching is close to the diffusion-controlled limit and subsequent proton transfer from the amine cation radical to $Q^{-\cdot}$ results in the formation of $QH^{\cdot}$. Numerous reactions of this type have been reported, and studied by a variety of methods including laser flash photolysis[42, 72, 80, 86, 87, 92, 93], CIDNP[80b, 94, 95], CIDEP[73,96], steady-state irradiation[97] and photoconductivity measurements[86, 98]. Electron transfer-induced fragmentation of the aminoalcohol **17** to benzaldehyde and *N,N*-dimethylaniline is effectively sensitized by AQ[99] (equation 2).



AQ (17) (18)

$$\xrightarrow{\text{Me}} \text{PhNCH}_2\cdot + \text{PhCHO} + \text{AQH}\cdot \qquad (2)$$

In the presence of triphenylamine (TPA), no products from $^3(DQ)^*$ photoreduction are detected by nanosecond laser flash photolysis in benzene. However, $^3(DQ)^*$ decays with a rate constant having a much higher value than in the absence of TPA. This is ascribed to the exciplex deactivation[42a]. Quenching of the triplet of **16** by TPA in non-polar solvents also occurs with the formation of triplet exciplex. In this case, however, characteristic absorption due to triplet exciplex, which possesses similar maxima to that of TPA^+ but substantially differs from the spectrum of $TPA^{\cdot+}$ has been successfully detected[80]. Quenching of the **16** triplet with the secondary aromatic amine, diphenylamine (DPA), in low-polar solvents yields, besides the short-lived triplet exciplex, a long-lived neutral radical $Ph_2N\cdot$. Interestingly, the triplet exciplex decay is not accompanied by $Ph_2N\cdot$ radical formation, indicating that proton transfer does not occur in the triplet ion pair (Scheme 2),



SCHEME 2

contrary to the normally accepted mechanism of photoreduction of quinones by amines[80a]. This seemingly important finding, analogous to the mechanism of CQ/durene system, may provide a direct experimental proof that H-atom transfer competes with electron transfer and both occur from the non-relaxed triplet encounter complex[80]. In a series of works by the same authors, activation energies higher than 7 kcal mol^{-1} for H shift in the non-relaxed encounter complex have been estimated[80b,100]. However, prototropic equilibrium prior to H-atom shift was recently considered by the same authors[93].

3. *Olefins*

Photo-induced addition of electron-rich diarylethylenes to 2-bromo-3-methoxy-1,4-naphthoquinone apparently proceeds via a charge transfer or an electron transfer interaction (see Section IV.B). *E–Z* isomerizations of 1-phenylpropene and stilbene are brought about by the electron transfer interaction with photoexcited quinones[88,101]. In connection with the photosensitized polymerization by CQ, the electron transfer reaction from a variety of vinyl monomers to excited triplet state of CQ has been studied by laser flash photolysis[75,102,103]. Cation radical of photogenerated *N*-vinylcarbazole undergoes cyclodimerization in polar solvents while cationic polymerization takes place in non-polar solvents without any induction period. ^{3}(CQ)* abstracts an electron even from electron-deficient vinyl monomers such as acrylonitrile and methyl methacrylate[44].

4. *Strained hydrocarbons*

p-Chloranil (CQ) has a lowest triplet (π,π^*) excited state as well as an exceedingly low reduction potential, rendering an electron transfer reaction strongly exothermic toward a wide range of substrates. By using CQ as an efficient electron acceptor, the structures and reactivities of short-lived radical cations are extensively studied by the photo-CIDNP method[94]. The method is very simple but provides valuable information about the electronic structures of the cation radicals derived from cyclopropanes[104a–c], norbornadiene[104a], quadricyclane[104a], methanobridged cyclophane[105a], bicyclo[1.1.0]butane[105b,c], methylenecyclopropane[106], 3,3′-dimethylbicyclopropenyl[104i], hexamethyl Dewar benzene[104g], pentacyclic caged cyclobutane[104f], methylenebicyclo[2.2.0]hexene[104h], dicyclopentadiene[107] and fulvene derivatives[108]. These radical ion-pair induced CIDNP effects are derived from competitive hyperfine coupling dependent in-cage electron return and separation by diffusion in triplet radical ion pair (scheme 3)[94]. According to the generally accepted radical pair theory of

$$^3(CQ)^* + D \longrightarrow {}^3\overline{CQ^{-\cdot}\ D^{+\cdot}} \qquad (3)$$

$$^3\overline{CQ^{-\cdot}\ D^{+\cdot}} \rightleftharpoons {}^1\overline{CQ^{-\cdot}\ D^{+\cdot}} \qquad (4)$$

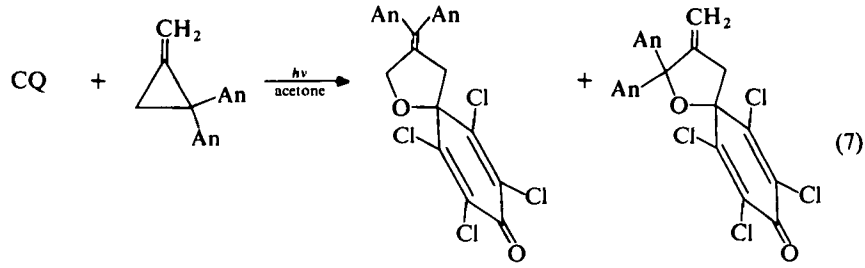
$$^1\overline{CQ^{-\cdot}\ D^{+\cdot}} \longrightarrow CQ + D\ddagger \qquad (5)$$

$$^3\overline{CQ^{-\cdot}\ D^{+\cdot}} \longrightarrow CQ^{-\cdot} + D^{+\cdot} \qquad (6)$$

D = strained hydrocarbon

SCHEME 3

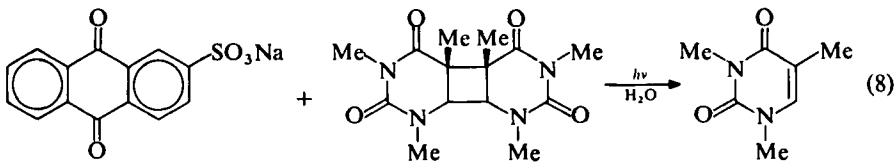
CIDNP[109], the directions and the intensities of these effects are determined by several parameters, including the spin multiplicity of the precursor (μ), the magnetic properties (electron g-factor(Δg), hyperfine coupling constants (a_i)) of the radical intermediates, and the type of reaction (ε) by which the polarized product is formed. Since three (Δg, μ, ε) of the four parameters are always the same, the directions and magnitudes of the polarization may reflect the electronic structure of the radical intermediates (a_i). Irradiation of an acetone solution of CQ and 2,2-dianisylmethylenecyclopropane (**19**) leads to the formation of cycloadducts **20** and **21** through the intermediacy of a radical ion pair (equation 7)[106]. Photo-induced monomerization of dimethylthymine dimers (**22**) by ASQ to **23** proceeds also by an initial one-electron transfer from the strained cyclobutane ring to the photoexcited quinone (equation 8)[110].



(7)

(19) **(20)** **(21)**

An = 4-methoxyphenyl

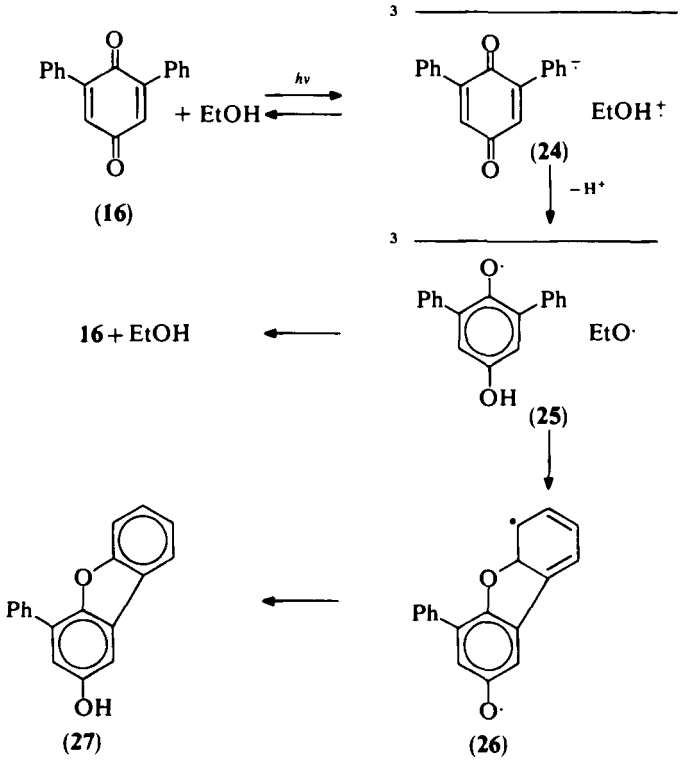


(8)

ASQ **(22)** **(23)**

5. *Alcohols and hydroquinones*

A laser photolysis technique combined with fast conductance measurements and kinetic spectroscopy are used to monitor the electron transfer reactions of ^{3}(DQ)* with ethanol in water/ethanol (2:1, v/v) and with acetone[86]. Similarly, electron transfer from benzyl alcohol to ^{3}(DQ)* proceeds with $k_q = 8 \times 10^5$ M^{-1} s^{-1} in water/methanol (4:1, v/v)[87]. 2-Hydroxy-4-phenyldibenzofuran (**27**) is the principal product in the photolysis of **16** in polar solvents (Scheme 4)[111,112]. CIDNP effects due to the reactants and the cyclized product **27** are interpreted as arising from the radical ion pair **24** or neutral radical pair **25** composed of semiquinone radical and ethoxy radical. These results are consistent with the mechanism in Scheme 4, where the primary process for the cyclization is a single electron transfer from ethanol to **16**[113]. Many observations are given as evidence for the primary electron transfer in the photoreduction of BQ in pure alcohol, in spite of the purely (n, π^*) nature of the lowest triplet state of BQ (see Section III.B.1).

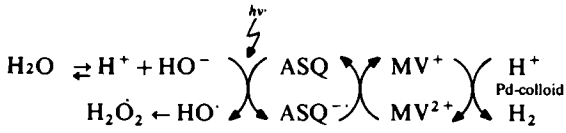


SCHEME 4

6. *Ions*

Organic anions[114] (alkoxides[115–118], $MeCO_2^-$, $CCl_3CO_2^-$), inorganic anions[6,78,90,114,119] (OH^-, SO_4^{2-}, SO_3^{2-}, SeO_3^{2-}, SCN^-, CO_3^{2-}, PO_4^{2-}, NO_3^-, X^-) can reduce photoexcited quinones via a single electron transfer. Photo-induced sulfonation of 1-aminoanthraquinone in aqueous solution containing Na_2SO_3 has been shown to involve electron transfer from SO_3^{2-} ion to the photoexcited quinone (see Section V). AQ, ASQ and **2** (R = piperidino) are readily photoreduced by hydroxide ion to produce the corresponding anions as the stable products[39,114,120,121], but the excited state involved is $T_1(n,\pi^*)$ for AQ and ASQ and T_2 (n,π^*) for **2** (R = piperidino)[120]. Recently, interest in this area has been heightened by suggestions for utilizing anthraquinone sulfonates, ASQ and ADSQ, as photocatalysts in solar energy storage, as in photooxidation of chloride ion to chlorine[122] and splitting of water into H_2 and H_2O_2[123]. Photogenerated anion radical from ASQ can reduce methyl viologen to its cation radical, which, in turn, splits water in the presence of colloidal platinum (Scheme 5).

In connection with the possible increase of the sensitivity of diazo-type light-sensitive materials, the photosensitized radical chain decomposition of arenediazonium salts has been extensively studied[124,125]. ASQ or ADSQ photosensitization leads to a considerable increase of ca. 10 times the rate of decomposition of the diazo compounds in the presence of appropriate electron and hydrogen donors. The following reaction mechanism is



SCHEME 5

suggested in the case of formate as electron and hydrogen donor:

$$^3(ASQ)^* + HCOO^- \rightarrow ASQ^{-\cdot} + HCOO^{\cdot} \quad (9)$$

$$ASQ^{-\cdot} + ArN_2^+ \rightarrow ASQ + Ar^{\cdot} + N_2 \quad (10)$$

$$Ar^{\cdot} + HCOO^- \rightarrow ArH + COO^{-\cdot} \quad (11)$$

$$COO^{-\cdot} + ArN_2^+ \rightarrow CO_2 + Ar^{\cdot} + N_2 \quad (12)$$

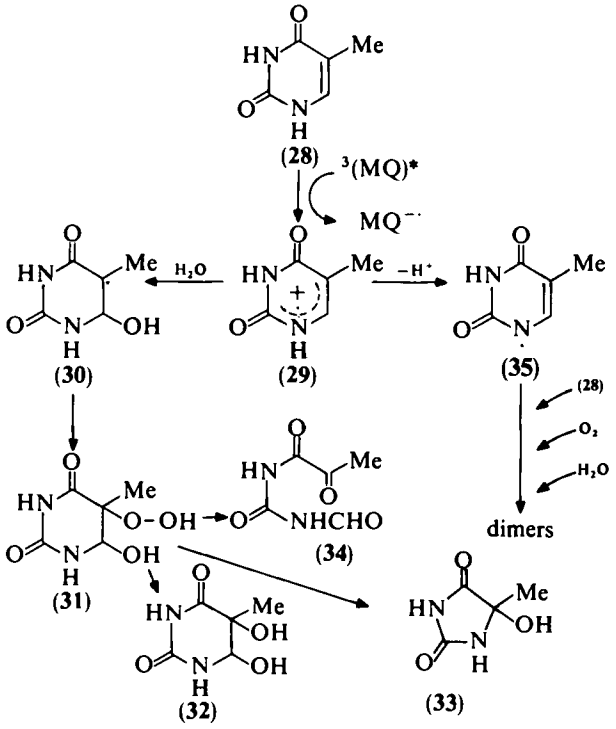
Photogenerated $ASQ^{-\cdot}$ (equation 9) reduces the diazonium salt, giving rise to an aryl radical (equation 10), which propagates the chain decomposition of the diazonium salt (equations 11 and 12). The chain length depends on the rate of initiation and on the nature of the donor molecules and is stated to reach 500 in solution and 20 in plasticized poly(vinyl alcohol) films[126].

7. *Miscellaneous*

The triplet state of DQ has a pK_a of -0.1. The protonated triplet state shows a different absorption spectrum (max 390 and 470 nm) from that of the neutral form (max 440 nm) and reacts with benzyl alcohol and Cl^- ion with rate constants which are about two orders of magnitude higher than those of the neutral form[87].

It is well known that thymine (**28**) and the other constituents of DNA are the principal targets for inactivation of cells by short-wavelength UV light. 2-Methyl-1,4-naphthoquinone (MQ) is also a target chromophore for the growth delay of *Bacillus subtilis* induced by near-UV light[127]. MQ and its bisulfate derivatives are among the most efficient radiation potentiating drugs as photosensitizers of mammalian cell killing by near-UV (365 nm) irradiation. The single-strand breaks in the supercoiled DNA of bacteriophage ϕX-174 are sensitized by MQ.

Photoexcitation of the quinone at 365 nm in oxygenated solutions leads to a number of products of **28**, including the *cis* and *trans* isomers of 5-hydroperoxy-6-hydroxy-5,6-dihydrothymine (**31**), the *cis*- and *trans*-thymine glycols **32**, 5-hydroxy-5-methylhydantoin (**33**) and *N*-formyl-*N'*-pyruvylurea (**34**), which are also formed by hydroxy radical attack upon **28** by ionizing irradiation (scheme 6)[41,128]. Interaction of $^3(MQ)^*$ in water with pyrimidine bases such as thymine, uracil, 6-methyluracil and orotic acid involves electron transfer to give the pyrimidine cation radical and the $MQ^{-\cdot}$ with a nearly diffusion-controlled rate (Table 4). Therefore the thymine photoproducts are considered to arise from the reaction of **29** with water and oxygen. Oxygen also readily quenches $^3(MQ)^*$; the usual reaction involves energy transfer to give ground state MQ and $^1O_2$. In dilute oxygenated solutions of MQ, this is the main process and MQ is subsequently altered by the reaction with $^1O_2$. When **28** is also present in the solution, however, it competes efficiently with oxygen towards $^3(MQ)^*$, the yield of $^1O_2$ is considerably decreased, and MQ is thus protected against its self-sensitized photodynamic oxidation[41]. Photochemical reductions of dibromothymoquinone in ethanol are studied in relation to its inhibitory function in photosynthesis[129].



SCHEME 6

Triplet states of polycyclic aromatic hydrocarbons are efficiently quenched by quinones via charge transfer interactions[130, 131]. The magnitudes of the quenching rate constants k_q are found to be correlated with the energy difference between the triplet state of the aromatic hydrocarbon donor and the triplet charge transfer state assuming electron transfer from the donor to the quinone. The deactivation route is shown to involve intersystem crossing from this intermediate ^{3}(CT)* state to the almost isoenergetic corresponding ^{1}(CT)* state, followed by a subsequent internal conversion to the weakly bound ground state of the charge transfer complex.

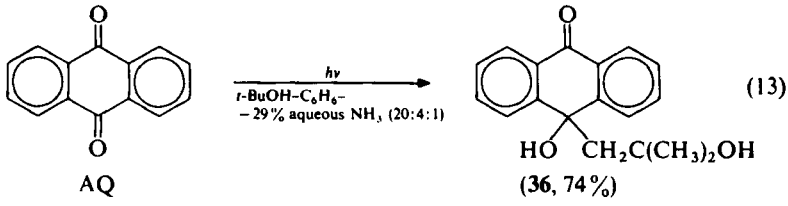
Quinones have often been used merely as electron acceptors in photosensitized electron transfer reactions. Both singlet and triplet excited chlorophyll molecules are efficiently quenched by quinones[410]. There is clear evidence that the triplet exciplex between chlorophyll a and quinone produce the chlorophyll a cation radical and semiquinone anion radical. However, no separate ions are detected from the singlet quenching[132].

B. Hydrogen Abstraction

The mechanism of H abstraction by photoexcited quinones has received considerable experimental and theoretical attention. Quantum yields for the reduction of 0.5–1.0 and even higher values have been reported for quinones with low-lying (n, π^*) electronic states[133]. Substitution of the quinones by electron-donating groups gives rise to low-lying intramolecular charge transfer (CT) or (π, π^*) states in these molecules with a concomitant decrease in photoreduction reactivities.

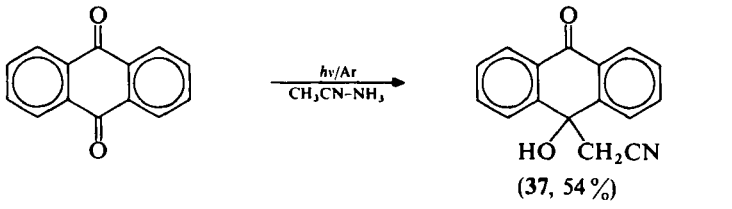
The hydrogen abstraction reactions of triplet states of AQ have been studied theoretically as radiationless transitions in terms of the tunnel-effect theory, in which the rates of reactions are controlled by the Frank–Condon factors of the vibrational stretching motions of the carbonyl group in the excited AQ and the C–H oscillators of the substrates and the C–O and O–H vibrations in the ground state of the final products. The rates are dependent on the electronic energy, the nature of the excited state, the vibrational frequencies, the reduced mass of the oscillators, the C–H bond strength and the distances of the reactive bonds of substrates[134]. The effects of substituents on the reaction rates can be accounted for by change in the reduction potentials of the quinones, and/or by the nature and energy of the excited states. It is predicted theoretically that (π, π^*) states have an intrinsic reactivity for H abstraction which is 10^{-2} to 10^{-4} times lower than that of (n, π^*) states, but when both levels are energetically close, the observed reactivity is due to the thermally equilibrated population of the two states[135].

As noted in Section III.A, photochemical H abstraction can occur by a two-step mechanism involving electron and proton transfer. As another mechanism, H abstraction by a triplet exciplex has been known. AQ/ammonia triplet exciplex abstracts a hydrogen from *t*-butanol or acetonitrile to give adduct **36** (equation 13) or **37** (equation 14), respectively[81,82]. The photoreaction of AQ in *t*-butanol-benzene (4:1, v/v) containing no ammonia or water proceeds much less rapidly, giving **36** in 29% yield[81]. In acetonitrile, the formation of the substituted anthrone (**37**) is not observed in the absence of ammonia, and is strongly suppressed by the presence of oxygen, which favors the amination of anthraquinone nucleus (see Section V.D.1)[82].

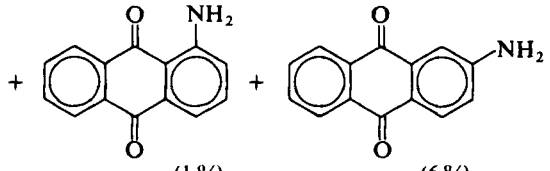


AQ

(36, 74%) (13)



(37, 54%) (14)



(1%) (6%)

Rate constants for H abstraction reaction of photoexcited quinones with hydrogen donors (i.e. quenching rate constants) are listed in Table 5. Generally, the resulting semiquinone radicals QH· rapidly decay via disproportionation to QH_2 and Q with diffusion-controlled rates (Table 6).

1. In alcohol

Although the photoreduction of quinones has long been studied, there is still controversy about whether the primary reaction of quinone triplets is an electron transfer or a direct H transfer. Photoreduction of quinones with the lowest lying (n, π^*) triplet state in basic alcoholic media, in general, is considered to involve H abstraction from the solvent by the quinone (equation 15), followed by dissociation of the semiquinone radical (QH·)

TABLE 5. Quenching rate constants of triplet quinone by hydrogen donors

Quinone	Hydrogen donor	k_q ($M^{-1}s^{-1}$)	Ref.
BQ	Ethanol	$> 6 \times 10^6$	70
TQ[a]	Ethanol	$> 6 \times 10^6$	70
DMBQ[b]	Ethanol	$> 6 \times 10^6$	70
TMBQ[c]	Ethanol	1.3×10^6	70
DQ	Ethanol	$0.64–1.6 \times 10^4$	70
	Ethanol	3.6×10^3	42b
	2-Propanol	1.8×10^4	70
	2-Propanol	6×10^3	74
	Phenol	2×10^8,[h]	136a
	2-MP[d]	4×10^8,[h]	136a
	PCP[e]	2×10^8,[h]	136a
	TEA[f]	3.6×10^8	95
	DQH_2	3.7×10^9,[h]	70
	DQH_2	3.9×10^9,[h]	42c
	DQH_2	2×10^9,[h]	74
DBQ[g]	2-Propanol	2×10^6	136c
CQ	Dioxane	2.6×10^5 (3.8×10^4)[j]	75
	CQH_2	1.7×10^9,[k] (0.9×10^9)[j]	137
	CQH_2	3.6×10^9,[i] (1.9×10^9)[j]	137
	CQH_2	4.7×10^9,[m] (4.3×10^9)[j]	137
	$MeCH_2CN$	1.6×10^5	138
AQ	Ethanol	$< 2 \times 10^7$	61
	Ethanol	3.3×10^6	138
	2-Propanol	4.0×10^6	61
	Hexane	8.6×10^5	138
	Benzene	4.8×10^5	138
1 (R = Cl)	Ethanol	2.3×10^6	89
6 ($R^1 = R^2 = Cl$)	Ethanol	1.6×10^4	89
ASQ	Ethanol	1×10^8,[n]	139

[a] TQ, toluquinone; [b] DMBQ, 2,5-dimethyl-1,4-benzoquinone; [c] TMBQ, trimethyl-1,4-benzoquinone; [d] 2-MP, 2-methylphenol; [e] PCP, pentachlorophenol; [f] TEA, triethylamine; [g] DBQ, 2,6-di-*t*-butyl-1,4-benzoquinone; [h] in ethanol; [i] in 2-propanol; [j] net hydrogen atom transfer rate; [k] in dioxane; [l] in 1,2-dichloroethane; [m] in acetonitrile; [n] in water/ethanol mixture.

TABLE 6. Second-order rate constant for decay of semiquinone radicals

Quinone	k_2 ($M^{-1}s^{-1} \times 10^{-9}$)	Solvent	Ref.
BQ	1.5	2-Propanol	137
	5.4	Dioxane	137
DQ	0.7	2-Propanol	137
	2.9	Dioxane	137
	2.1	—	74
NQ	0.23	2-Propanol	137
	0.90	Dioxane	137
CQ	0.17	2-Propanol	137
	0.76	Dioxane	137
FQ[a]	3.2	2-Propanol	140
DBQ[b]	1.7×10^{-3}	2-Propanol	136c
DMBQ[c]	0.3	2-Propanol	136c
AQ	1.3	—	138b
	1.2	Dioxane	137
AQ^-	0.049	2-Propanol	137
1 (R = Cl)	1.2	Ethanol	89
6 ($R^1 = R^2 = Cl$)	0.58	Ethanol	89
ASQ	3.0	Water	61
ADSQ	3.2	Water	61
1 (R = piperidino)	0.7	Methanol	61
2 (R = piperidino)	0.62	Methanol	61

[a] FQ, tetrafluoro-1,4-benzoquinone; [b] DBQ, 2,6-di-*t*-butyl-1,4-benzoquinone; [c] DMBQ, 2,6-dimethyl-1,4-benzoquinone.

to the semiquinone anion radical (equation 16). In the absence of base the subsequent disproportionation reaction results in the formation of hydroquinone (QH_2) (equation 17).

$$^3Q^* + RCH_2OH \rightarrow QH^{\cdot} + R\dot{C}HOH \quad (15)$$

$$QH^{\cdot} \rightleftharpoons Q^{-\cdot} + H^+ \quad (16)$$

$$2QH^{\cdot} \rightarrow QH_2 + Q \quad (17)$$

The flash photolysis technique has provided evidence favoring the direct H-abstraction mechanism by detection of $QH^{\cdot}$ as the primary intermediate[4, 6, 7, 42b]. Formation of $QH^{\cdot}$ has also been indicated by ESR studies under steady-state[4, 6, 7] or flash photolysis[141, 142] conditions. Even DQ, whose lowest triplet excited state is entirely of (π, π^*) character, shows a high H-abstraction reactivity toward ethanol and cyclohexane[42b]. However, a nanosecond flash photolysis combined with a fast flash conductance measurement reveals that $^3(DQ)^*$ in a 2:1 v/v mixture of water/ethanol does not abstract hydrogen but an electron from ethanol[86]. Both $BQ^{-\cdot}$ and $BQH^{\cdot}$ are observed by ESR during the continuous photolysis of a flowing solution of BQ in ethanol at room temperature[143]. Based on the concentration effects of BQ and flowing rate upon their relative yields, it is proposed that $BQ^{-\cdot}$ is formed directly by a photo-induced electron transfer from the solvent to BQ (equation 18, Q = BQ) and that $BQH^{\cdot}$ is formed by hydrogen abstraction of BQ from BQH_2[143, 144]. The latter is produced by disproportionation of $BQH^{\cdot}$ followed by protonation (equation 20, Q = BQ). Halogenated benzoquinones behave similarly[143b]. Further, the formation of free ethoxy radical which appears to arise from the deprotonation of cation radical of ethanol (equation 19) gives support for the anionic reduction pathways[113, 143c, 145, 146]. But one must take the possible complication from

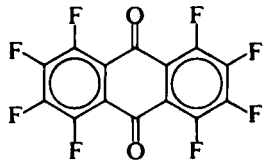
CIDEP effects of the system into consideration in interpreting the steady-state ESR data, since the steady-state ESR signal is not a simple measure of the concentration of radicals in a system where CIDEP effect operates[96].

$$Q^* + MeCH_2OH \rightarrow Q^{-\cdot} + MeCH_2OH^{+\cdot} \quad (18)$$

$$MeCH_2OH^{+\cdot} + MeCH_2OH \rightarrow MeCH_2O^{\cdot} + MeCH_2OH^{+} \quad (19)$$

$$2Q^{-\cdot} \rightarrow Q^{2-} + Q \quad (20)$$

However, the results obtained by CIDEP[96, 141, 147–151, 408] and CIDNP[96, 138, 147] support a direct H abstraction as the main pathway in the photoreduction of BQ and NQ in pure alcohols. Initial polarizations observed in the CIDEP experiments provide a great deal of information on the primary radical intermediates; this technique appears particularly suitable for the determination which of the two, electron transfer or H abstraction, occurs in the reaction[148–150]. Polarized emissions for $BQH^{\cdot}$ and $NQH^{\cdot}$ are observed in the photoreduction of BQ and NQ in pure 2-propanol and 2-butanol, as well as in the presence of pyridine[96, 151], but no emission from the anion $BQ^{-\cdot}$ nor $NQ^{-\cdot}$ can be detected. These are attributed to the formation of optically spin polarized triplets of the parent quinone and their subsequent H abstraction with retention of the polarization in the resultant semiquinone radicals. The spin polarization of the triplet quinone is believed to be a consequence of the spin selective intersystem crossing from the excited singlet. Further study using a benzene solution of BQ or NQ in the presence of 2,6-di-*t*-butyl-4-methylphenol as the hydrogen donor has established that both the semiquinone radical and the corresponding phenoxy radical exhibit total emission, consistent with the photochemical triplet polarization theory[148, 149, 152]. Polyhalogenated anthraquinones such as perfluoroanthraquinone (**38**), 1,2,3,4-tetrafluoroanthraquinone (**39**) and 1,2,3,4-tetrachloroanthraquinone (**40**) have the lowest triplet excited states having mixed (n,π^*)–(π,π^*) character or pure (π,π^*) character and are likely to be photoreduced in ethanol via electron transfer from ethanol[36]. On the other hand, **1** (R = Cl) and **5** ($R^1 = R^2 = Cl$), which have a lowest triplet excited state quite similar to **38**–**40**, are reported to be photoreduced via H abstraction. No evidence for electron transfer from ethanol to **1**(R = Cl) and **5**($R^1 = R^2 = Cl$) is obtained[37]. Prolonged irradiation of **5**($R^1 = R^2 = Cl$) gives AQH_2 as a final product via a consecutive H abstraction and dechlorination sequence[153, 154] (equation 21).



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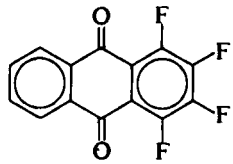
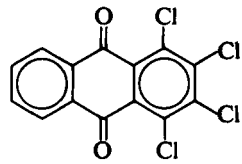


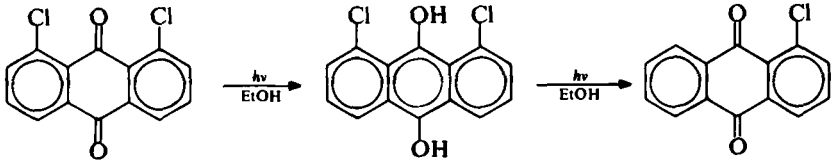
(39)



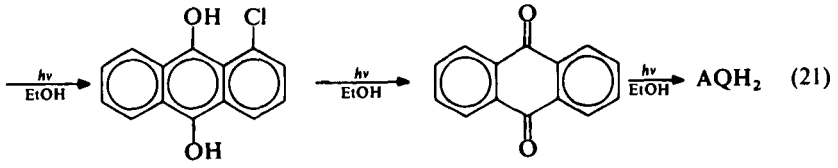
(40)

Based on the dependency of the CIDEP polarization magnitude upon the phenol concentration, the relative rate of formation of the radical **42** is estimated to be five to seven times higher than that of the formation of **43** in the photoreduction of 2-*t*-butyl-1,4-benzoquinone (**41**). Independently how the radicals are produced the concentration of **42** is about twice that of **43**, which indicates their equilibration, possibly via a radical anion of **41** (equation 22)[152d]. Further, CIDEP technique is utilized to evaluate the triplet quenching rate by H donors[136a, 140].

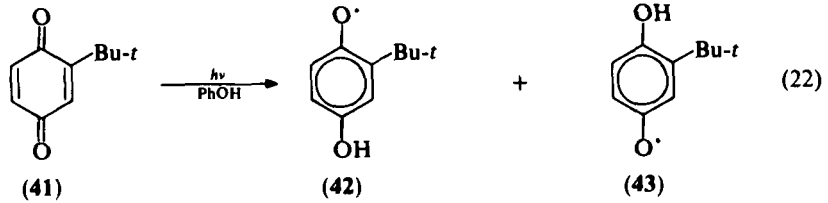
Visible-light irradiation of the yellow polycyclic quinone **44** in acidic alcoholic solvents leads to a blue doubly reduced salt (**45**), which upon exposure to an oxidant (air or H_2SO_4) is converted back to **44** (equation 23)[155]. This represents a new, recyclable photochromic



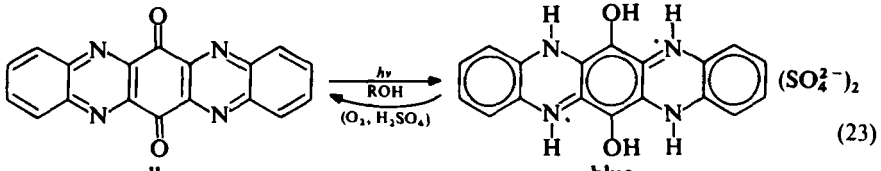
(5, $R^1 = R^2 = Cl$)



(21)



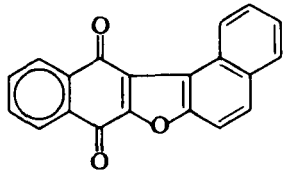
(41) (42) (43) (22)



yellow (λ_{max} 342, 360, 380 nm) (44)

blue (λ_{max} 630 nm). (45) (23)

system on an hour time-scale. Polycyclic furanonaphthoquinones **46** and **47** are photoreduced in basic alcohol solution with quantum yields of 10^{-3} to 10^{-2}, consistent with the (π, π^*) nature of the low-lying electronic states of these furanoquinones[156].



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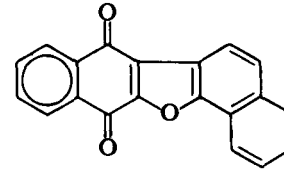
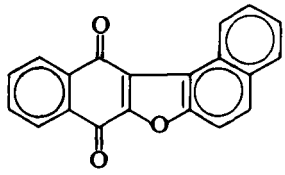


(47)

These structures can be represented by



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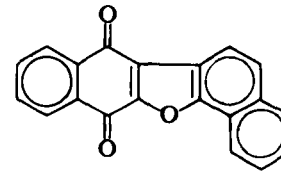
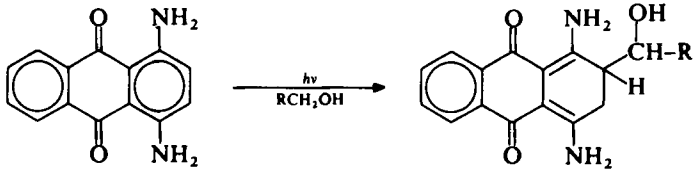
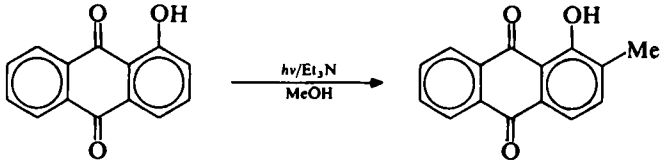


Solvent addition product **49** is formed upon irradiation of 1,4-diaminoanthraquinone (**48**) in alcohols (equation 24)[157]. 1-Hydroxyanthraquinone (**1**, R = OH) is photochemically methylated at the 2-position to **50** in methanol in the presence of triethylamine (equation 25)[409].



(**48**) R = H, Me (**49**, 30–40%) (24)



(**50**, 54%) (25)

ASQ-photosensitized hydroxylation of benzene to phenol is accomplished in water/ethanol (1 : 1) solution in the presence of Cu^{2+} under aerobic conditions. Photogenerated ASQH· reduces oxygen to hydroperoxy radical (equations 26 and 27), which hydroxylates aromatic compounds in the presence of Cu^{2+} ion. In the absence of oxygen, metallic copper is formed by the reactions shown in equations 28 and 29. The maximum quantum yield for the formation of phenol is 0.04[139].

$$^3(ASQ)^* + MeCH_2OH \rightarrow ASQH^{\cdot} + MeCHOH \quad (26)$$

$$ASQH^{\cdot} + O_2 \rightarrow ASQ + HOO^{\cdot} \quad (27)$$

$$ASQH + Cu^{2+} \rightarrow ASQ + Cu^{+} + H^{+} \quad (28)$$

$$2Cu^{+} \rightarrow Cu^{0} + Cu^{2+} \quad (29)$$

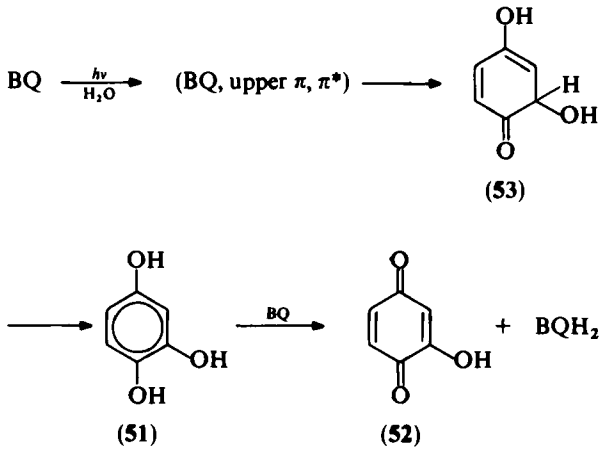
Nitro-substituted anthraquinones are reduced to the corresponding aminoanthraquinones upon irradiation in alcohols, whereas carbonyl group is not reduced at all. The reduction probably proceeds via the lowest triplet state (n, π^*) of the nitro group[158–160].

Normally the rate constants of $^3(Q)^*$ photoreduction by QH_2 are diffusion controlled and are two or three orders of magnitudes higher than those for reduction by alcohol (Table 5). The ^{19}F CIDNP signals of both tetrafluoro-1,4-benzoquinone (FQ) and tetrafluorohydroquinone (FQH_2) observed in the photolysis of the FQ/FQH_2 pair in benzene are interpreted in terms of the triplet mechanism[136b, 161]. At relatively low magnetic field, two other mechanisms, a radical pair route and a biradical-induced polarization, are suggested[161]. Clear evidence for the primary electron transfer from QH_2 to Q is provided by CIDNP[162].

2. *In water*

Photolysis of BQ in water affords 1,2,4-trihydroxybenzene (**51**) as the sole primary photochemical product and 2-hydroxy-1,4-benzoquinone (**52**) and BQH_2 as the secondary

products via **53** (equation 30)[163]. Formation of **51** is not affected by addition of a radical scavenger such as *p*-nitro-*N*,*N*-dimethylaniline and the isotope effect in the reaction ($k_H/k_D = 1.15$) is small[164]. These results are not compatible with the radical mechanism involving H abstraction from water and suggest an ionic mechanism for the ring hydroxylation of BQ in water[165,166]. Quantum yields for the photoreduction in water are 0.55 at 313 nm and 0.31 at 436 nm, indicating the participation of the upper (π, π^*) triplet state of BQ. Accordingly, a direct nucleophilic addition of water to the (π, π^*) excited state of BQ is postulated (equation 30)[165]. Photolysis of BQ in water in the presence of micelles[166] or cyclodextrin[167] results in the increase of the quantum yields for the formation of BQH_2 along with the decrease of the quantum yield for the formation of **51** through the inclusion of BQ into the micelle or the cyclodextrin. This is consistent with the polar mechanism[167].



(30)

On the other hand, laser flash photolysis experiments have shown the formation of both short-lived and long-lived transients upon irradiation of BQ in water[71]; the short-lived one (λ_{max} 410 nm) is assigned to ^{3}(BQ)* which gives rise to the long-lived BQH$^{\cdot}$ and $BQ^{-\cdot}$ transients, as well as to a species considered to be the benzoquinone–hydroxy radical adduct (BQOH$^{\cdot}$). Based on these results, H-atom abstraction by ^{3}(BQ)* from water is suggested by the authors[71]. Photooxidation of water by BQ is also shown by Raman technique[168].

Increases in the triplet lifetimes of trimethyl-1,4-benzoquinone, 2,6-dimethoxy-1,4-benzoquinone and DQ in water are certainly related to an increase in the (π, π^*) character of the lowest triplet of these compounds.

3. From alkyl aromatics

Photochemical reactions of BQ, NQ and PQ with alkyl aromatics have been extensively studied by CIDNP technique, which can provide definitive evidence for the caged radical pair and unstable photoproducts[169–172]. Preparative irradiation of a benzene solution of BQ and xanthene (**54**) leads to a clean reduction of BQ to BQH_2 with the concurrent formation of 9,9′-bixanthenyl (**60**) (Scheme 7). The CIDNP effects observed during the irradiation indicate the intermediate formation of unstable adducts such as **55**, **56** and **57** as the in-cage recombination products of BQH and the 9-xanthenyl radical (**59**) formed via (**58**) (Figure 1)[170]. Polarized signal 1 in Figure 1a was due to the ring hydrogen of BH_2.

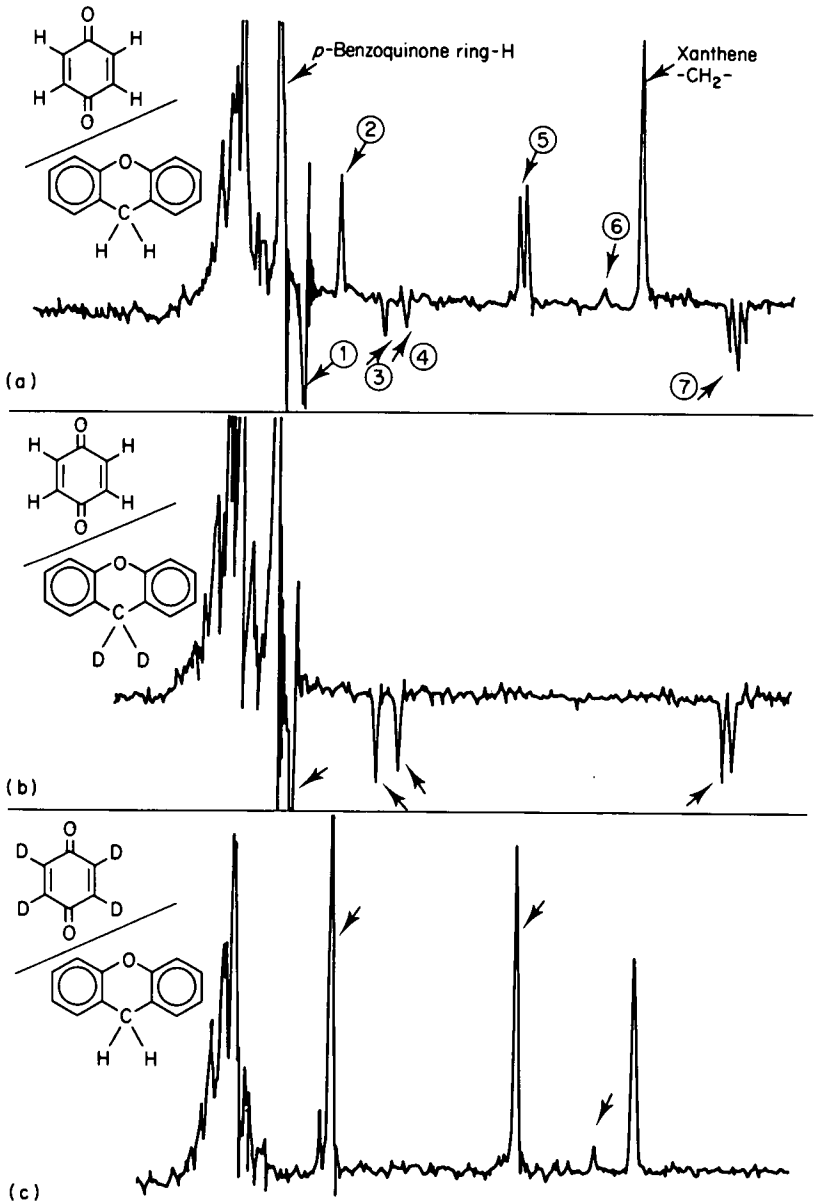
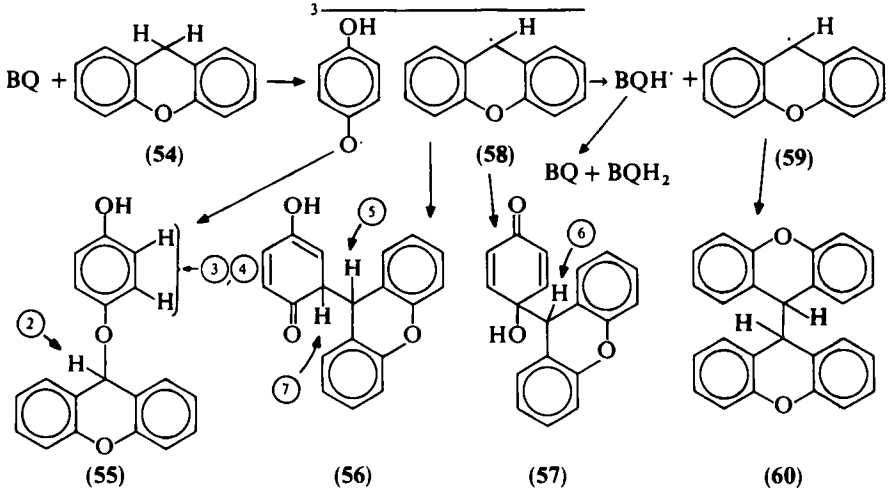
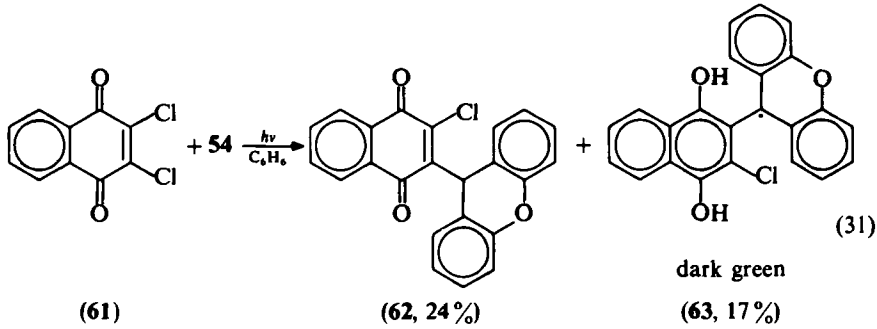


FIGURE 1. ^{1}H-NMR spectra observed in the photochemical reaction of BQ with xanthene in CCl_4 at 22°C: (a) BQ/xanthene, (b) BQ/xanthene-9,9-d_2, (c) BQ-d_4/xanthene

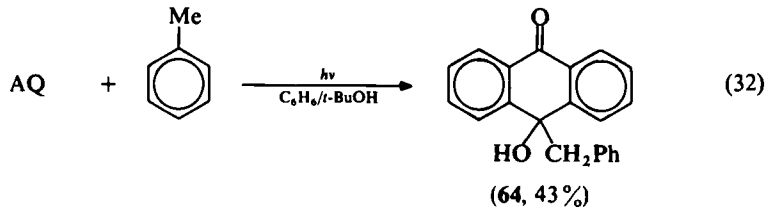


SCHEME 7

Based on the CIDNP effects obtained with xanthene-9,9-d_2 and BQ-d_4, polarized signals 2, 3, 4, 5, 6 and 7 indicated in Figure 1a were assigned as shown in Scheme 7. Alkyl-substituted naphthoquinones are photochemically reduced to the corresponding hydronaphthoquinone by **54**, while 2,3-dichloro-1,4-naphthoquinone (**61**) gives cross-coupling product **62** and a green-colored stable radical **63** in addition to the corresponding hydronaphthoquinones (equation 31)[170]. Photochemical reaction of AQ with toluene in the presence of *t*-butyl peroxide gives an adduct **64** in 43% yield (equation 32)[173].



(31)



(32)

Since the quinone nucleus is quite susceptible to radical addition, photochemically generated organic and inorganic radicals attack quinone and semiquinone molecules, giving diamagnetic adducts or radical adducts[142, 169–170, 174]. These adducts can be detected by CIDNP or CIDEP, regardless of their thermal stabilities. The 9-xanthenyl radical is shown to add to semiquinone radicals at almost all the possible sites, as disclosed by CIDNP technique and shown in Figure 2.

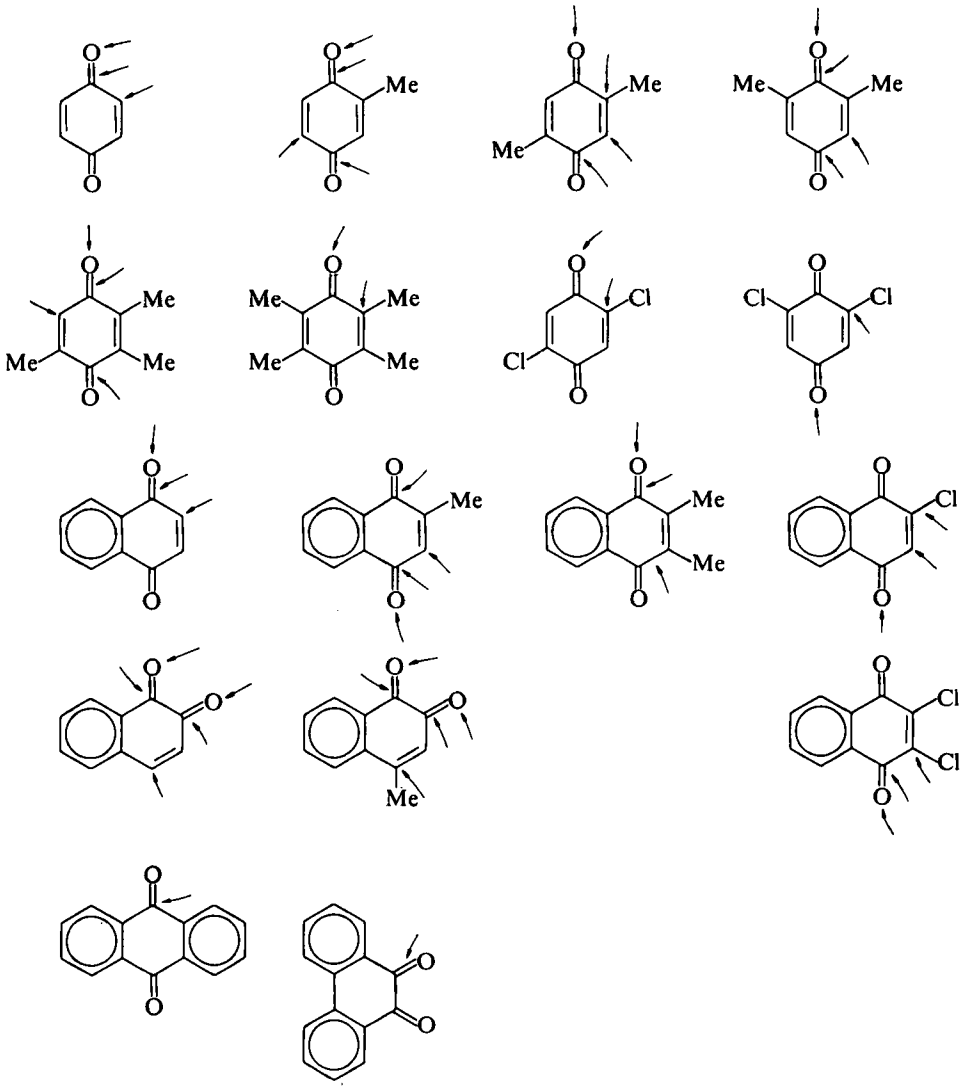
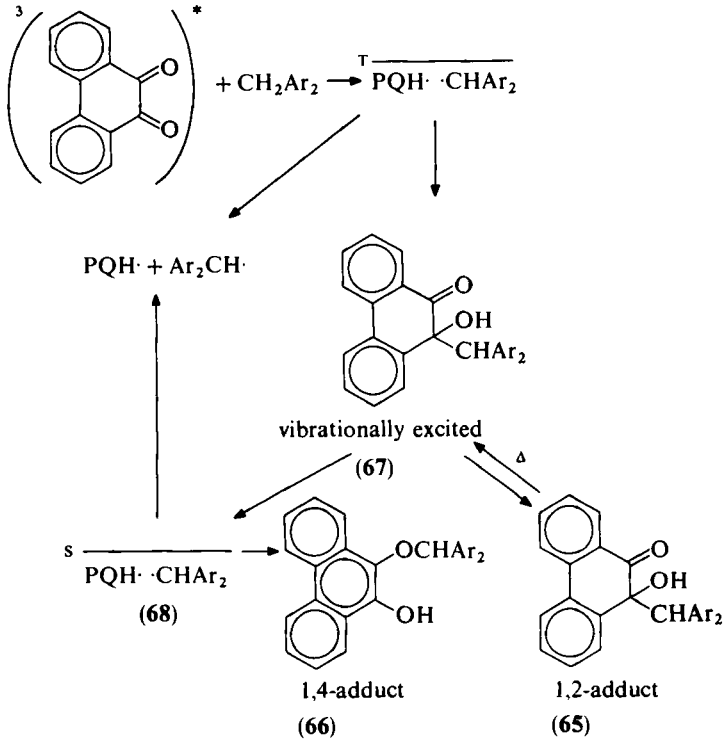


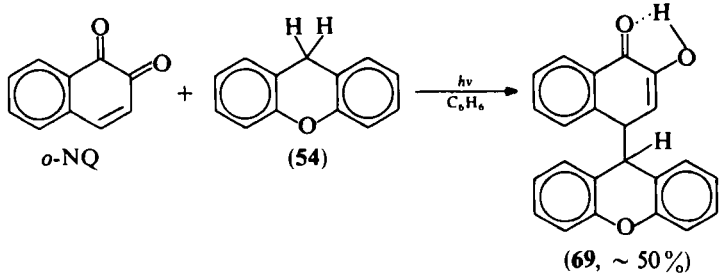
FIGURE 2. 9-Xanthenyl radical addition sites to semiquinone radicals

In the photochemical reaction with alkyl aromatics, PQ affords the 1,2-adduct **65** and the 1,4-adduct **66** with a ratio which depends on the structure of the hydrogen donor. During the course of this reaction, the methine hydrogens of **65** and **66** are strongly polarized but in opposite directions to each other. The formation of **66** has been explained in terms of a mechanism involving the homolysis of vibrationally excited **67** and subsequent in-cage recombination in singlet radical pair **68** (Scheme 8)[169, 172].



SCHEME 8

In the photochemical reaction of *o*-NQ with xanthene, a 1:1 adduct (**69**) is exclusively formed (equation 33), while 4-substituted *o*-NQ gives *o*-NQH_2 as a major product. Investigation by means of the CIDNP technique indicates that **69** is formed via in-cage

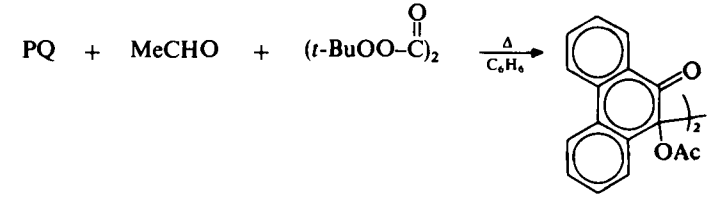


(33)

recombination of a triplet radical pair and that an unstable adduct is also formed but does not accumulate in the reaction mixture[175, 176].

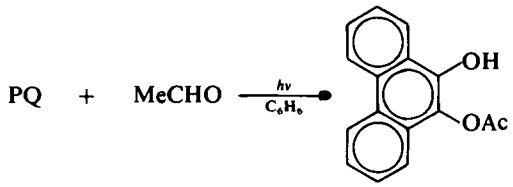
4. From aldehydes

Products of the photochemical H-abstraction reaction of quinones from aldehydes are generally the acyl hydroquinone by C attack and the hydroquinone monoester by O attack. Although it was previously proposed that these products arose via scavenging of acyl radicals by a ground-state quinone[2, 4], an in-cage recombination of acyl radical and semiquinone radical is now well recognized as a main pathway for their formation. This is due to two reasons: (*a*) CIDNP effects due to in-cage coupling products are generally observed[172, 177] and (*b*) thermal generation of an acyl radical in the presence of quinone leads to reaction products which are quite different from those obtained from the photochemical reaction. For example, the thermal reaction of the acetyl radical with ground state PQ gives isomeric dimers **70** (equation 34), in contrast to a clean production of the acetate **71** from the photochemical reaction of PQ with acetaldehyde (equation 35)[1-4, 178].



(34)

(**70**, 90%)



(35)

(quant.)

(**71**)

Irradiation of benzene solution of *o*-NQ and aliphatic aldehydes gives 3-acyl-1,2-naphthalenediol **72** and 1,2-naphthalenediol monoacyl esters **73a** (R = alkyl) and **73b** (R = alkyl) (equation 36)[179-182]. On the other hand, only **73a** (R = aryl) and **73b** (R = aryl) are formed in the reaction of *o*-NQ with aromatic aldehydes. This remarkable regioselectivity is ascribed to decreasing nucleophilic character of aroyl radical in the order: $CH_3\dot{C}{=}O > CH_2{=}CH{-}\dot{C}{-}O > C_6H_5\dot{C}{=}O$[182]. With phenylacetaldehyde, *o*-NQ gives **74**, **75**, **76**, **77** and 1,2-diphenylethane (equation 37)[180]. Benzyl and 9-xanthenyl radical attack the 4-position of *o*-NQH$^{\cdot}$, whereas acyl radicals attack the 3-position and the oxygen atom of *o*-NQH$^{\cdot}$. The different pattern of attack by alkyl and acyl radicals on *o*-NQH$^{\cdot}$ are successfully interpreted by taking into consideration the charge densities of the radicals concerned (Figure 3)[183]. The charge on C(4) of *o*-NQH$^{\cdot}$ is positive, while both C(3) and oxygen atom have negative charge. Therefore, benzyl radical (which has negative charge at the benzylic position) attacks the 4-position, and acetyl radical (which has

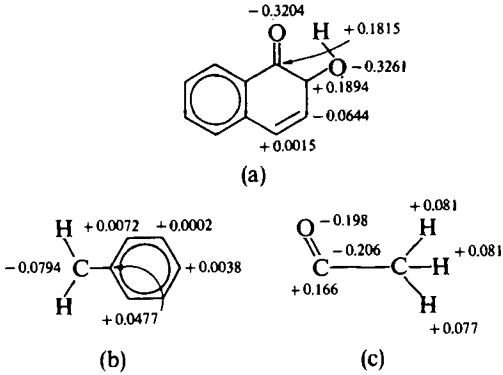
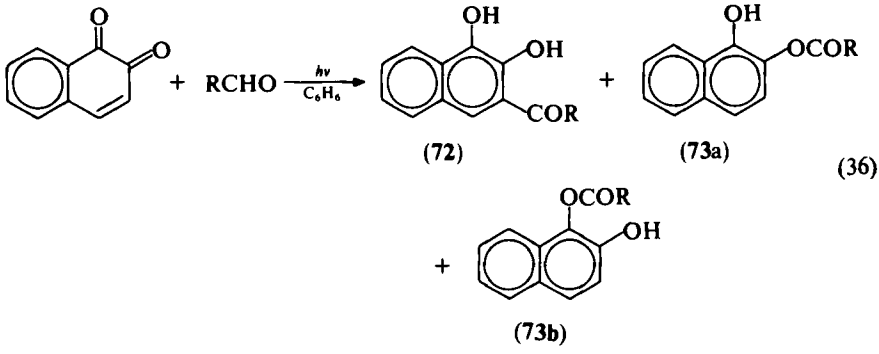
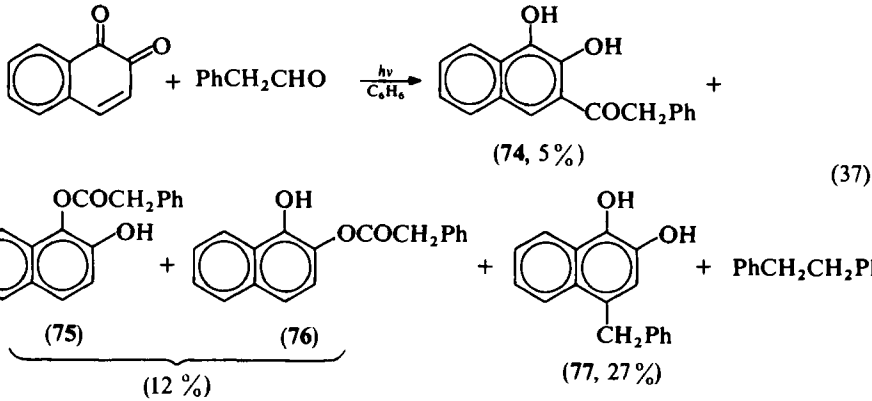


FIGURE 3. Charge densities of (a) 1,2-naphthosemiquinone radical, (b) benzyl radical and (c) acetyl radical

positive charge) attacks both the 3-position and the 3-position and the oxygen atom in *o*-NQH·. The photochemical reaction of *o*-NQ with acetaldehyde was investigated in order to assess the relative contribution of 'in-cage' and 'out-of-cage' mechanisms. At a low temperature, almost all parts of the reaction proceed via an 'in-cage' mechanism but at 20°C at least 6.7% of the reaction proceeds via an 'out-of-cage' mechanism[184].

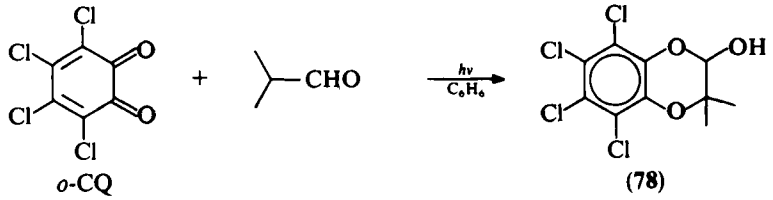


(36)

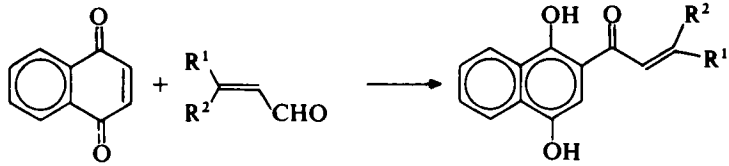


(37)

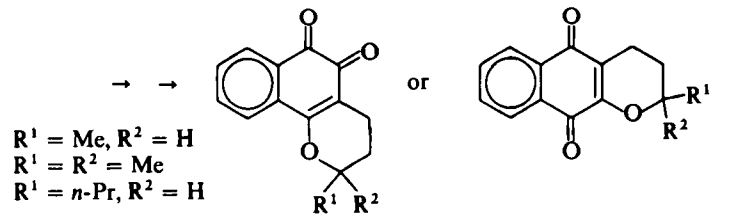
Irradiation of *o*-CQ in the presence of isobutyraldehyde affords **78** which is likely to arise from abstraction of the tertiary hydrogen α to the formyl group (equation 38)[185]. Photochemical reaction of NQ with α,β-unsaturated aldehydes gives adducts **79**, which are converted into α- and β-lapachones, **80** and **81** (equation 39)[186].



o-CQ (78) (38)



(79, 43 ~ 48%)



(80) (81) (39)

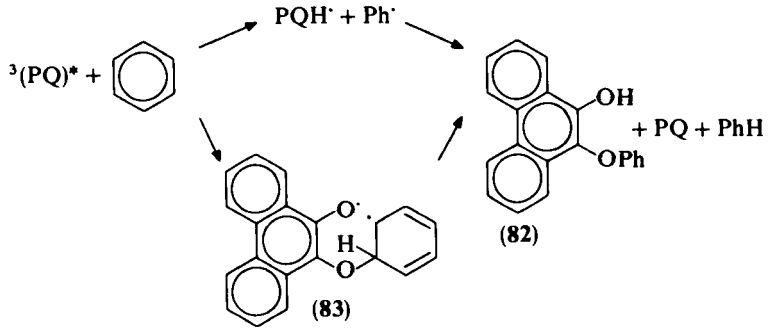
5. *Miscellaneous*

Photochemical reaction of PQ and benzene under nitrogen atmosphere affords mainly a 1:1 adduct **82** as well as biphenyl and PQH_2[187]. It is suggested that a triplet PQ either abstracts hydrogen from benzene to give PQH and phenyl radical or adds to benzene to give the biradical **83**. Adduct **82** may be formed either from **83** or by the geminate pair of $PQH^{\cdot}$ and phenyl radical (Scheme 9)[187]. A similar biradical adduct **84** is also postulated as the precursor for the ^{19}F polarization in the photolysis of *p*-fluoranil (FQ) in benzene[161].

Triplet excited quinones efficiently abstract hydrogen from oximes to yield iminoxy radicals (equation 40)[188].

$$^3(Q)^* + R_2C{=}N{-}OH \rightarrow QH^{\cdot} - R_2C{=}N{-}O^{\cdot} \quad (40)$$

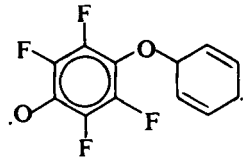
When AQ is irradiated in $CHCl_3$ in the presence of CF_3CO_2Ag, the adduct **85** is obtained as the result of the recombination of CCl_3 radical and $AQH^{\cdot}$ (equation 41)[73]. This reaction is suppressed by the presence of oxygen or the radical scavenger 2,6-di-*t*-butylphenol.



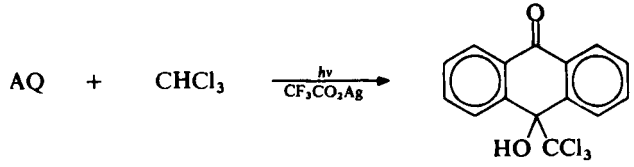
(82)

(83)

SCHEME 9



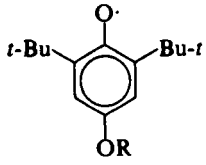
(84)



(41)

(85, 30–40%)

Photolysis of various quinones in the presence of organotin and organolead compounds yields paramagnetic organometal adducts of the quinones. Time-resolved CIDEP observations indicate that organometals having relatively low ionization potentials quench the carbonyl triplet via a charge transfer mechanism[174]. Photochemically generated trimethylstannyl radical adds to the carbonyl oxygen of 2,6-di-*t*-butyl-1,4-benzoquinone to give **86** (R = $SnMe_3$), while $Mn(CO)_5$ radical attacks only at the carbon–carbon double bond of the quinone to give **87** (R = $Mn(CO)_5$)[174]. Trimethylsilyl radical adds both to the carbonyl oxygen and to the ring carbon to give **88** (R = $SiMe_3$) and **89** (R = $SiMe_3$) (equations 42 and 43)[142].



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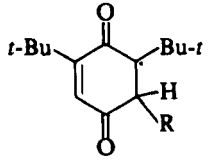
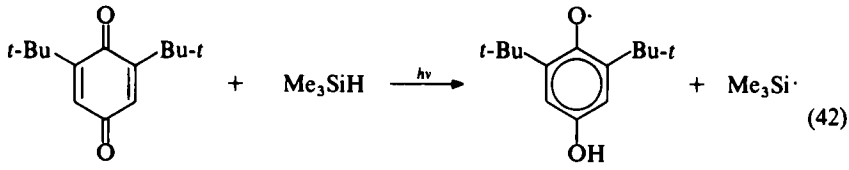


(87)



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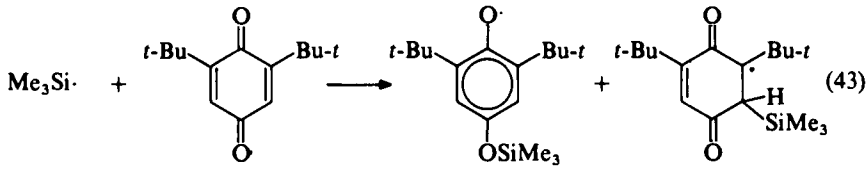


(43)

(**88**, R = $SiMe_3$) (**89**, R = $SiMe_3$)

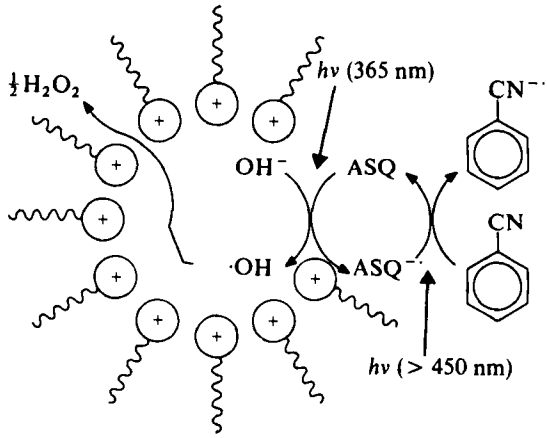
C. Photoreduction in Organized Assemblies

Photoreductions of quinones in organized assemblies have attracted considerable interest in view of their potential use for an efficient charge separation as well as because of the structural similarity of these assemblies to natural membranes. Photochemical solar energy conversion, in which quinones are often used as photosensitizers as well as electron acceptors, has been extensively treated in recent books and reviews[132, 189]. The most important role of the microscopic heterogeneous environment imposed by micelles, microemulsions, vesicles and polyelectrolytes may be the significant retardation of the back electron transfer in the photochemically generated ion pairs[83].

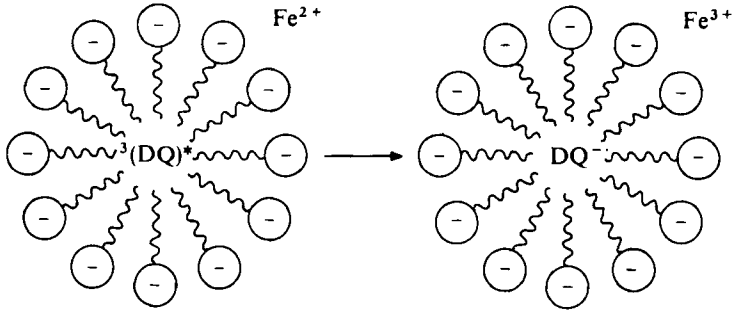
In the presence of anionic and non-ionic micelles, irradiation of ASQ and ADSQ in aerobic phosphate buffer (pH 8.0) gives $ASQ^{-\cdot}$ and $ADSQ^{-\cdot}$, respectively. These are considerably long-lived as compared with irradiation without surfactants[166, 190, 191]. Interestingly, photohydroxylation of ASQ does not occur, since the hydroxy radicals are efficiently scavenged by the surfactants (see Section V.D.2). The remarkable stability of $ASQ^{-\cdot}$ and $ADSQ^{-\cdot}$ under micellar conditions has been ascribed to the formation of association complex between the quinone and the surfactant[190]. Photoreductions of 9,10-phenanthraquinone-3-sulfonate and ASQ are greatly enhanced by the presence of cationic surfactants, whereas photoreduction of 1,2-naphthoquinone-4-sulfonate is highly retarded[12, 192]. Apparently, the anionic quinone forms a complex with the cationic head of the micelles, whose surface is also expected to be covered with excess hydroxide ion, and therefore supplies effective high concentration of hydroxide ion for the photoreduction of the quinone. An irreversible electron transport system is developed in a cationic reversed micelle by using ASQ as the photosensitizer (Scheme 10)[121]. The key step is a photo-induced electron transfer from $ASQ^{-\cdot}$ to benzonitrile which can be induced with red light ($\lambda > 450$ nm).

In the presence of anionic sodium lauryl sulfate micelles, electron transfer from $^3(DQ)^*$ to Fe^{3+} ion is markedly accelerated[86]. Laser photolysis experiments have shown that the intramolecular electron transfer proceeds via electron flux from the donor on the surface to the acceptor inside the micelle with a rate constant of $2.5 \times 10^7\ s^{-1}$ (Scheme 11)[86]. Photoreduction of ASQ and ADSQ was also studied in plasticized and non-plasticized polymer films[193, 194].

Photolysis of AQ in aqueous sodium dodecyl sulphate (SDS) led to the formation of AQH_2 and the surfactant–AQ adduct **90**, according to Scheme 12[195–197, 201]. The triplet

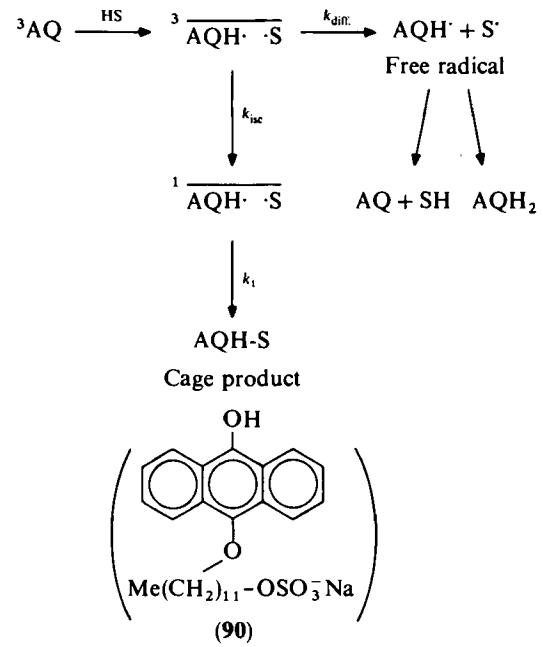


SCHEME 10



SCHEME 11

radical pair of AQH· and the surfactant radical (S·) undergoes competitive intersystem crossing (ISC) to the singlet pair and separation by diffusion. The triplet–singlet ISC of the radical pair occurs via electron-nuclear hyperfine interaction and should be reduced in a magnetic field because of the Zeeman splitting of triplet sublevels. Consistent with this theory, an external magnetic field (2600 G) increases the yield of free radicals at the expense of the competing ISC[195, 197, 201]. Similar external magnetic field effects are observed in BQ[198], DQ[198], 2,5-dimethyl-1,4-benzoquinone[198, 199], 1,2-benzanthraquinone[198], anthraquinone-2-carboxylic acid[198] and ASQ[198] in the SDS micelle as well as in the ion radical pair photochemically generated from DQ and diphenylamine[200]. However, external magnetic field effects which are still observed at much higher field (1.34 T) apparently require another mechanism (e.g. relaxation mechanism)[202b] instead of the hyperfine coupling mechanism. CIDEP studies on the NQ/SDS system reveal the total emission pattern of the spectra due to NQH· and surfactant radical at an early stage after pulsed excitation, and this should be correlated with the triplet mechanism[92, 202a].



HS, Sodium dodecyl sulfate

SCHEME 12

IV. PHOTOADDITION

A. Cycloaddition to Simple Alkenes and Related Compounds

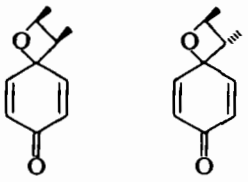
In common with other saturated and unsaturated carbonyl compounds, *p*-quinones afford cycloaddition products upon irradiation with alkenes. With BQ itself, which has a lowest triplet state of (n, π^*) configuration, addition to the carbonyl group is the only mode of cyclization that has so far been observed, although reaction at the olefinic bond to give a cyclobutane might have been possible. Indeed, cyclobutane formation was found with other *p*-quinones such as CQ and DQ having lowest triplet (π, π^*) states[4].

Therefore it may be attractive to propose that *p*-quinones whose lowest triplet state is (n, π^*) should react with alkenes to give oxetanes, while cyclobutanes would result from the corresponding reactions of quinones whose lowest triplet state is (π, π^*)[4, 203].

A theoretical calculation predicts that progressive introduction of methyl groups into the nucleus of 1,4-benzoquinone will lower the energy level of $^3B_{3g}(\pi, \pi^*)$ and raise that of $^3B_{1g}(n, \pi^*)$[204].

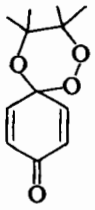
Of particular interest in this regard are quinones such as 1,4-naphthoquinones that are capable of forming both kinds of adducts simultaneously[203, 205]. Calculations on NQ suggest that the lowest triplet is again of (n, π^*) character, in agreement with experiment. An examination of these calculations and the photochemistry of NQ, however, suggests that several excited triplets lie very close in energy, and that all of them may be populated within the lifetime of the lowest triplet state[204].

Support for the intermediacy of a preoxetane biradical is provided by two observations: (1) *cis*- and *trans*-2-butene add to photochemically excited BQ to afford the same mixture of spiro oxetanes **91a** and **91b**[206]; (2) 1,2,4-trioxane (**92**) and sulfone **93** are formed by trapping of the preoxetane biradicals by molecular oxygen[207, 208] and sulfur dioxide[209], respectively.

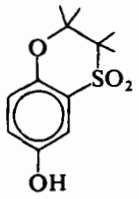


(**91a**)

(**91b**)



(**92**)



(**93**)

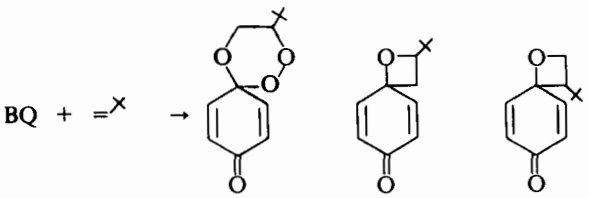
Elegant and extensive studies on the biradical trapping by molecular oxygen have led to three conclusions.

(1) The yields of 1,2,4-trioxane adducts are markedly raised by the use of monochromatic light from an argon ion laser in non-polar solvents (CCl_4 and $CFCl_3$) at high oxygen pressure (ca. 11 atm).

(2) Under these conditions the biradical trapping is quite general in both inter- and intramolecular photocycloaddition reactions of *p*-quinones.

(3) The intermediates which are trapped by oxygen are frequently not the preoxetane biradicals but rather the charge transfer exciplex species[210].

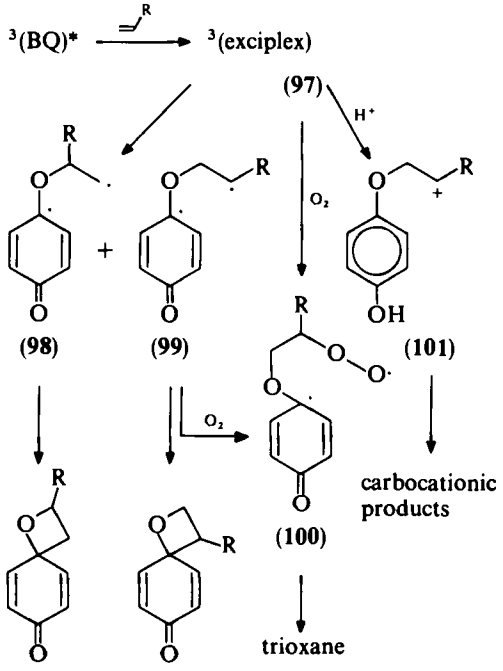
The last conclusion, which is of most mechanistic importance, is obtained from the study of photocycloaddition of BQ to unsymmetrical olefins such as *t*-butylethylene (Scheme 13)[210, 211]. When this reaction is conducted under anaerobic conditions, oxetanes **95** and **96** are formed with a **95**/**96** ratio of 0.25. Reactions conducted under increasing pressure of oxygen lead to the formation of a single trioxane (**94**), which appears to result from oxygen trapping of the more stable biradical that gives rise to **96**. The independence of the oxetane isomer ratio (**95**/**96**) of the oxygen pressure implies that oxygen is not trapping the more



	(**94**)	(**95**)	(**96**)
No O_2	0	25	75(%)
11 atom O_2	43	13	44(%)

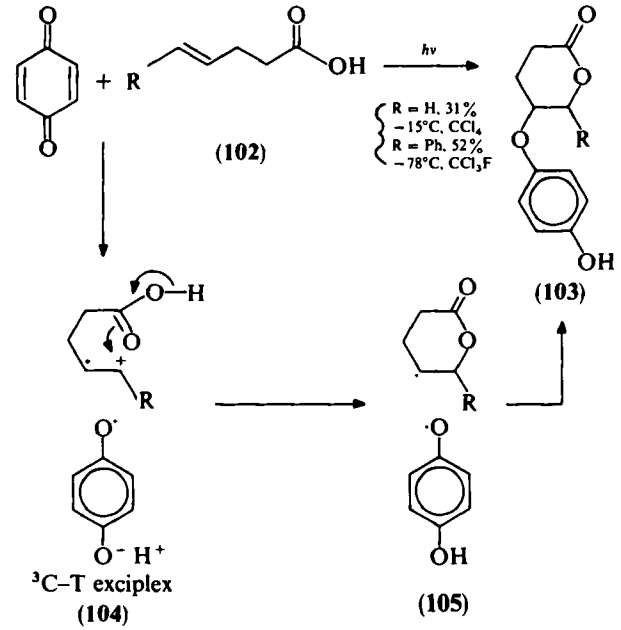
SCHEME 13

stable preoxetane biradical, but trapping instead a species **97** that precedes the partitioning to the two preoxetane biradicals **98** and **99** (Scheme 14)[210]. Triplet exciplex may be trapped by oxygen or proton, leading to a biradical (**100**) or to a cation (**101**). Presumed triplet

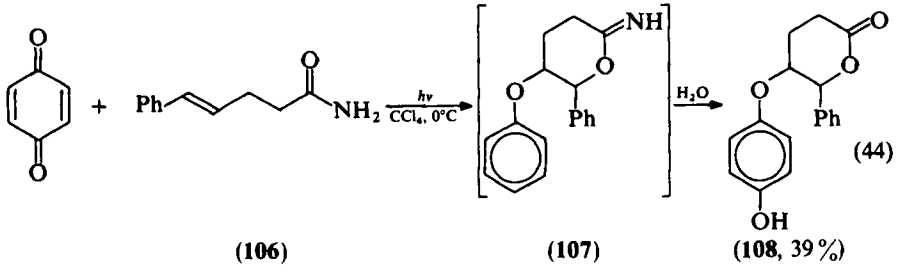


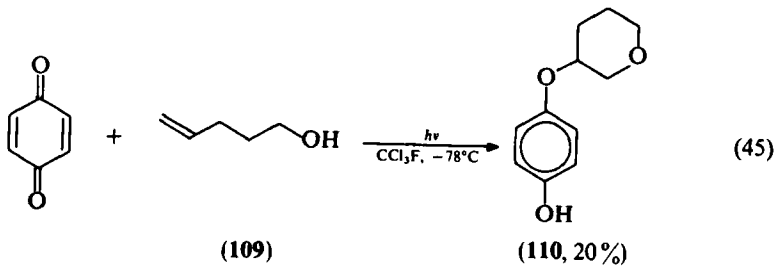
SCHEME 14

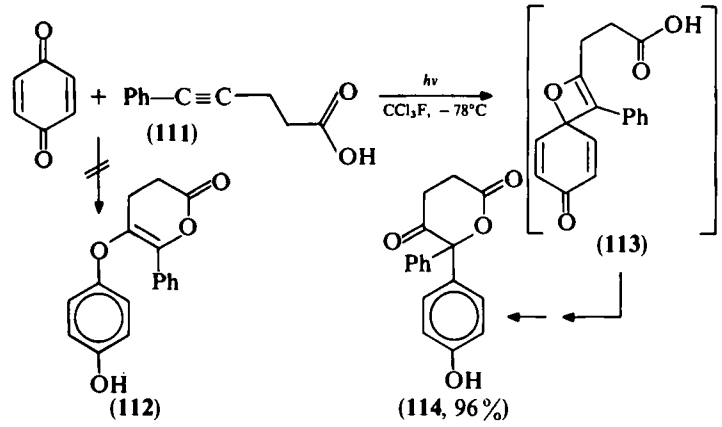
BQ–olefin charge transfer exciplex apparently has a polar character as it can be trapped by a carboxyl group both intermolecularly and intramolecularly. Thus, argon ion laser irradiation of BQ in the presence of 4-pentenoic acid (**102**, R = H) or *trans*-5-phenyl-4-pentenoic acid (**102**, R = Ph) in non-polar media affords δ-lactones **103**[212]. Formation of these products is explained in terms of intramolecular carboxylic acid trapping of the charge transfer complex (cf. **104**) (Scheme 15)[212]. Analogous products **108** and **110** are produced in the photochemical reactions of BQ with *trans*-5-phenyl-4-pentenamide (**106**) (equation 44) and 4-penten-1-ol (**109**) (equation 45), respectively. This type of collapse in a triplet charge transfer exciplex would require a tight radical ion pair, and indeed these reactions occur only in very non-polar solvents such as CCl_4 and CCl_3F[212]. On the other hand, the photoreaction of BQ with 5-phenyl-4-pentynoic acid (**111**) leads to the formation of ketolactone **114** via **113**, indicating that the polarity of the quinone–acetylene exciplex is insufficient to induce trapping by carboxylic acid to give **112** (Scheme 16)[212]. Irradiation of BQ along with cyclooctatetraene **115** in acetic acid under anaerobic conditions leads to the formation of **116** and **117** which appear to arise from a carbocationic intermediate (**118**)[209] (Scheme 17). CNDO calculations for the triplet BQ–ethylene system predict the existence of a quite stable charge transfer exciplex, in line with a mechanism involving a triplet exciplex between BQ and olefin[211].


+ R
OH
(102)
hν
R = H, 31%
−15°C, CCl4
R = Ph, 52%
−78°C, CCl3F
(103)
O–H
O⁻ H⁺
³C–T exciplex
(104)
(105)

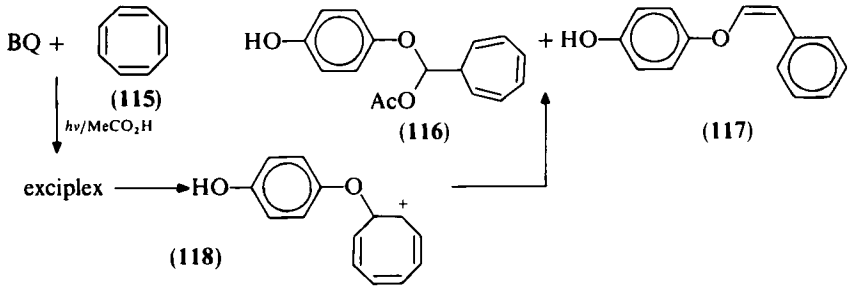
SCHEME 15


+ Ph
NH2
hν
CCl4, 0°C
NH
Ph
H2O
(106)
(107)
(108, 39%)
(44)


+
OH
hν
CCl3F, −78°C
(109)
(110, 20%)
(45)

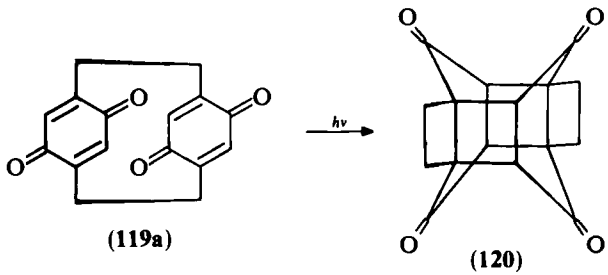


SCHEME 16

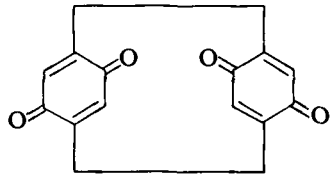


SCHEME 17

Photochemistry of cyclophane compounds **119a** and **119b** is apparently configuration-dependent; irradiation of **119a** leads to an efficient formation of cage compounds **120** in 90 % yield (equation 46), while only a higher molecular weight product is formed from **119b**[66, 213]. Photoaddition of BQ to the nitro allyl compound **121** proceeds with

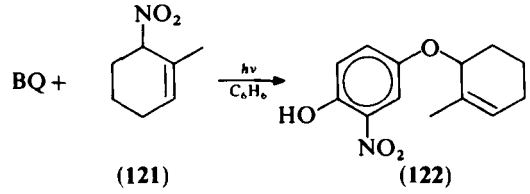


(46)

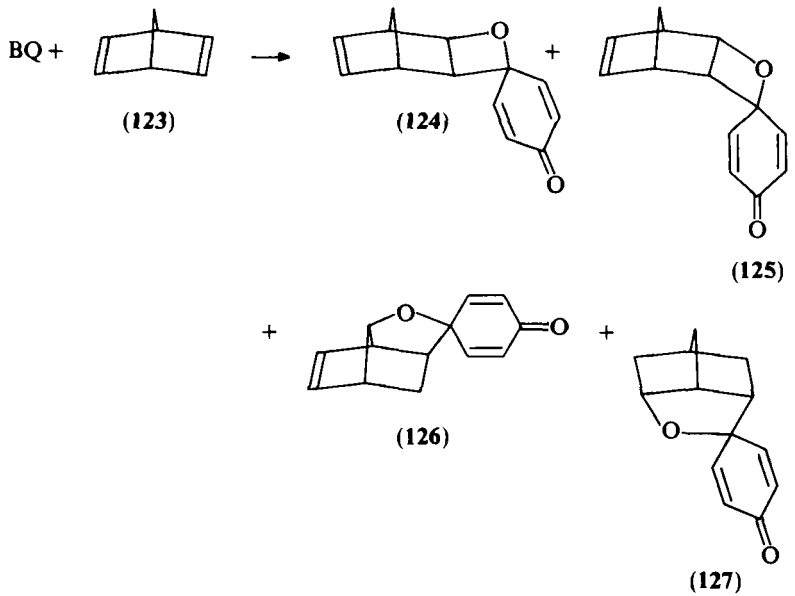


(119b)

migration of nitro group to furnish **122** in a low yield (equation 47)[214]. Photocycloaddition of BQ to norbornadiene (**123**) gives the isomeric 1:1 adducts **124**, **125**, **126** and **127** in a ratio of 48:16:21:15 (equation 48), whereas irradiation of a solution of BQ and quadricyclane under the same conditions yields a mixture of the two *exo* adducts **124** and **125** in a ratio of 56:44[215].

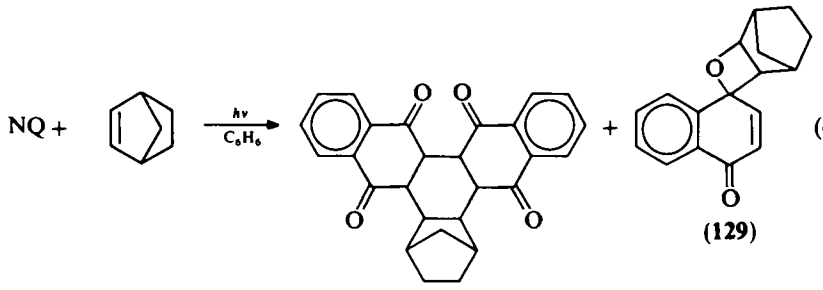


(121) (122) (47)



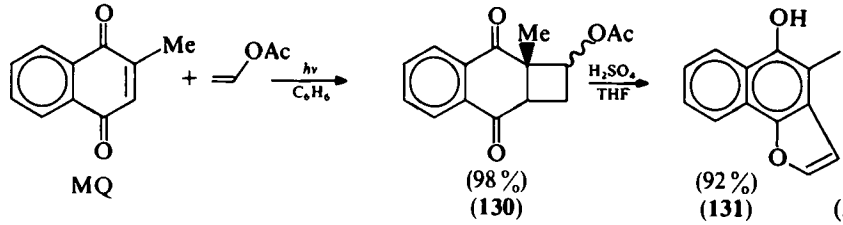
(123) (124) (125) (126) (127) (48)

An interesting example of the formation of the 2:1 adduct **128** together with the monoadduct **129** has been reported in the photoreaction of NQ with norbornene (equation 49)[216]. Although the reaction mechanism for the formation of this unusual adduct has not been revealed yet, it may be formed via the reaction of triplet exciplex between NQ and norbornene with another NQ molecule.

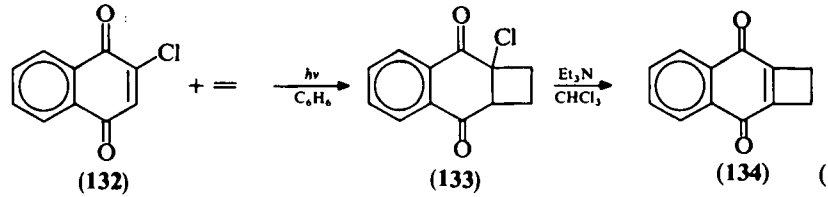


(49)

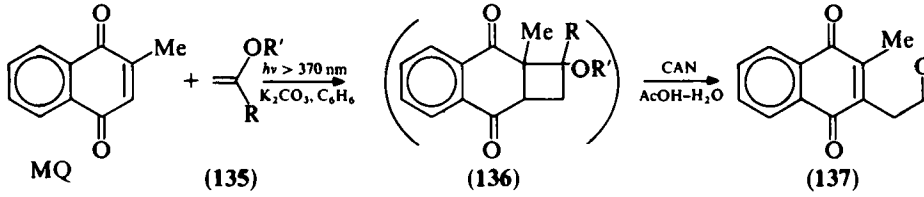
Substituted naphthoquinones such as MQ and 2-chloro-1,4-naphthoquinone (**132**) undergo facile photocycloadditions with electron-rich olefins to give the corresponding cyclobutanes **130**, **133** and **136** in good yields (equations 50–52). These cyclobutane



(50)

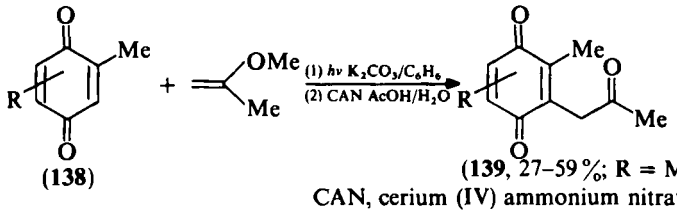


(51)



R′ = Me or $SiMe_3$ CAN, cerium (IV) ammonium nitrate (52)

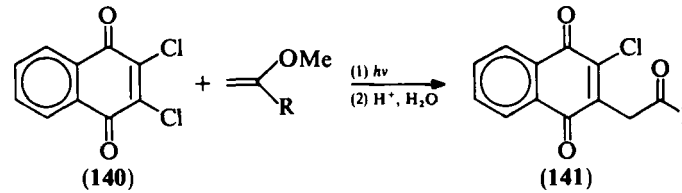
photoproducts are photo-, acid-, or base-labile, and can be transformed, depending upon their substitution patterns, into a variety of useful compounds such as naphthofurans (**131**), 1,2-dihydrocyclobuta[*b*]naphthalene-3,8-dione (**134**) and β-oxoalkyl-substituted 1,4-naphthoquinones (**137**)[217–220]. Introduction of a β-oxoalkyl chain into the *p*-benzoquinone nucleus is also achieved by this photocycloaddition method (**138** → **139**) in



(53)

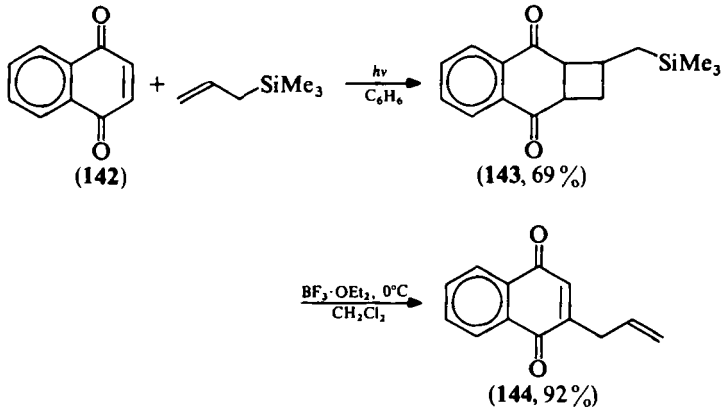
CAN, cerium (IV) ammonium nitrate

moderated yields (equation 53)[221]. Analogous β-oxoalkyl-substituted naphthoquinones (**141**) are directly formed in the photoreaction of **140** and 2-methoxy-1-alkenes (equation 54)[221]. 2-Allyl-1,4-naphthoquinone (**144**) is synthesized by a two-step sequence including

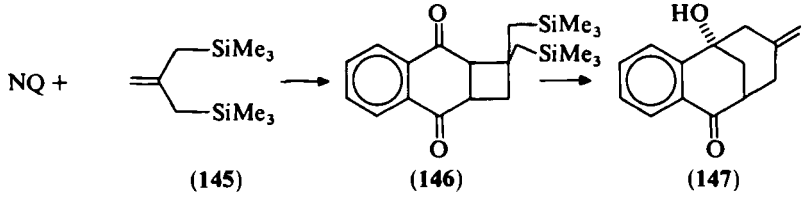


(54)

photocycloaddition of NQ to allyltrimethylsilane (**142**) and subsequent treatment of the cyclobutane adduct **143** with a Lewis acid (equation 55)[222]. The same reaction sequence with olefin **145** leads to the formation of the tricyclic compound **147** via the cyclobutane **146** (equation 56)[222].

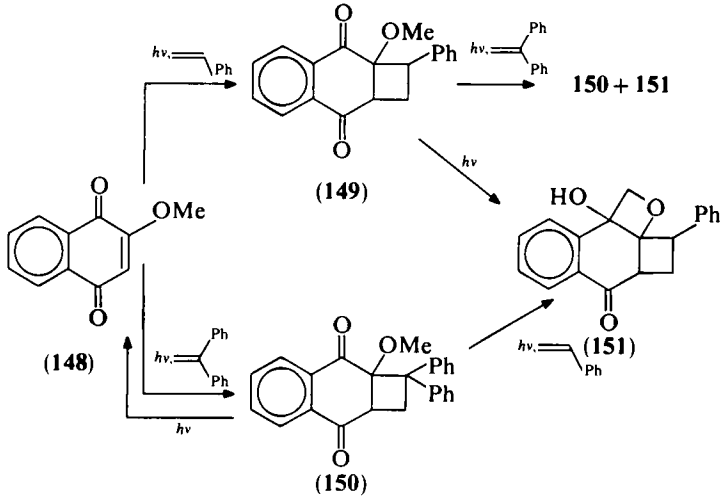


(55)



(56)

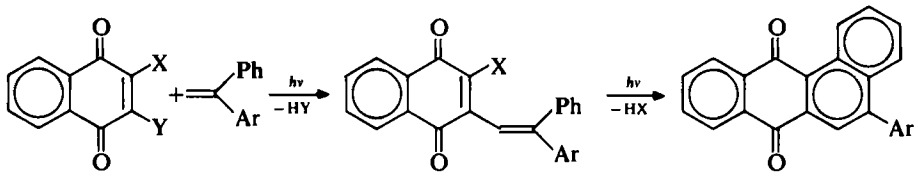
Upon irradiation, 2-methoxy-1,4-naphthoquinone (**148**) adds to styrene and 1,1-diphenylethylene in yields better than NQ[223]. Cycloadduct **149** undergoes a secondary photochemical hydrogen abstraction to yield **151**, while the same type of cycloadduct (**150**) is photochemically cleaved to the parent naphthoquinone and 1,1-diphenylethylene (Scheme 18)[223]. Thus, irradiation of **150** in the presence of styrene results in the formation of **151**.



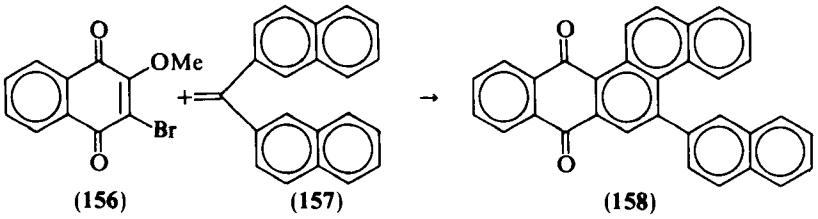
SCHEME 18

B. Addition to Olefins and Heteroaromatic Compounds via Electron Transfer

Photochemical reactions of electron-deficient 1,4-naphthoquinone **152** with 1,1-diarylethylene **153** constitute a novel synthetic route to polycyclic aromatic compounds **155** (equation 57)[224]. Typically, dinaphtho[1,2-*c*; 2,3-*e*]pyrene (**159**) is synthesized by three steps starting from **156** and **157** via this photocyclization (equation 58)[225]. The photocyclization involves two key photochemical reactions, (1) the initial substitution of an electronegative halogen atom, Y in **152**, by the ethylenic group to give an adduct **154** and (2) the subsequent $[4_\pi + 2_\pi]$ cyclization of **154** with the liberation of HX to give **155**. The first step is apparently induced by charge transfer interaction between the quinone and diarylethylene and is highly dependent upon the reduction potential of quinone and the oxidation potential of the diarylethylene. Therefore the first step competes with usual

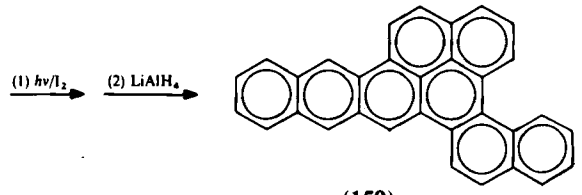


(152) (153) (154) (155) (57)



(156) (157) (158)

(58)



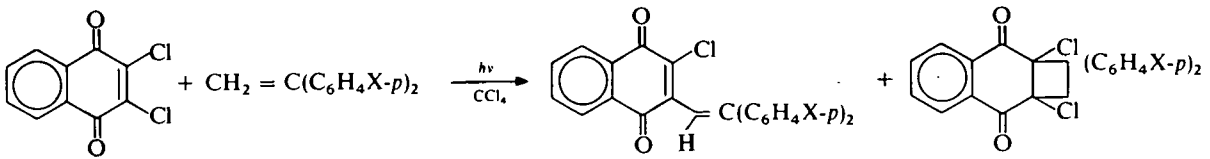
(159)

cyclobutane formation when the charge transfer interactions are weak (Scheme 19)[226]. Cyclobutane **162** is not a precursor of **161**, since it does not give **161** under the same photolytic conditions. A definitive evidence for an electron transfer process is provided by CIDNP in the reaction of **140** with **160** (X = OMe)[227]. Besides 1,1-diarylethylenes, other electron-rich heterocyclic aromatic compounds[62, 228, 229], silyl enol ether[230, 231] and dicyclopropyl ether[232] can be employed in this type of electron transfer reaction. In the photochemical reaction of **156** with dicyclopropyl ethylene (**210**), compounds **211** and **212** are obtained as the coupling products (equation 59), indicating that the coupling takes place via the ionic intermediate **213** rather than via the biradical **214**[232]. Irradiation of naphthoquinones **140**, **156** and **195** with electron-rich heterocyclic aromatic compounds such as furans, thiophenes and pyrroles give rise to the coupling of heterocycles to the naphthoquinone nucleus[62, 228, 229]. In non-polar solvents such as benzene, **140** and furan or pyrrole form charge transfer complexes, which upon photoexcitation give coupling products. Interestingly, selective excitation at the CT bands gives a better yield of the coupling products[62], in contrast to the CQ/durene and **16**/DPA systems. Preferential coupling at the α-position of these heterocycles can be explained in terms of formation of their cation radical intermediates[62, 228, 229].

Since the original report[233a] on the photochemical synthesis of 5-phenyl-7,12-benz[*a*] anthracenedione from **156** and 1,1-diphenylethylene which appeared in 1975, more than 150 new polycyclic aromatic and heteroaromatic compounds have been synthesized by this reaction. These results are summarized in Table 7.

C. Cycloaddition to Conjugated Dienes and Acetylenes

Photocycloadditions of quinones to cyclic dienes and trienes afford a variety of products, depending upon the structure of substrate[209, 240–242]. Cage compound **216** is isolated in the reaction of DQ with cycloheptatriene together with **215** (equation 60)[243]. Irradiation of furanobenzoquinone **217** along with 1,3-pentadiene produces cyclobutane **218** in good yield (equation 61)[413]. Irradiation of BQ in the presence of a ketenimine gave an imino-oxetane **219** as the primary cycloadduct and β-lactam **221** presumably via ring-opening to the diradical **220** as the secondary photoproduct. The latter photoproducts are



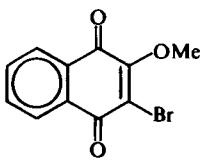
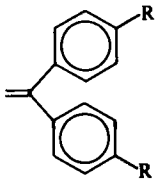
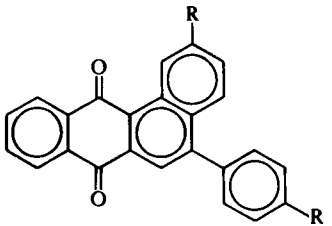
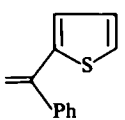
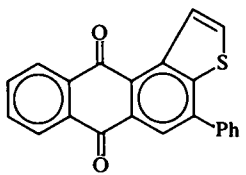
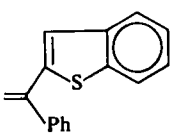
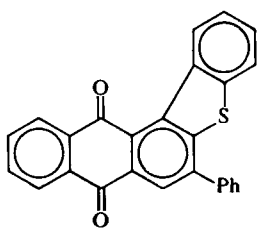
(140) **(160)** **(161)** **(162)**

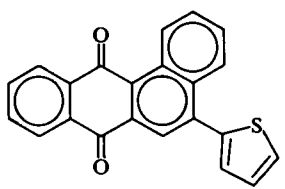
X	Product distribution (%)[a] (161)	(162)
F	17	71
Cl	11	15
H	41	0
Me	9	0
OMe	100	0

[a] Isolated yields

SCHEME 19

TABLE 7. Synthesis of polycyclic quinonoid compounds by photochemical reaction of electron-deficient quinones with double bond containing substrates

Quinone	Double bond substrate	Products (% yield)	Ref.
 (156)	 R, see text (160)	 (161) (22–68)	233
	 (162)	 (163) (62)	234, 235
	 (165)	 (166) (32)	235


(164) (8)

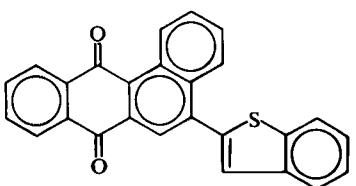
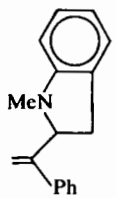
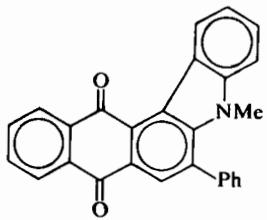
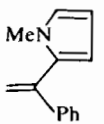
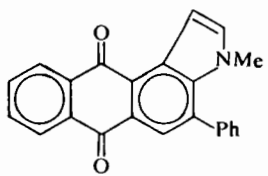
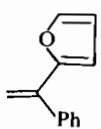
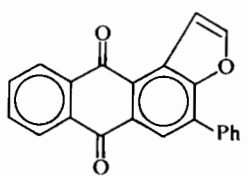
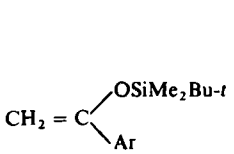
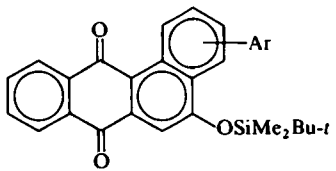
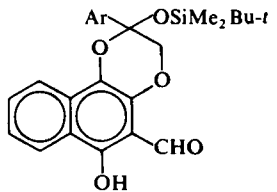
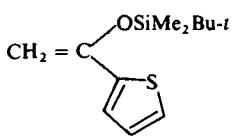
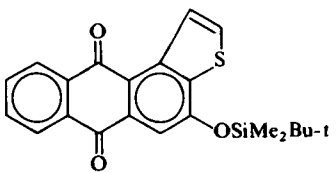
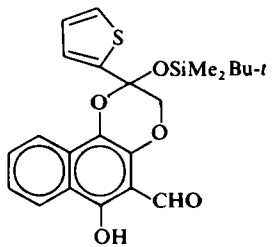
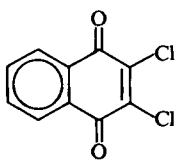
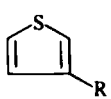
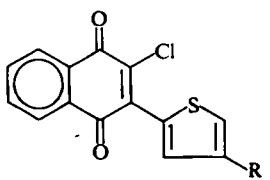

(167) (17)

TABLE 7. (*Contd.*)

Quinone	Double bond substrate	Products (% yield)	Ref.
	 **(168)**	 **(169)** (61)	235, 236
	 **(170)**	 **(171)** (50)	235
	 **(172)**	 **(173)** (30)	235

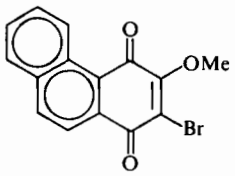
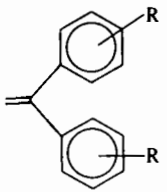
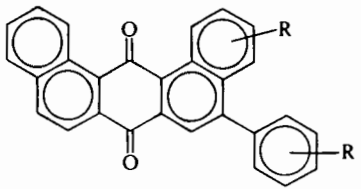
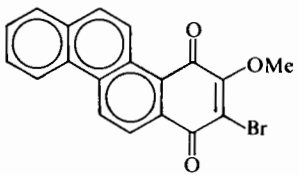
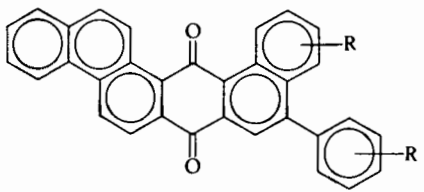
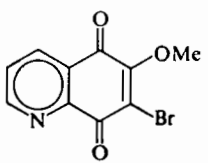
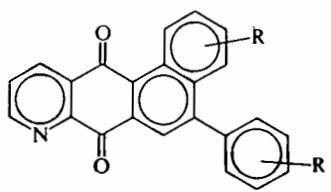
235
237
238
230
(174)
(175) (4)
Ph— ≡ —H
(176)
(177) (63)
(178)
(179) (36–51)
(156)
(180)
(181) (21–28)
(182) (12–21)

TABLE 7. (*Contd.*)

Quinone	Double bond substrate	Products (% yield)	Ref.
	 (183)	 (184) (12–24)  (185) (4–10)	231
	 (186)	 (187) (24)  (188) (5)	231
 (140)	 (189)	 (190) (R = H, 57) (R = Me, 53)	228

62
229
229
229
(156)
(191)
(192) R = H, Me, CH2OMe, CH2OEt (22–92)
(193)
(194) (64)
(193)
(196) (75)
(195)
(156)
(197)
(198) (50)
(199) (10)

TABLE 7. (*Contd.*)

Quinone	Double bond substrate	Products (% yield)	Ref.
 (200)	 (160) R = H, *o*-Me, *m*-Me, *p*-Me, *m*-OMe, *p*-OMe	 (201) (14–23)	226
 (202)	(160)	 (203) (19–42)	226
 (204)	(160)	 (205) (17–44)	226 239b

(206)

(160)

226
239b

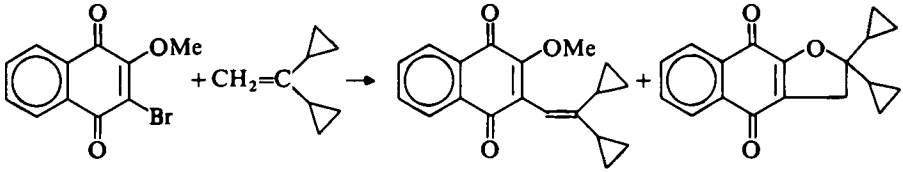
(207) (7–13)

(208)

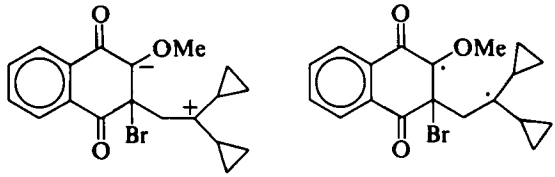
(160)

226

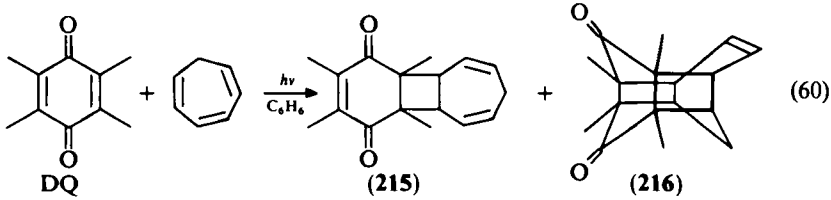
(209) (4–23)



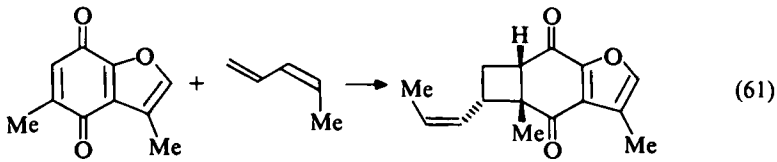
(156) (210) (211) (212) (59)



(213) (214)

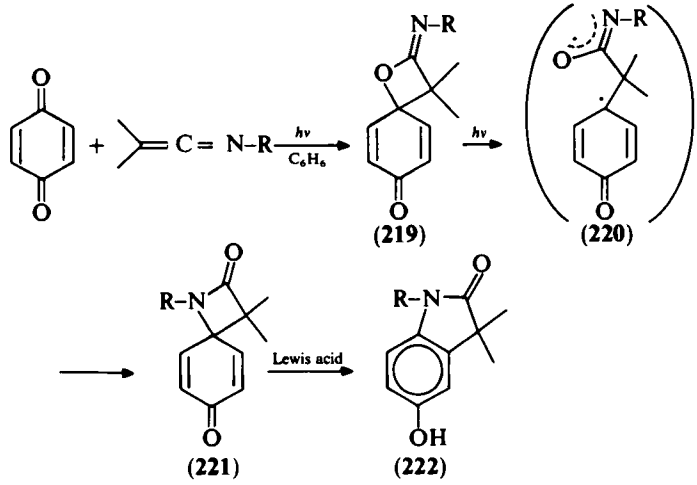


DQ (215) (216) (60)

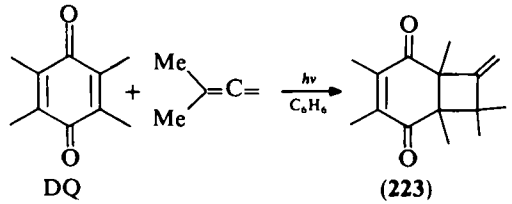


(217) (218, 65%) (61)

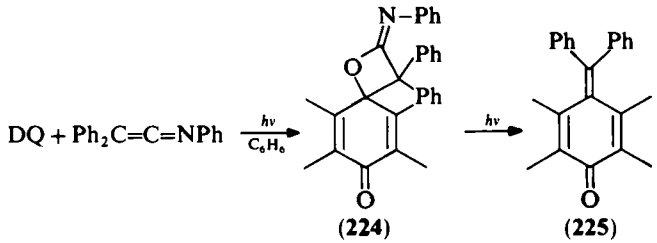
extremely acid-labile, being transformed into **222** upon treatment with a Lewis acid (equation 62), and are isolated by direct crystallization from the reaction mixture[244, 245]. On irradiation in the presence of 1,1-dimethylallene, DQ affords cyclobutane **223** exclusively (equation 63), whereas photocycloaddition to triphenylketenimine occurs at the carbonyl function of DQ to give **224** in spite of its (π, π^*) triplet excited state[246]. Prolonged irradiation of **224** leads to the formation of duroquinone diphenylmethide (**225**) (equation 64). Analogous iminooxetane adduct **226** is formed in the reaction of DQ with dimethyl-*N*-phenylketenimine. However, the photochemistry of **226** is quite different from either that of **218** or **223**, in that it gives lactoneimine (**228**) upon irradiation presumably via **227**[246]. Hydrolysis gives **229** (equation 65). Oxetanone adduct **230** is produced (together with the cyclobutanones **231** in the case of DQ) in the photochemical reaction of tetra-substituted quinones such as DQ, CQ and AQ, with diphenylketene, although their lowest triplet excited states are (π, π^*) (Scheme 20). These results are explained in terms of dipole–dipole interaction of the reactants[247].



(62)



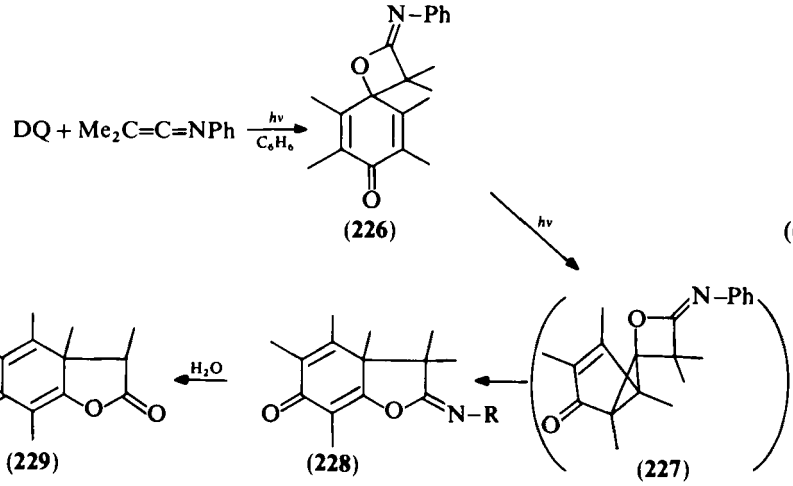
(63)

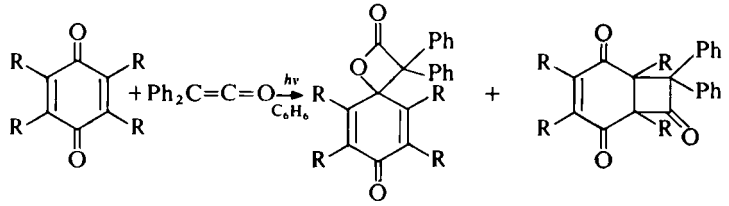


(64)

Anthraquinone **1** (R = NH_2), whose lowest excited state is an intramolecular charge transfer (π, π^*) state, undergoes a cycloaddition reaction with dienes in ethanol to produce the corresponding oxetane (**232**) when subjected to visible-light irradiation (equation 66)[248–250]. Apparently this reaction is not a conventional photocycloaddition via the (n, π^*) triplet state of the quinone, since it is not affected by the presence of triplet quenchers such as dissolved oxygen and anthracene[249]. Singlet exciplex between the aminoanthraquinone and the diene is proposed as the key intermediate, based on the fluorescence quenching of **1** (R = NH_2) by the diene[250].

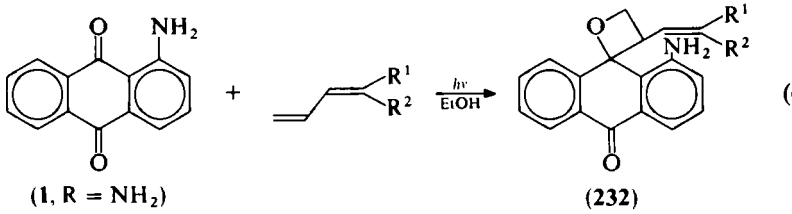
Naphthoquinones (**233**) undergo photocycloaddition with acetylenes to give cyclobutenes **234** (equation 67)[251, 252].





Quinone	Yield (%) 230	231
DQ R = Me	49	25
CQ R = Cl	38	—
AQ R − R = -(CH = CH)$_2$	53	—

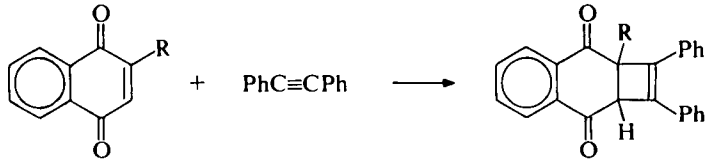
SCHEME 20



(66)

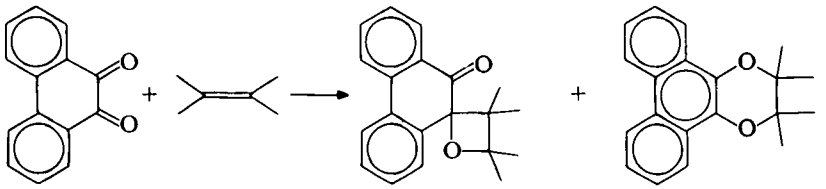
D. Cycloaddition of *o*-Quinones to Alkenes and Alkynes

Photocycloaddition of PQ to olefins gives mainly two types of products, the keto oxetane **235** and the 1,4-dioxine **236** along with H-abstraction products (equation 68)[253-255]. Keto oxetane **235** predominates in the reaction with highly strained olefins[256]. With 1-methoxypropyne, PQ affords a 1,3-dioxole adduct **238** via a 1,2-H shift



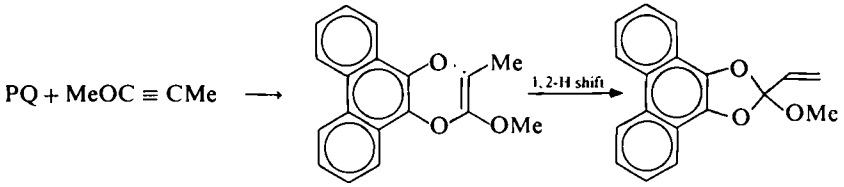
R = OMe, Cl, Br

(233) (234) (67)

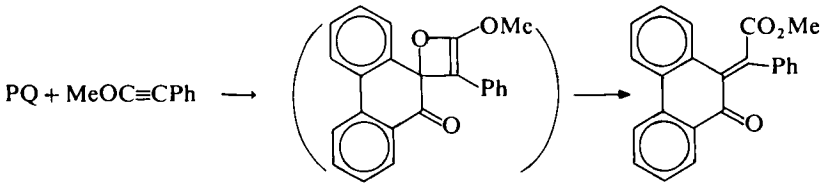


PQ (235) (236) (68)

in the intermediate **237** (equation 69)[257], while α,β-unsaturated keto ester **240** is formed in the reaction with methoxyphenylacetylene, presumably by way of keto oxetane **239** (equation 70)[258]. In the reaction with conjugated alkenynes, PQ and *o*-CQ add to the double bond predominantly rather than to the triple bond[259]. Thermal and photochemical additions of PQ to alkylthio- and dialkylamino-substituted acetylenes were reported[260].



(237) (238) (69)



(239) (240) (70)

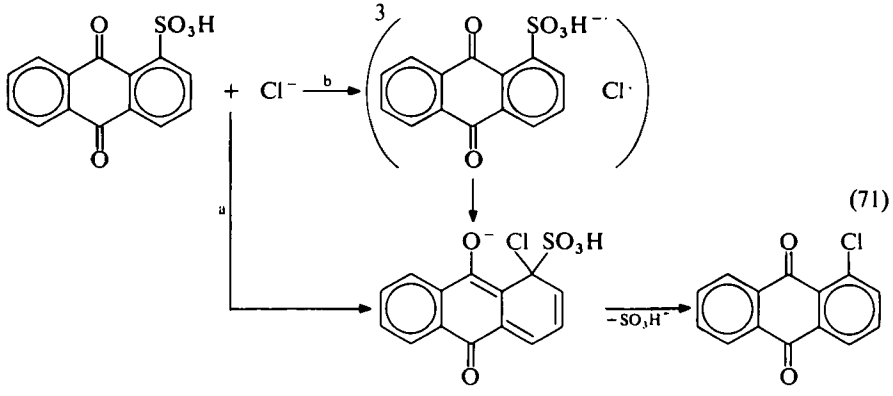
V. PHOTOSUBSTITUTION

Many types of photochemical substitution reactions have been discovered mainly in anthraquinone systems, which have been extensively studied because of their structural

relationship to vat dyes. Photosubstitution reactions discussed in this section include the displacement of halogen, alkoxy group, or a sulfonate group by other groups as well as the displacement of hydrogen by an amino group (photoamination), a hydroxy group (photohydroxylation), or a sulfonate group (photosulfonation). In the displacement of hydrogen, photosubstitution often gives predominantly one isomer, which is difficult to synthesize by thermal reactions. In order to clarify the mechanism of the photosubstitution, one must examine many parameters such as the nature of the excited states of the quinones (singlet or triplet), the dependence of the reaction rates or the product distributions on the presence of additives such as oxygen or amines, on the solvent polarity, and on the HOMO or LUMO coefficients of the reactive intermediates involved. The photosubstitution mechanisms are very versatile, and involve a direct addition of a nucleophile to the excited quinone, an electron transfer or a charge transfer induced substitution, or aromatic radical substitution by photogenerated free radicals. Photosubstitutions of quinones are classified to two main groups according to the nature of the excited state of the quinone. Group 1 is a photosubstitution of quinones having the lowest (n, π^*) excited state (strong sensitizer according to the classification of Phillips[39]) and group 2 is a photosubstitution of quinones having the lowest (π, π^*) or CT state (weak sensitizer). In the former case, a direct nucleophilic substitution in the excited state is difficult, since the excitation energy is localized at the carbonyl group. Normally, an electron transfer or a charge transfer reaction precedes the photosubstitution of group 1. In contrast, many examples of direct nucleophilic substitution have been reported for group 2. The results are summarized in Table 8.

A. Substitution of a Sulfonate Group

The irradiation of anthraquinone-1-sulfonate (**1**, R = SO_3^-) in aqueous solutions containing chloride ions or ammonia gives rise to substitution of the sulfonate group by a chlorine atom or by an amino group, respectively[261-264]. Two hypotheses have been put forward concerning the reaction pathways in these processes. The first involves a direct nucleophilic substitution of the sulfonate group by Cl^- or NH_3 by way of intermediate **241** or the analogous zwitterion with ammonia (equation 71a). The second involves an aromatic radical substitution, where a chloride radical generated by electron transfer from Cl^- to the excited molecule of **1** (R = SO_3^-) attacks the 1-position of **1** in the ground state. The adduct **241** can be then formed by in-cage recombination of radical ion-pairs



(241)

TABLE 8. Photosubstitution reactions of quinones

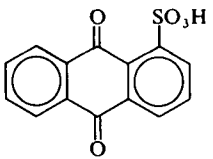
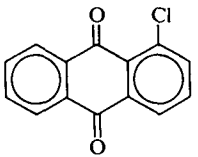
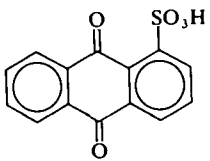
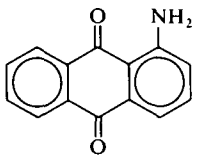
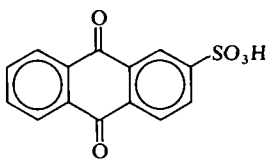
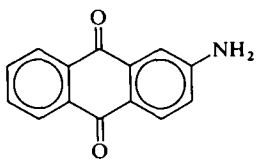
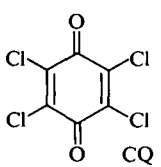
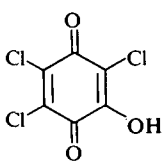
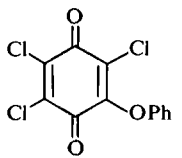
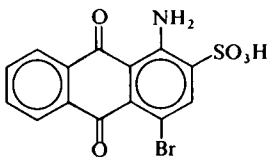
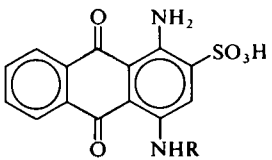
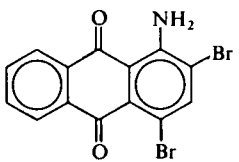
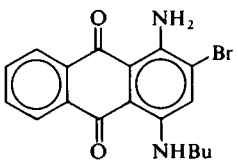
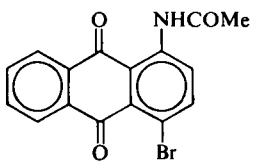
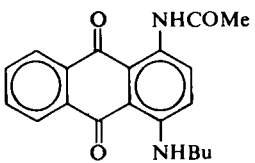
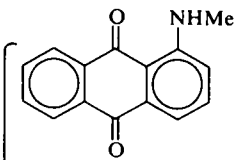
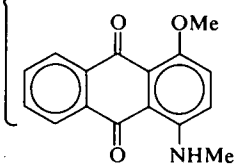
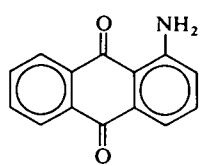
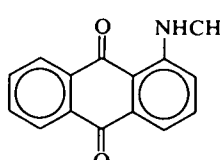
Reaction mode	Starting quinone	Conditions	Product quinone (isolated yield, %)		Ref.
$SO_3H \rightarrow Cl$		Cl^-/H_2O			6, 7
$SO_3H \rightarrow NH_2$		NH_3/H_2O		(45)	6, 7, 264
		NH_3/H_2O		(60)	264
$Cl \rightarrow OR$		EtOH		(28)	300

TABLE 8. (*Contd.*)

Reaction mode	Starting quinone	Conditions	Product quinone (isolated yield, %)		Ref.
	CQ	PhOH		(30)	300
Br → NHR	 (242)	RNH_2/O_2 $MeCN/H_2O$	 (243)		265–267
	 (244)	$BuNH_2/O_2$ $MeCN/C_6H_6$	 (245)	(41.7)	269
	 (246)	$BuNH_2$ $EtOH/C_6H_6$	 (247)	(92)	268, 270

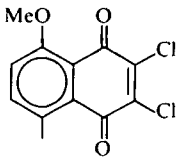
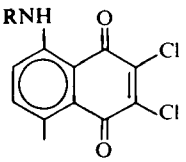
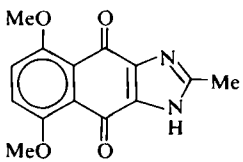
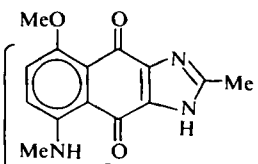
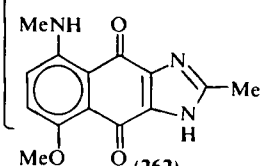
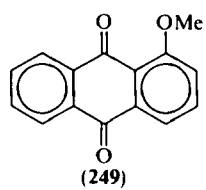
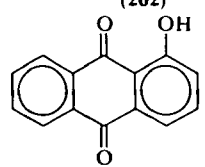
NH2
X
(248, X = Cl, Br)
Aqueous NH3
EtOH
301
Cl → OH
Cl
97% H2SO4
(62)
+ other hydroxylated product (16)
271
OMe → NHR
OMe
(249)
NH3
H2O/MeCN (1:1)
(96)
(0.5)
272, 273

TABLE 8. (*Contd.*)

Reaction mode	Starting quinone	Conditions	Product quinone (isolated yield, %)	Ref.
	(249)	$MeNH_2$ $H_2O/MeCN$ (1:1)	 (81)  (7)	272, 273
	(249)	^-NCO $H_2O/MeCN$ (1:1)	 (87)	273
	(249)	$HOCH_2CH_2NH_2$ $H_2O/MeCN$ (1:1)	 (30) (250)	273

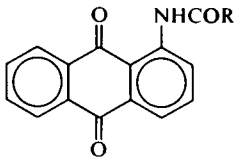
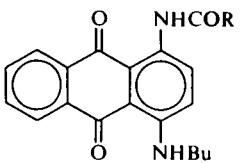
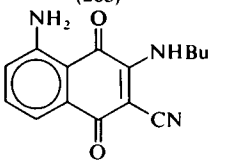
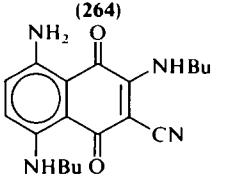
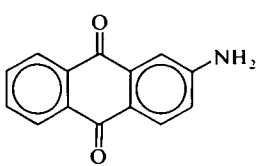
273
NH3/air
H2O/MeCN
(251)
NH2
(22)
NH2
OMe
(18)
(252)
NH3/N2
273
MeNH2/air
H2O/MeCN
(251)
NHMe
(4)
NHMe
OMe
(34)
(255)
302
RNH2/CH2Cl2
(256)
NHR
(2–51)
OMe
(257)

TABLE 8. *(Contd.)*

Reaction mode	Starting quinone	Conditions	Product quinone (isolated yield, %)		Ref.
	 (258)	RNH_2/CH_2Cl_2	 (259)	(38)	274
	 (260)	$MeNH_2/CH_2Cl_2$	 (261)	(53)	303, 304
			 (262)	(30)	
OMe → OH	 (249)	^-OH, air $H_2O/MeCN$ (1:1)		(84)	273

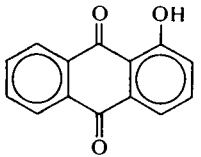
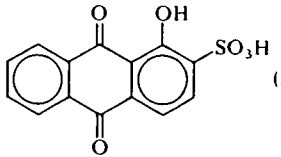
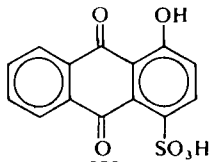
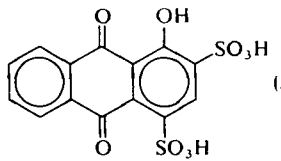
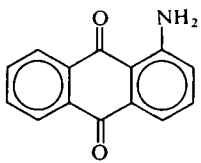
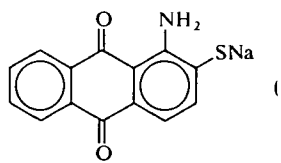
OMe
O
O
(251)
H → Cl
(249)
$^-$OH, air
H_2O/MeCN (1:1)
(7)
OH
273
Cl$^-$
H_2O/MeCN (1:1)
(7)
OMe
Cl
273
H → NHR
OMe
O
O
MeNH$_2$
−40°C
CH_2Cl_2
(66)
OMe
NHMe
275
MeO
MeNH$_2$
−40°C
CH_2Cl_2
(3)
275
AQ
Pyridine
(20)
N
(268)
126

TABLE 8. (*Contd.*)

Reaction mode	Starting quinone	Conditions	Product quinone (isolated yield, %)	Ref.
	 (263)	$BuNH_2/O_2$ C_6H_6	 (264) (R = Ph, 64) (R = *p*-$NO_2C_6H_4$, 58) (R = Me, 71) (R = Et, 77) (R = *n*-Pr, 78) (R = PhCH = CH, 60) (R = EtO, 60)	276
	 (265)	$BuNH_2/O_2$ C_6H_6	 (266) (91)	277
	AQ	NH_3/O_2 H_2O-2-PrOH	 (33)	278 279
H → OH	AQ	conc. H_2SO_4 100%	1 (R = OH) (30–32) 2 (R = OH) (65–66)	282
		96% H_2SO_4[a]	1 (R = OH) (7)[e], (11)[d] 2 (R = OH) (74)[e], (85)[d]	282
		90% H_2SO_4[b]	1 (R = OH) (14)[e], (16)[d] 2 (R = OH) (71)[e], (81)[d]	282
		98% H_2SO_4	1 (R = OH) (68)	281

77% H_2SO_4
(81)
305
H_2O
306
t-$BuNH_2/O_2$
C_6H_6
(81)
277
Na_2SO_3
Pyridine/H_2O
R = H, (92.6)
R = Cl, (96)
294, 295
$H \rightarrow SO_3H$
Na_2SO_3
Pyridine/H_2O
(18)
294, 295
(265)
(267)
(269)

TABLE 8. (*Contd.*)

Reaction mode	Starting quinone	Conditions	Product quinone (isolated yield, %)	Ref.
		Na_2SO_3 Pyridine/H_2O	 (31) (271)	295
			 (18) (272)	
			 (24) (273)	
H → SNa		Na_2S Pyridine/H_2O	 (70) (274)	295

[a] Besides quinone products, anthrone and bianthronyl were formed in 6 and 13% yields, respectively under N_2 atmosphere.
[b] Besides quinone products, anthrone and bianthronyl were formed in 10 and 5% yields, respectively under. N_2 atmosphere, and bianthronyl was formed in 2% yield even under O_2 atmosphere.
[c] Under N_2 atmosphere.
[d] Under O_2 atmosphere.

generated by electron transfer (equation 71b). However, the radical substitution mechanism does not seem to explain fully the high regioselectivity of the substitution reactions.

B. Substitution of Halogen Atom

Photosubstitutions proceed very well in the photolysis of anthraquinones whose lowest singlet or triplet excited states are (π, π^*). The displacement of the bromine from 1-amino-4-bromoanthraquinone-2-sulfonic acid (**242**) by ammonia or alkylamines has been reported [265-267]. Under similar conditions, 1-bromoanthraquinone whose lowest singlet or triplet excited state is (n, π^*) is inert. The fact that the rate of the photosubstitution increases as the polarity of the solvent is increased is evidence for a polar intermediate. Interestingly, the photosubstitution does not occur without oxygen. Oxygen probably does not act as a simple oxidizing agent but forms exciplex with the singlet (π, π^*) of **242**[267]. 1-Amino-2,4-dibromoanthraquinone (**244**) is similarly photoaminated to give **245** but the multiplicity of the (CT) states responsible for the reaction is mainly singlet in acetonitrile and in ethanol but triplet in benzene[268-270]. In the former solvents, oxygen increases the reaction rates through the formation of exciplex but it acts as a triplet quencher in the latter solvent. This change in nature of the reactive excited state is attributed to a change in the disposition of the energy levels of the substrate when the solvent polarity is altered (Figure 4).

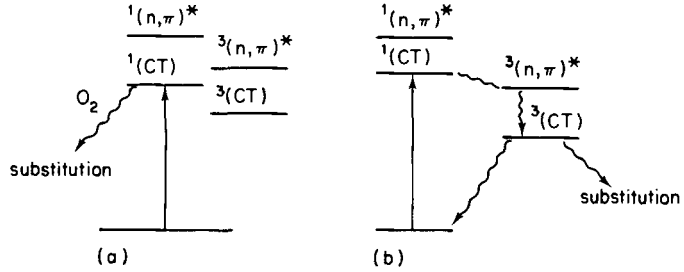
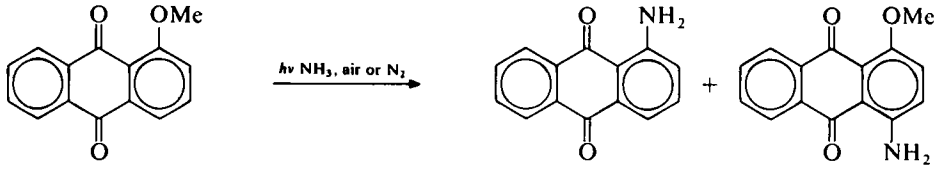


FIGURE 4. Energy diagram of **244**; (a) in MeCN or in EtOH; (b) in C_6H_6

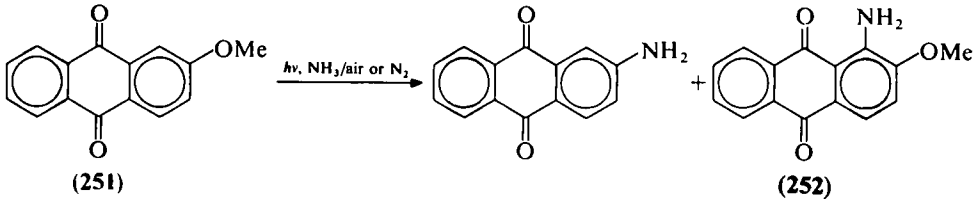
Photolysis of 1-chloroanthraquinone (**1**, R = Cl) in 97 % sulfuric acid affords mainly 1-hydroxyanthraquinone (**1**, R = OH) along with minor hydroxylated products, while 2-chloro and 2-bromoanthraquinone give no dehalogenated products[271]. Reaction of **1** (R = Cl) with Fenton's reagent gives mainly hydroxydeprotonated products, but does not give the dehalogenated hydroxylation product, precluding a simple aromatic substitution by a free hydroxy radical.

C. Substitution of Alkoxy Group

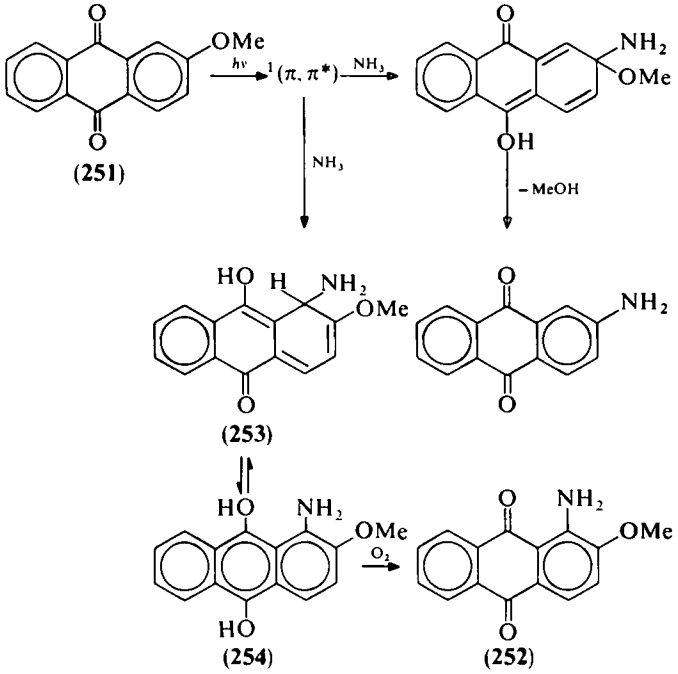
Photosubstitution of 1-methoxyanthraquinone (**249**) with ammonia gives 1-aminoanthraquinone in 96 % yield (equation 72), while under identical conditions 2-methoxyanthraquinone (**251**) reacts less rapidly to give 2-aminoanthraquinone and 1-amino-2-methoxyanthraquinone (**252**) whose relative proportions depend on the availability of oxygen during the reaction (equation 73)[272,273]. These substitution reactions are not affected by the presence of a radical scavenger. Formation of **252** involves formal replacement of hydrogen by an amino group and a possible mechanism is shown in Scheme 21. The leuco-compound **253** formed by the direct nucleophilic addition of



(249) (72)



(251) (252) (73)

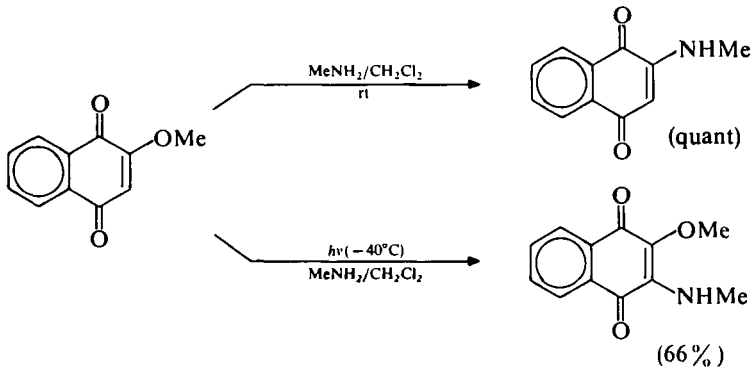


(251) (253) (254) (252)

SCHEME 21

ammonia to the singlet (π, π^*) excited state of methoxyanthraquinone would be oxidized by dissolved oxygen, in agreement with the observation that oxygen favors the formation of **252**. Whereas thermal reaction of 2,3-dichloro-5,8-dimethoxy-1,4-naphthoquinone (**258**) with methylamine leads to halogen replacement, the photochemical reactions result

in methoxy replacement to give **259** only[274]. Irradiation of 2-methoxy-1,4-naphthoquinone in the presence of methylamine results in the formation of 2-methoxy-3-methylamino-1,4-naphthoquinone in contrast to the exclusive replacement of the 2-methoxy group by the thermal reaction (equation 74)[275]. 2,6-Dimethoxy-1,4-



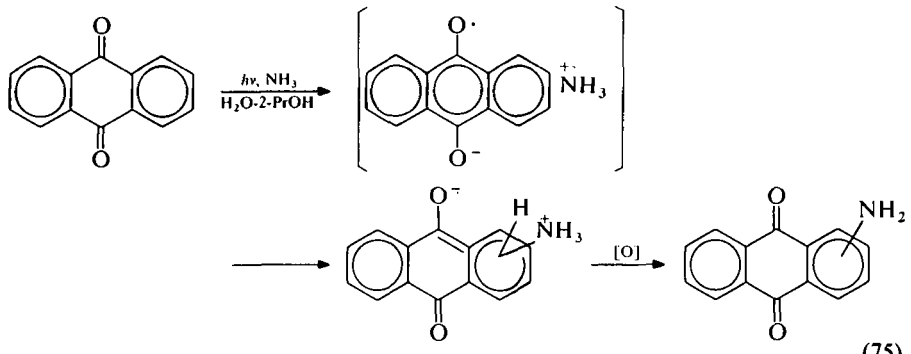
(74)

benzoquinone shows a similar reactivity[275]. These results are consistent with a direct nucleophilic addition of amines to the (π, π^*) excited state of the quinone, since there is a significantly larger decrease in a calculated electron density at the 3-position than the 2-position of 2-methoxy-1,4-naphthoquinone in its lowest excited (π, π^*) state.

D. Substitution of Hydrogen

1. Photoamination

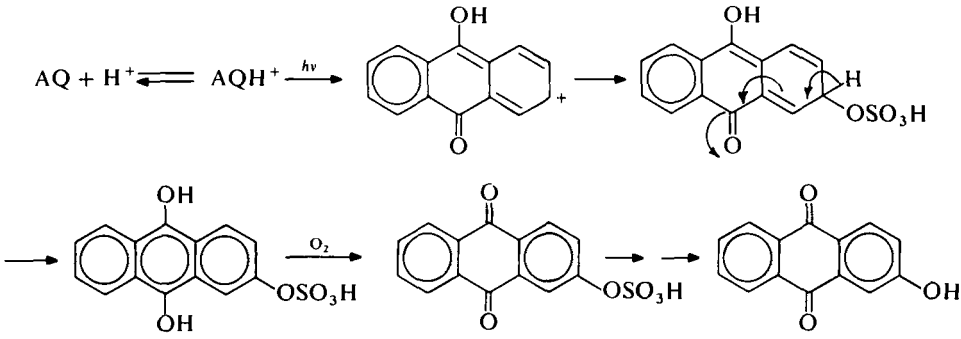
Photosubstitutions involving replacement of hydrogen by an amino group are of apparent synthetic importance. Photochemical reaction of 1-acylaminoanthraquinones (**263**, R = Ph, *p*-$O_2NC_6H_4$, Me, Et, *n*-Pr, PhCH = CH, EtO) with primary aliphatic amines gives the corresponding 1-acylamino-4-alkylaminoanthraquinones **264** in 56–78 % yields[276]. Based on the sensitivity of the reaction to the steric hindrance of the amines used and the need for oxygen, a mechanism involving a HOMO-controlled addition of alkylamine to the triplet excited (CT) of **263**, followed by oxidation to give **264** was proposed. The 5-amino-naphthoquinone **265** is selectively alkylaminated or hydroxylated at the 8-position by photochemical reaction[277]. Alkylamination occurs on irradiation of a benzene solution of **265** and a primary alkylamine under a nitrogen atmosphere, while hydroxylation has been achieved upon irradiation in the presence of a tertiary alkylamine in the presence of oxygen. Tertiary alkylamines do not add to **265** due to steric hindrance, but are essential for the hydroxylation[277] (Table 8). Anthraquinone itself[278, 279] as well as chlorinated anthraquinones[308] can be photochemically aminated in aqueous ammonia solutions containing organic solvents such as 2-propanol or dioxane under aerated conditions. Electron transfer from ammonia to triplet AQ followed by in-cage combination would give the intermediate **268** which would then be oxidized by oxygen to the aminoanthraquinone (equation 75). When a similar photolysis is conducted in acetonitrile–aqueous ammonia solution, adduct **37** is formed along with the direct amination product (equation 14)[82].



(268) (75)

2. Photohydroxylation

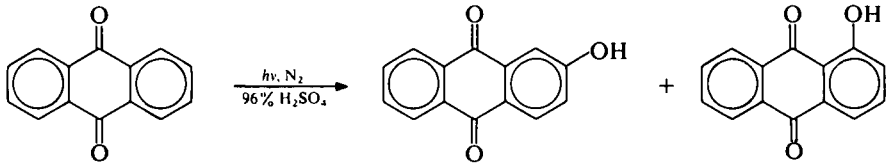
AQ is readily photohydroxylated in concentrated sulfuric acid to give 2-hydroxyanthraquinone **2** (R = OH) as a major product[280–283]. Nucleophilic addition of an hydrogen sulfate ion to the photoexcited conjugated acid of AQ is suggested (Scheme 22)[281]. However, detailed examination of this reaction has shown that besides **2**



SCHEME 22

(R = OH) other minor products such as 1-hydroxyanthraquinone, polyhydroxyanthraquinone and reductive products such as anthrone and bianthronyl are also formed and that the yields of these minor products are markedly influenced by the presence of water and oxygen in the sulfuric acid (equation 76)[282, 284]. It seems therefore that the mechanism of photohydroxylation of AQ in sulfuric acid is more complex than that shown in Scheme 22. An alternative mechanism initiated by an electron transfer from a bisulfate ion to the photoexcited AQ is also proposed. In this mechanism, hydroxylated products would arise by oxidation of the sulfate radical–AQ adduct, and polyhydroxy derivatives would result from interception of the sulfate radical adduct by oxygen. However, a definite conclusion regarding the mechanism of the overall reaction has not yet been established.

The photohydroxylation of ASQ and ADSQ is a topic that has attracted the interest of several groups over the years[44, 78, 90, 283, 285–290]. A considerable amount of work has been devoted to this reaction under aerobic and anaerobic conditions and three alternative



(76)

mechanisms have been proposed. Since the intersystem crossing is highly efficient[44], all three mechanisms start with the triplet ASQ. The first mechanism, which is favored by the Russian school[6, 7], involves a free hydroxy radical produced by the reactions of equations 77 and 78, which attacks ground state ASQ to give an hydroxy–ASQ radical adduct. The involvement of a hydroxylated radical adduct ASQOH· and its decay to permanent hydroxyanthraquinone (equations 80 and 81) is a common feature of all the three mechanisms.

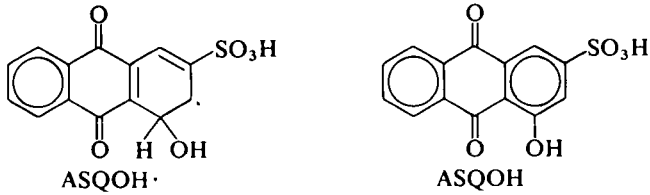
$$^3(ASQ)^* + H_2O \rightarrow ASQ^{-\cdot} + HO^{\cdot} + H^+ \quad (77)$$

$$^3(ASQ)^* + HO^- \rightarrow ASQ^{-\cdot} + HO^{\cdot} \quad (78)$$

$$ASQ + HO^{\cdot} \rightarrow ASQOH^{\cdot} \quad (79)$$

$$ASQOH^{\cdot} + O_2 \rightarrow ASQOH + {}^{\cdot}OOH \quad (80)$$

$$2ASQOH^{\cdot} \rightarrow ASQOH + ASQ + H_2O \quad (81)$$



In the second mechanism, it has been assumed, on the basis of the dependence of the quantum yield on the ASQ concentration, that electron transfer between triplet excited ASQ and ground state ASQ occurs as the primary step and subsequent oxidation of water by the $ASQ^{+\cdot}$ generates the hydroxy radical (equations 82 and 83).

$$^3(ASQ)^* + ASQ \rightarrow ASQ^{+\cdot} + ASQ^{-\cdot} \quad (82)$$

$$ASQ^{+\cdot} + H_2O \rightarrow ASQ + HO^{\cdot} + H^+ \quad (83)$$

However, a comparative study of the effects of pH and various hydroxy radical scavengers

on the photolysis and γ-radiolysis of aqueous solution of ASQ seems to be at variance with these free hydroxy radical mechanisms[124, 283, 289, 291, 292]. In addition, the second mechanism should be unfavorable on energetic grounds[6,7]. Consequently, a third mechanism is suggested, whereby $^3(AQS)^*$ undergoes photosolvation to form a water–ASQ adduct which, upon reaction with ground state ASQ, gives the hydroxylated radical (equations 84 and 85).

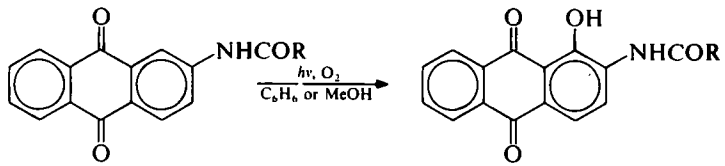
$$^3(ASQ)^* + H_2O \rightarrow (ASQ\cdots H_2O) \quad (84)$$

$$(ASQ\cdots H_2O) + ASQ \rightarrow ASQOH + ASQ^{-\cdot} + H^+ \quad (85)$$

Recently the photohydroxylation of ASQ has been subjected to an intensive investigation involving laser photolysis, steady-state reactions and study of the inhibition of the photohydroxylation by inorganic anions[44, 78, 90]. $^3(ASQ)^*$ and two other intermediates were detected and the decay of the former was found to be independent of the initial ASQ concentration whereas the latter products were formed in parallel reactions of the triplet species with water[78]. One of the intermediates (λ_{max} = 600 nm) appears to react with ground-state ASQ, and this reaction is considered to lead to the photohydroxylation process, in line with the third mechanism (equations 84 and 85)[78].

Anthraquinone itself is photohydroxylated in water–2-propanol (1:2) solutions. The efficiency of the reaction is greatly reduced by deaeration of the reaction solutions and is enhanced by addition of hydroxide ion[124, 291].

Another type of photohydroxylation has recently been described, whereby 2-acylaminoanthraquinone is hydroxylated in either benzene or methanol with high selectivity at the 1-position under aerated conditions (equation 86)[293]. Apparently the hydroxylation takes place on account of oxygen dissolved in the organic solvent, although the detailed mechanism has not been studied.



(86)

R = Ph, Me or CF_3

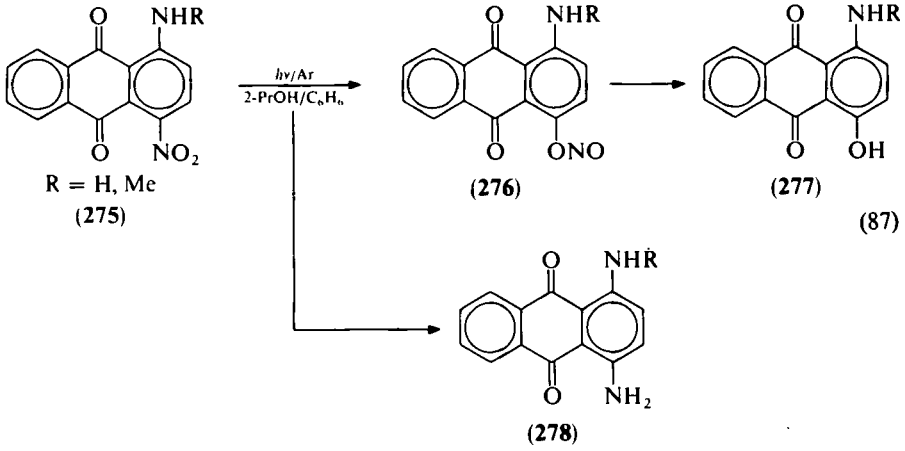
3. *Photosulfonation*

Photosulfonation of 1-amino- or 1-hydroxyanthraquinone has been reported[294, 295]. Irradiation of 1-aminoanthraquinone and sodium sulfite in aqueous pyridine with visible light results in the formation of 1-aminoanthraquinone-2-sulfonate (**269**) in 92.6% yield (Table 8). When the *ortho* position to the amino group is blocked, little or no reaction occurs. Initial electron transfer from the sulfite ion to the excited anthraquinone will give an SO_3 radical which will attack the anthraquinone in the ground state. On the other hand, 1-hydroxyanthraquinone gives a mixture of the 2-sulfonate **271** (31%), the 4-sulfonate **272** (18%), and the 2,4-disulfonate **273** (24%). The different substitution pattern observed for 1-aminoanthraquinone and 1-hydroxyanthraquinone has been rationalized by application of semiempirical molecular orbital theory[295].

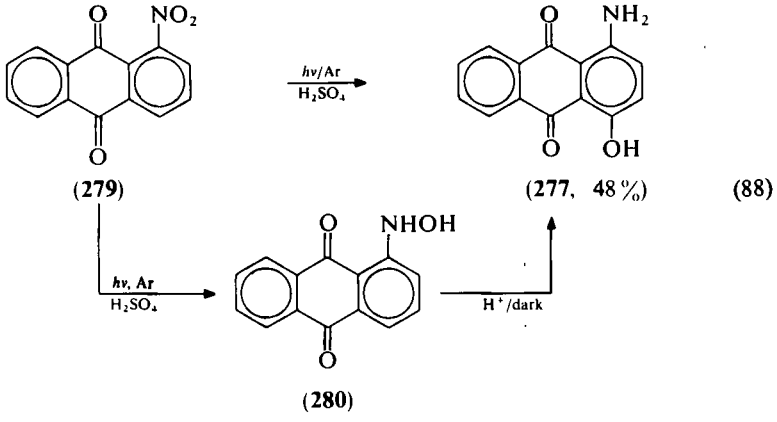
E. Miscellaneous

Photochemical transformation of 1-amino- and 1-methylamino-4-nitroanthraquinone **275** to 1-amino- and 1-methylamino-4-hydroxyanthraquinone **277** has been reported[296].

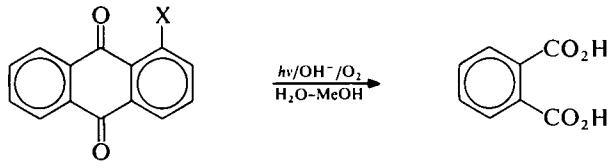
A nitro–nitrite photorearrangement **275** → **276** was suggested to explain these reductive substitutions[296]. However, in aqueous 2-propanol, a reduction of the 4-nitro group to give **278** occurs concurrently with the nitro–nitrite rearrangement (equation 87). It seems likely that the former process occurs from the (n, π^*; NO_2) electronic configuration. Support for this interpretation have been obtained by several sensitized experiments[158].



An interesting example of the photochemical formation of **277** from **279** has been realized in concentrated sulfuric acid[280, 297]. It is suggested that **279** is photochemically reduced to 1-hydroxylaminoanthraquinone (**280**), which rearranges into **277** in an acid-catalyzed dark reaction (equation 88).



Anthraquinones **242** and **244** and 1-hydroxy and 1-aminoanthraquinones are photochemically oxidized under irradiation with visible light in an aerated alkaline solution to give phthalic acid as the main oxidation product (equation 89)[298, 299]. A singlet exciplex between the anthraquinone and oxygen is suggested to be involved in this photooxidation process.



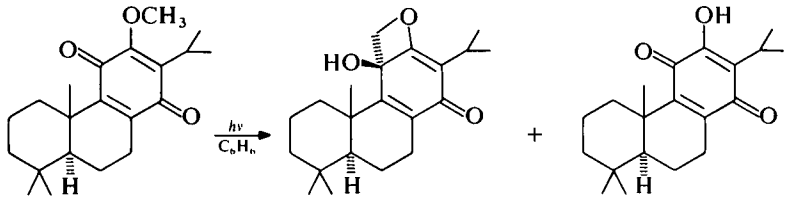
(89)

VI. UNIMOLECULAR PHOTOREACTION OF QUINONES

A. Intramolecular Hydrogen Abstraction

Intramolecular photochemical reduction of quinones bearing hydrocarbon side chains (**281**) almost always involves the abstraction of a hydrogen atom from the 2'-position of the side chain via a readily achieved six-membered transition state, similar to the Norrish type II photoreaction of aromatic ketones. Therefore, quinones whose lowest triplet excited states are (n, π^*) are reactive in this intramolecular H-atom abstraction reaction. However, quinones with a lowest triplet (π, π^*) excited state can also undergo this reaction via a charge transfer or an electron transfer when heteroatoms such as nitrogen or sulfur are present in the side chain. Several characteristic features of the intramolecular H abstraction of quinones are distinct from the usual Norrish type II photoreaction of aromatic ketones.

(1) Since the ketyl radical site in the intermediate biradical **282** is stabilized as a semiquinone radical, the main decay pathway is the cyclization to the dihydrobenzofuran (**284**). Formation of the cyclobutanol **287** is very rare with the exception of the photolysis of **288**, which gives **289** and **290** in 45% and 13% yields, respectively (equation 90)[307]. Fragmentation, which is usually the main decay process of a Norrish type II biradical, is apparently unfavorable and has never been reported.



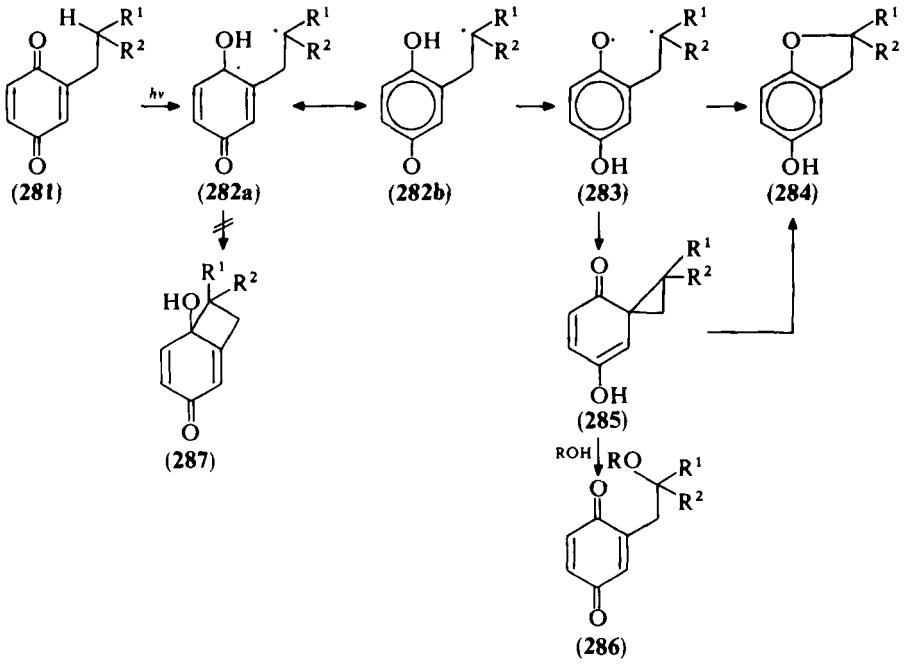
(**288**) (**289**, 45%) (**290**, 13%)

(90)

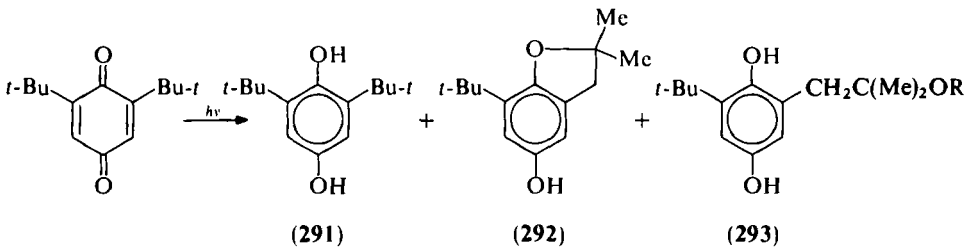
(2) Since the double bonds of the quinone ring are susceptible to radical attack, a radical center in the alkyl side chain may add to the quinone double bond to give a spirocyclopropane intermediate **285**, which gives the solvent addition product **286** (Scheme 23). This is exemplified in the formation of side chain rearranged products **292** and **293** together with **291** in the photolysis of 2,6-di-*t*-butyl-1,4-benzoquinone (Scheme 24)[112]. In nucleophilic solvents, the solvent adduct **293** is favored over **292**.

(3) When the alkyl radical center is stabilized by an adjacent heteroatom such as nitrogen or sulfur, a zwitterionic character becomes significant in the intermediate.

(4) Abstraction of an allylic hydrogen from the side chain often leads to a unique structure of *o*-quinone methide intermediates.



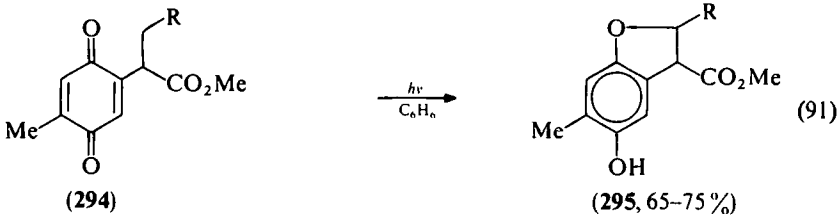
SCHEME 23



Solvent	Product distribution (%) (291)	(292)	(293)
MeOH	0	0	92
EtOH	40	—	58
2-PrOH	25	—	62
t-BuOH	10	42	48
AcOH	—	37	52* (as acetate)
Toluene	75	25	—
Benzene	14	36	—
C_6F_6	33	66	—

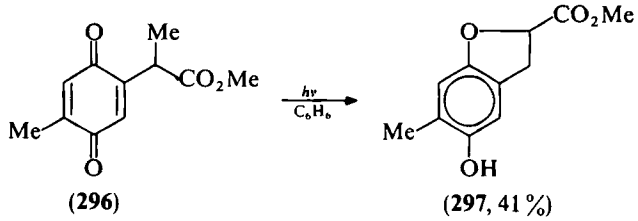
SCHEME 24

The formation of dihydrobenzofuran derivatives (**295**) has been reported in the photolysis of quinones (**294**) (equation 91), while the rearranged product **297** is obtained from **296** (equation 92)[309]. Apparently the stability of the resultant radical determines the



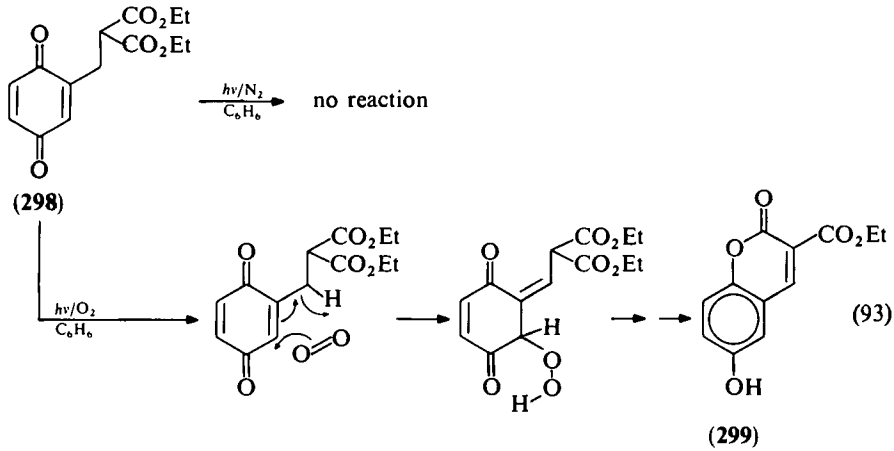
(**294**) (**295**, 65–75%) (91)

R = Me, Et, CO_2Me, $(CH_2)_3N$



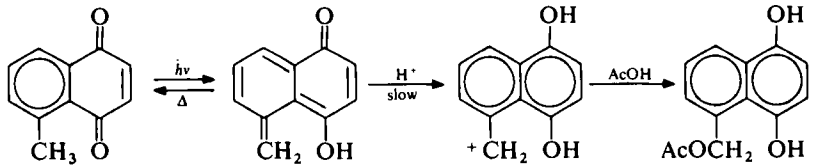
(**296**) (**297**, 41%) (92)

secondary course of the reaction. In contrast, **298** is unusual in being stable under these conditions, but it yields ethanol and 45–50% of the coumarin **299** when a catalytic amount of air or oxygen is present (equation 93). An 'ene reaction' with singlet oxygen formed *in situ* is suggested for the formation of **299**[310].



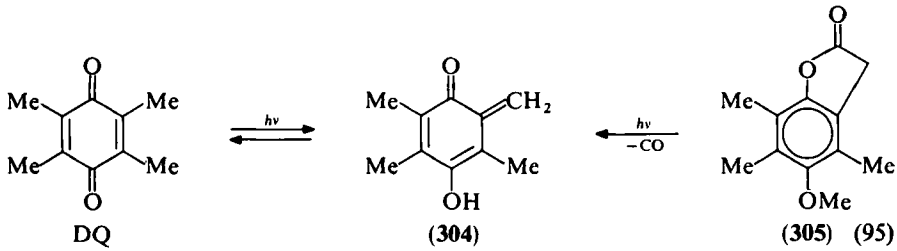
(**298**) (**299**) (93)

Irradiation of the pale yellow 5-methyl-1,4-naphthoquinone **300** yields the blue photoenol **301** which is stable at 77 K. At room temperature the enol retautomerizes back to the starting material, the reaction rate being strongly dependent on the hydrogen-bond-accepting ability of the solvent. The enol is trapped by acetic acid to give **303** (equation 94)[311]. Analogous reversible photoenolization is observed for 1,4-dimethylanthraquinone

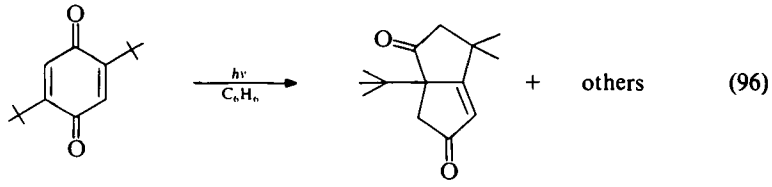


(300) (301) (302) (303) (94)

at 2-methyltetrahydrofuran matrix at 2 K[69a, 312]. *o*-Quinone methide **304** is apparently an intermediate in the photodimerization of DQ in aqueous solution, but its formation is not a major pathway for decay of the DQ triplet state[70, 313]. Flash photolysis of lactone **305** gives rise to a transient with the broad visible absorption spectrum (λ_{max} (EtOH) 445 nm), which is assigned to **304** (equation 95)[313a]. Bicyclic diketone **306** was isolated in the photolysis of 2,5-di-*t*-butyl-1,4-benzoquinone in benzene with UV light (equation 96)[314].

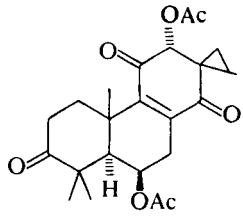


DQ (304) (305) (95)

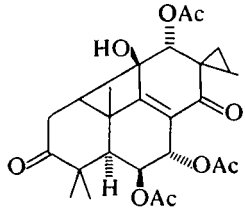


(306) (96)

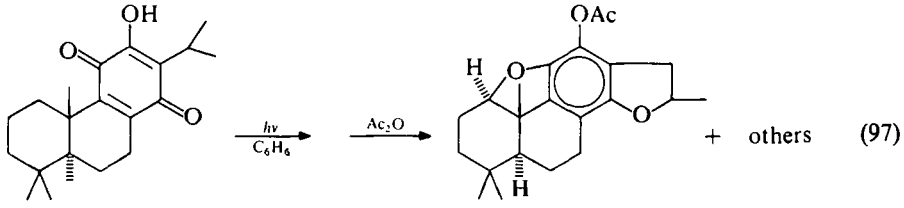
The photochemistry of the naturally occurring diterpenoid quinone royleanone **290** and its derivatives has been examined with the hypothesis that barbatusin (**307**) and cyclobutatusin (**308**) in which the common isopropyl side chain appears as a spirocyclopropyl unit, could be formed from photochemical transformation of royleanone-like precursors in the plants[307]. However, intramolecular hydrogen abstraction takes place at the other carbonyl group to give products having a cyclic ether linkage such as **309** (equation 97).



(307)

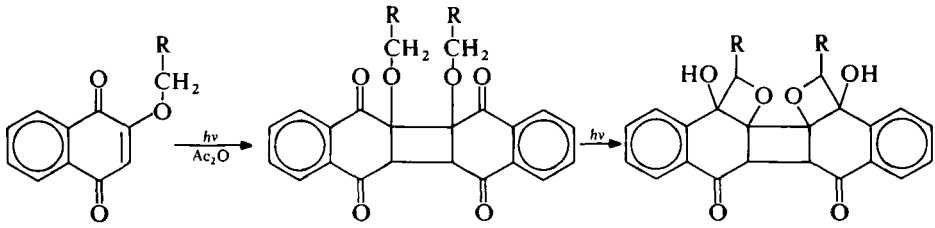


(308)

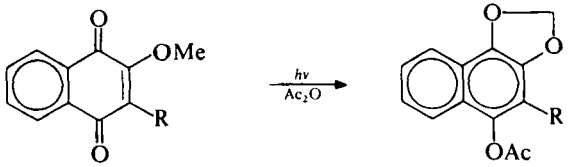


(290) (309) (97)

The photolysis of 2-methoxy- or 2-ethoxy-1,4-naphthoquinone leads to the formation of cyclobutane dimers **310** and **311** (equation 98)[315], while under similar conditions 3-substituted 2-alkoxy-1,4-naphthoquinones (**312**, R = Me, Br) give, after treatment with acetic anhydride, the ring-closed compounds **313** (equation 99)[315, 316]. The differences are

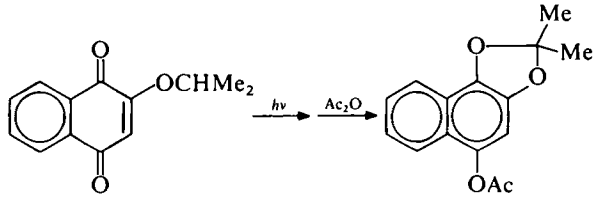


R = H, Me (310) (311) (98)

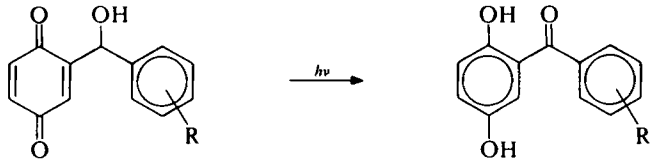


(312, R = Me, Br) (313) (99)

obviously due to the buttressing effects rather than to the electronic effects of 3-substituents. Similar photolysis of 2-isopropoxy-1,4-naphthoquinone produces none of the dimer but a cyclized product **314** via intramolecular hydrogen abstraction (equation 100)[315]. Photochemical intramolecular redox reaction of **315** to **316** (equation 101) occurs smoothly[316].

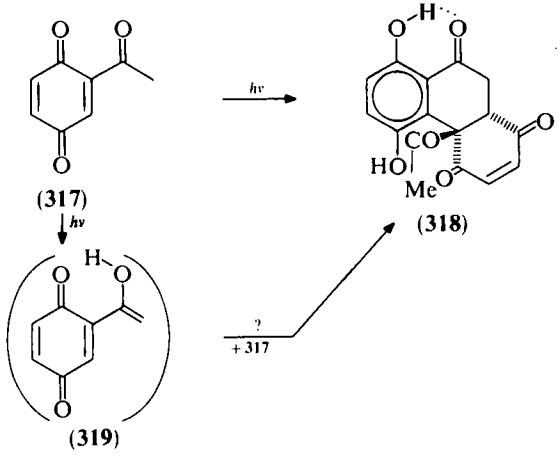


(314) (100)



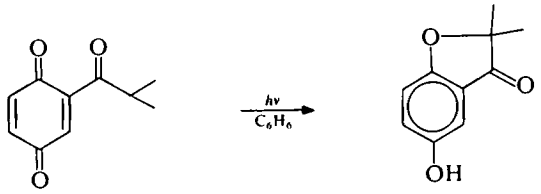
(315) (316) (101)

Irradiation of 2-acyl-1,4-benzoquinone **317** in non-polar solvents gives dimer **318** with high regio- and stereoselectivity (equation 102)[317-319]. The structure of **318** was



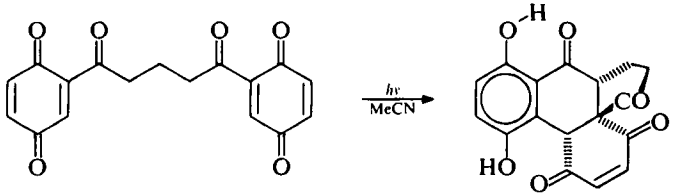
(102)

determined by X-ray analysis[318,319]. However, irradiation of isobutyryl-1,4-benzoquinone **320** gives the dihydrobenzofuranone product **321** (equation 103)[319]. It seems reasonable to assume that the dimerization proceeds through the *o*-quinone



(320) (321) (103)

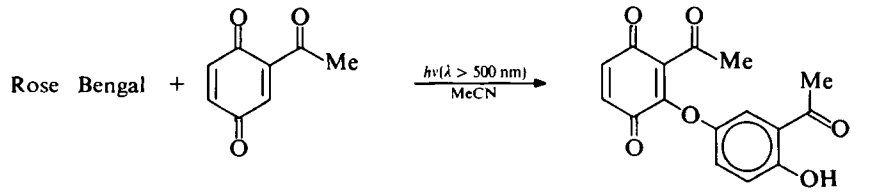
methide intermediate **319**, which, however, cannot be trapped by any other dienophiles such as *N*-phenylmaleimide or dimethyl acetylenedicarboxylate. Even in a system (**322**) where two acyl benzoquinone units are connected by a methylene bridge, intramolecular regio- and stereoselective cycloaddition takes place to give **323** (equation 104)[319]. On the



(104)

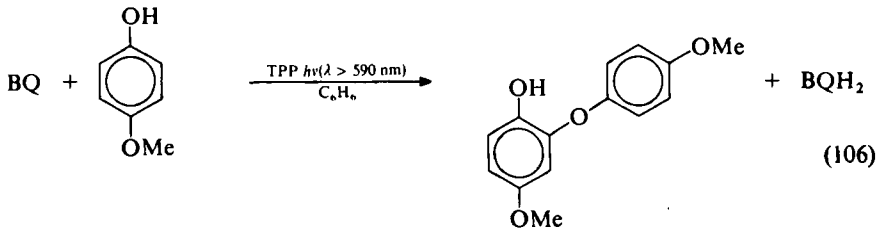
(322) (323)

other hand, a different dimer (**324**) is formed in the Rose Bengal sensitized photoreaction of **317** (equation 105)[320, 321]. In the latter dimerization reaction, electron transfer from



(317) (324, 60%) (105)

singlet excited Rose Bengal to the electron-deficient acylbenzoquinone seems to be the initial process[322]. Porphyrin-sensitized electron transfer reactions with quinones as electron acceptors are utilized in the oxidative dimerization of 4-methoxyphenol (**325**) to



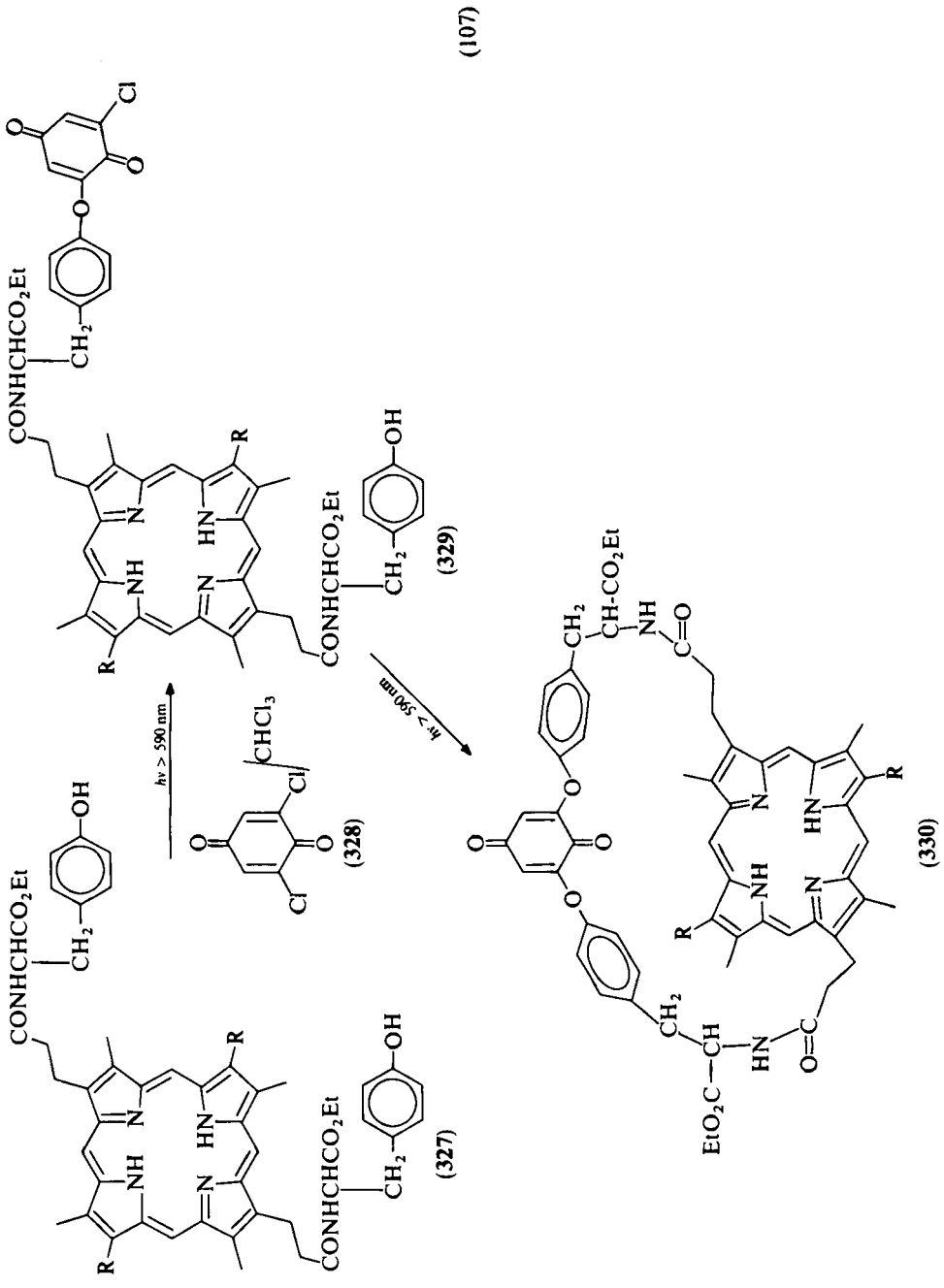
(106)

(325) (326)

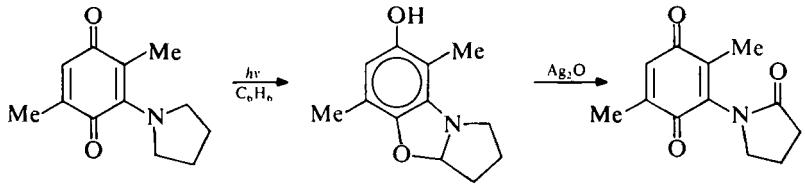
(TPP: meso-tetrakisphenylporphyrin)

326 (equation 106)[323]. In an extension of this process, a novel synthesis of exotic quinone-linked and quinone-capped porphyrins **329** and **330** has recently been achieved by self-photosensitization of tyrosine-linked prophyrin **327** in the presence of halogenoquinone (equation 107)[324].

Photo-induced intramolecular hydrogen abstraction reactions of aminoquinones have attracted considerable interest due to their potential use in synthetic routes toward

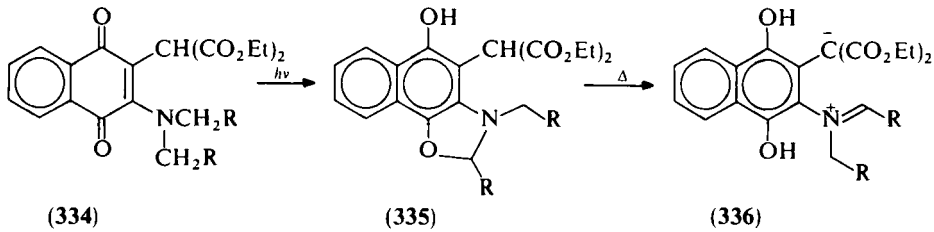

(107)
(327)
(328)
(329)
(330)
hν > 590 nm
hν > 590 nm
CHCl3

mitomycins[325-332]. The photolysis of **331** with a sunlamp to produce **332** proceeds cleanly. The oxazole **332** is characterized by NMR and is isolated as **333** after oxidation with silver oxide (equation 108)[328]. After allowing an irradiated solution of **334** to stand



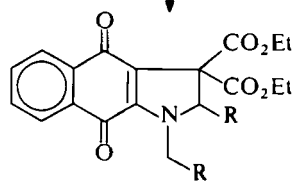
(331) (332) (333) (108)

for more than 24 h at room temperature, ring-closed quinone **337** has been obtained in high yield (equation 109). An aziridine-containing pyrroloindoloquinone **339** is synthesized by analogous intramolecular photoreaction of **338** (equation 110)[329].

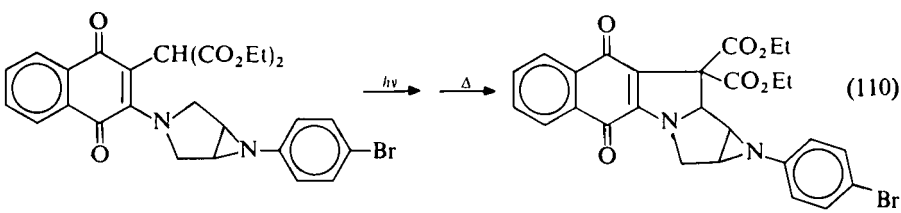


(334) (335) (336)

(109)

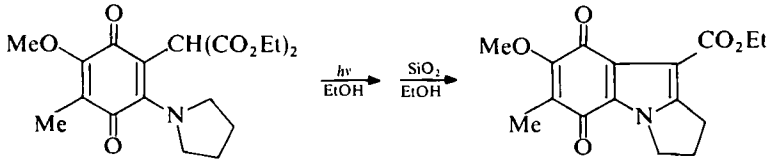


(337, 55–78%)



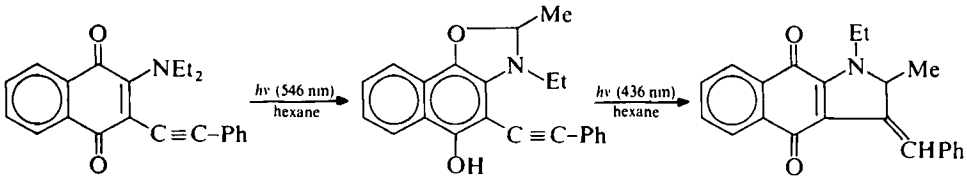
(338) (339, 63%) (110)

Isomerization of **335** to zwitterionic intermediate **336**, followed by intramolecular nucleophilic attack, is proposed to explain a formation of **337**[329]. Analogous irradiation of aminobenzoquinone **340** in ethanol followed by contact with SiO_2 for a few days gives rise



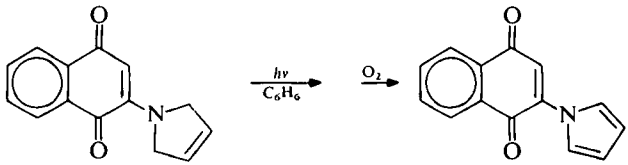
(340) (341, 68%) (111)

to pyrro[1,2-*b*] indoloquinone **341** (equation 111)[325]. 2-Diethylamino-3-phenylethynyl-1,4-naphthoquinone (**342**) is transformed into tricyclic quinone **343** by a two-step photoreaction (equation 112)[333].

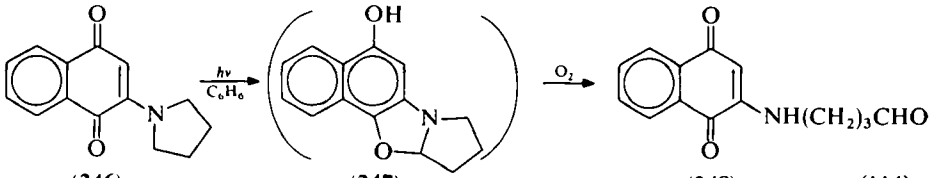


(342) (343, 45%) (112)

The photolysis of naphthoquinone **344** gives 2-pyrryl-1,4-naphthoquinone (**345**) after oxidation with air (equation 113)[330], while the main product obtained in the irradiation of **346** is the ring-opened aminonaphthoquinone **348** (equation 114). The latter product is



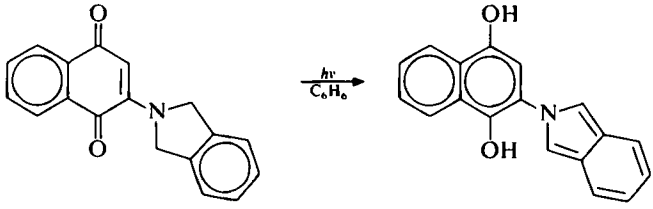
(344) (345) (113)



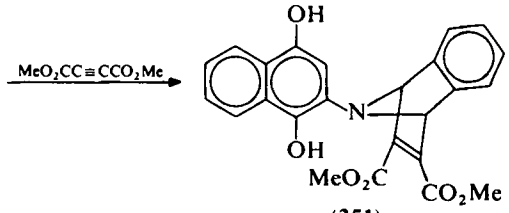
(346) (347) (348) (114)

shown to arise from a secondary dark reaction of the cyclized product **347** with oxygen[330]. Photolysis of **349** affords quantitatively isoindolylnaphthohydroquinone **350**, which can be trapped by suitable dienophiles to produce compound **351** (equation 115)[331].

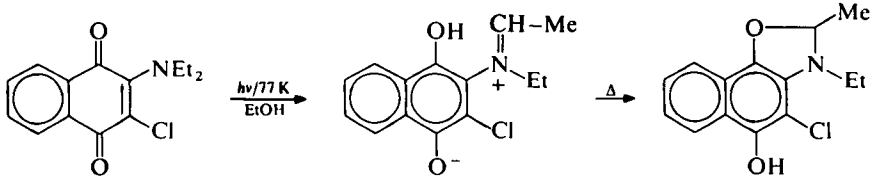
Zwitterionic intermediate **353** (with a contributing diradical hybrid **354**) is reported to be detected in the photolysis of an ethanol solution of **352** at 77 K. Upon warming to room temperature, **353** cyclizes to give **355** (equation 116)[334,335]. Irradiation of aminomethyl-substituted naphthoquinone **356** in heptane gives the photosensitive 1,4-dihydroxy-3-methyl-2-naphthaldehyde **357** as the main photolysis product along with the secondary



(349) (350) (115)

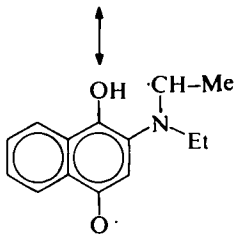


(351)



(352) (353) (355)

(116)

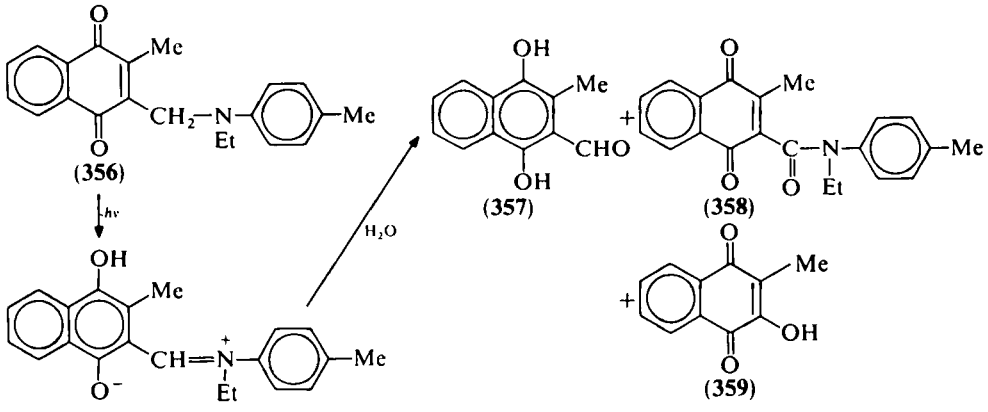


(354)

products **358** and **359**. Initial electron transfer and subsequent hydrogen transfer are suggested to give the immonium intermediate **360** which will be hydrolyzed by water to **357** (equation 117)[336].

B. Photoreaction of Quinones Bearing Side-chain Double Bonds

The plastoquinones (PLQ) are a class of trisubstituted isoprenyl-1,4-benzoquinones found in algae and in the chloroplasts of green plants, and PLQ-9 is believed to function in photosynthetic electron transport and coupled photophosphorylation[337, 338]. The photochemistry of PLQ-9 and related electron-transport quinones is of considerable interest for three main reasons.



(117)

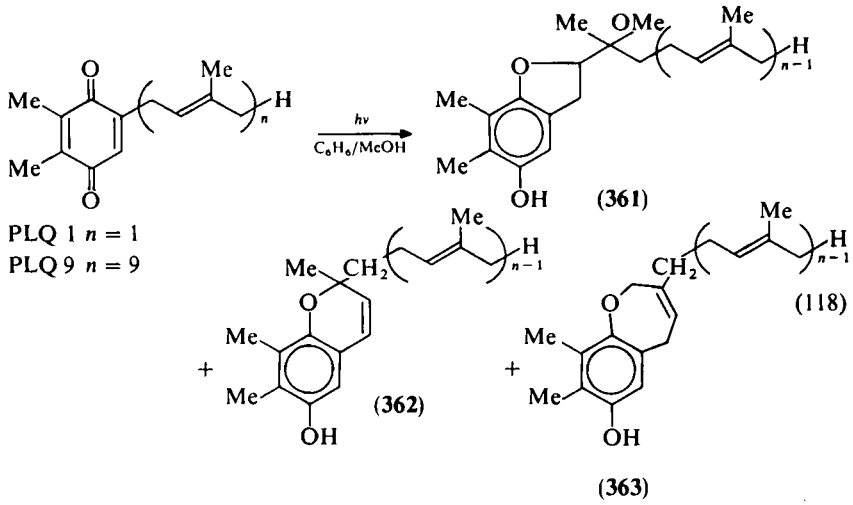
(1) It may provide some insight into the function of these quinones *in vivo*.

(2) The *in vivo* destruction of electron-transport quinones may be responsible for some of the biological effects of UV irradiation on living cells.

(3) A comparison of the photoreactions of quinones and other cellular constituents *in vitro* and *in vivo* may give some indications of the molecular environment of the photolyzed molecules *in vivo*.

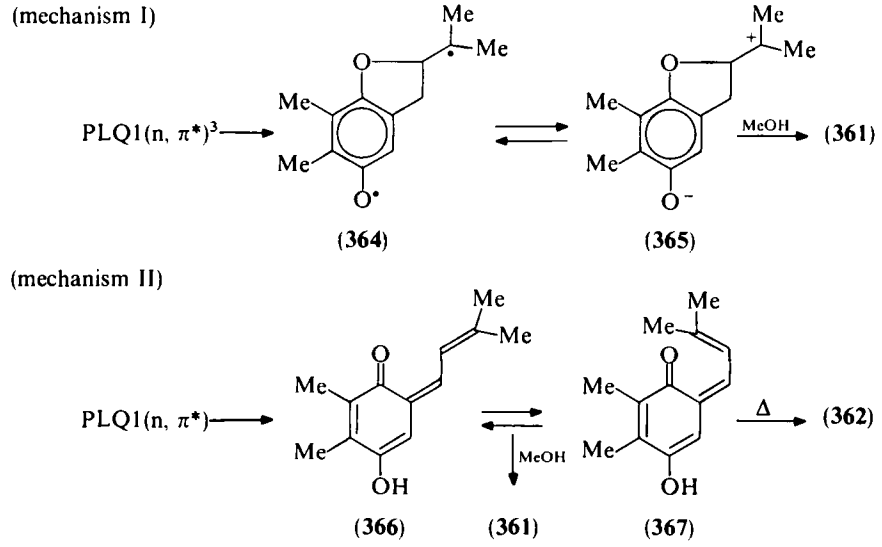
So far only two photoproducts of PLQ-9 have been reported in cells; plastohydroquinone and a partially characterized dimer[339]. The dimer may arise from the addition of the quinone ring of one molecule to one of the nine double bonds of the second molecule. However, it is noted that it may be an artifact of the isolation procedure.

In vitro photolysis of isoprenoid quinones usually leads to a mixture of many products. Detailed study on the photolysis of PLQ-1 and PLQ-9 in benzene in the presence of methanol[340], revealed the formation of the isomeric dihydrobenzofuran **361** as the major product along with the minor formation of chromenol (**362**) and benzoxepin (**363**) (equation 118). Two mechanisms were proposed for the formation of **361**; (1) addition of



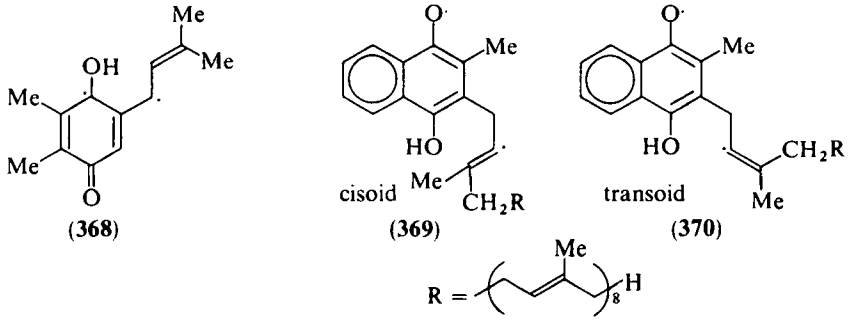
(118)

methanol to the zwitterionic species **365**, which can be formed via electron reorganization of the initially formed biradical **364**, and (2) addition of methanol to the *o*-quinone methides **366** and **367**. The formation of the chromenol **362** was used as evidence for supporting the latter route (Scheme 25). Formation of **363** can be explained by intramolecular hydrogen abstraction via an eight-membered transition state.

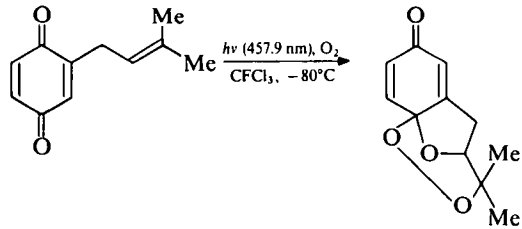


SCHEME 25

Irradiation of PLQ-1 in ethanol leads to the formation of a short-lived species (λ_{max} = 420 nm) which decays to a long-lived species (λ_{max} = 500 nm); the former is tentatively assigned to the biradical **368** and the latter is assigned to a mixture of cisoid and transoid *o*-quinone methide[341]. Similar transients are observed in the photolysis of vitamin K_1 in heptane, toluene, or CCl_4 at 77 K[341, 342]. The short-lived species (λ_{max} = 440 nm) whose decay can be analyzed by two exponential components has also been studied by ESR. From ESR spectra, a dipole–dipole interaction constant, $D = 200 \pm 3$ *G*, is determined; this corresponds to the mean distance between unpaired electrons of $r = 5.2$ Å. Based on these observations, the short-lived transients are suggested to be the biradicals **369** and **370**, and they may be transformed into cisoid and transoid *o*-quinone methides.



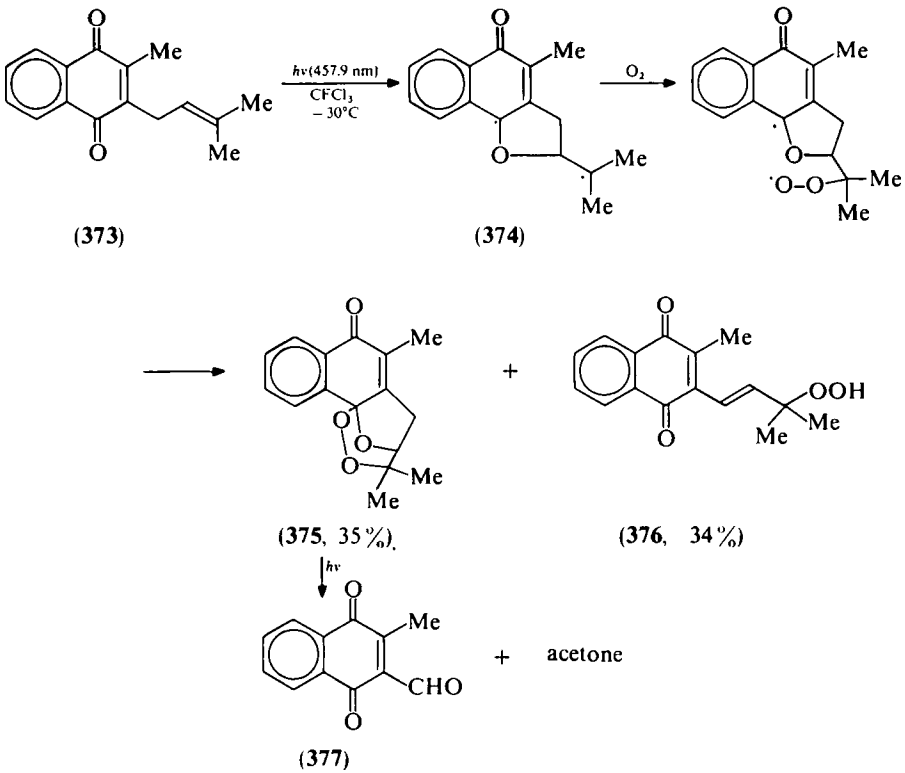
Argon ion laser excitation of 3-methyl-2-butenyl-1,4-benzoquinone **371** in $CFCl_3$ under high pressure of oxygen (11 atom) at $-80\,^{\circ}C$ affords the trioxane adduct **372** quantitatively (equation 119)[210]. Under similar conditions, 2-methyl-3-(3-methyl-2-butenyl)-1,4-naphthoquinone (**373**) gives trioxane (**375**) and hydroperoxide **376**. The



(119)

(**371**) (**372**, 98%)

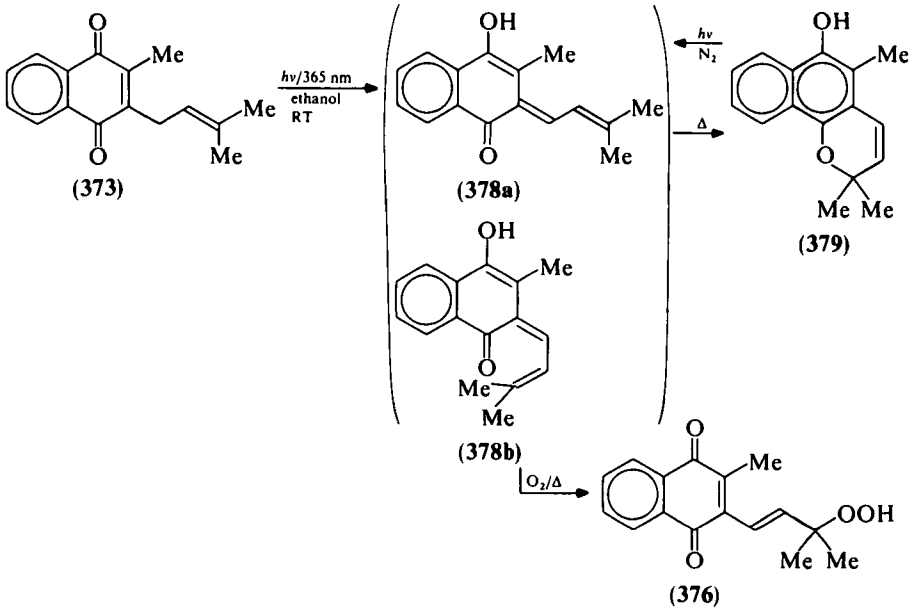
trioxanes **372** and **375** are thermally very stable but extremely photolabile; UV irradiation of **375** induces a cleavage to acetone (89%) and a very photolabile quinone aldehyde **377** (24%)[343]. Formation of **372** and **375** can be most easily rationalized as a trapping of a 1,4-preoxetane biradical **374** (or an intramolecular charge transfer complex between quinone and olefin) by oxygen (Scheme 26). However, a different report shows that in



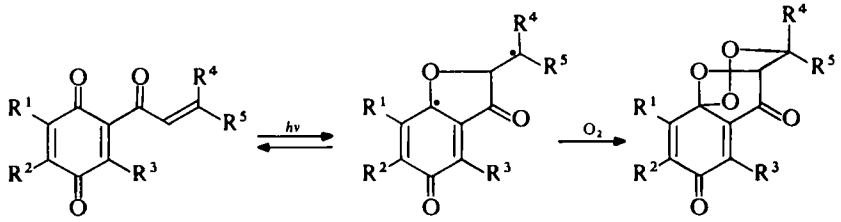
(**373**) (**374**) (**375**, 35%) (**376**, 34%) (**377**)

SCHEME 26

ethanol **376** is formed in the dark reaction of metastable ground-state intermediate (λ_{max} 550 nm), probably *o*-quinone methide **378a** or **378b** with oxygen (Scheme 27)[344, 345]. Even at atmospheric oxygen pressure, quinone–oxygen adducts **382** are



SCHEME 27

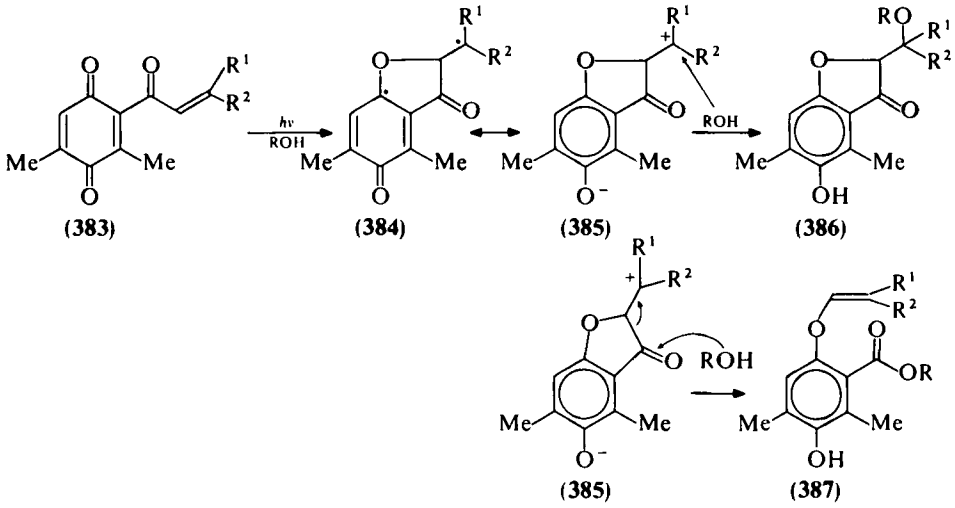


	Recovery (%)	Isolated yields (%) of **382**
a $R^1 = R^2 = R^3 = R^5 = Me$, $R^4 = H$	30	25
b $R^1 = R^2 = R^3 = R^4 = R^5 = Me$	14	31
c $R^1 = R^3 = R^4 = H$, $R^2 = R^5 = Me$,	0	36
d $R^1 = R^2 = -CH=CH-CH=CH-$, $R^3 = R^4 = H$, $R^5 = Me$	0	83
e $R^1 = R^2 = -CH=CH-CH=CH-$, $R^3 = H$, $R^4 = R^5 = Me$	0	81
f $R^1 = R^2 = -CH=CH-CH=CH-$, $R^3 = R^4 = H$, $R^5 = Ph$	0	88

SCHEME 28

formed in the photochemical reaction of 2-alkenoyl-1,4-quinones **380** in good yields[346]. Reversible interconversion of the precursor quinone **380** and the biradical **381** is evident by the *E–Z* isomerization of the olefinic side chain when the photolysis is conducted under anaerobic conditions (Scheme 28)[346].

In more polar solvents, the zwitterionic structure **385** appears to be much favored over **384**, since dihydrobenzofuranone **386** and alkenyl ether **387** are produced in the photochemical reaction of **383** in alcoholic solvents (Scheme 29)[347]. Nucleophilic addition

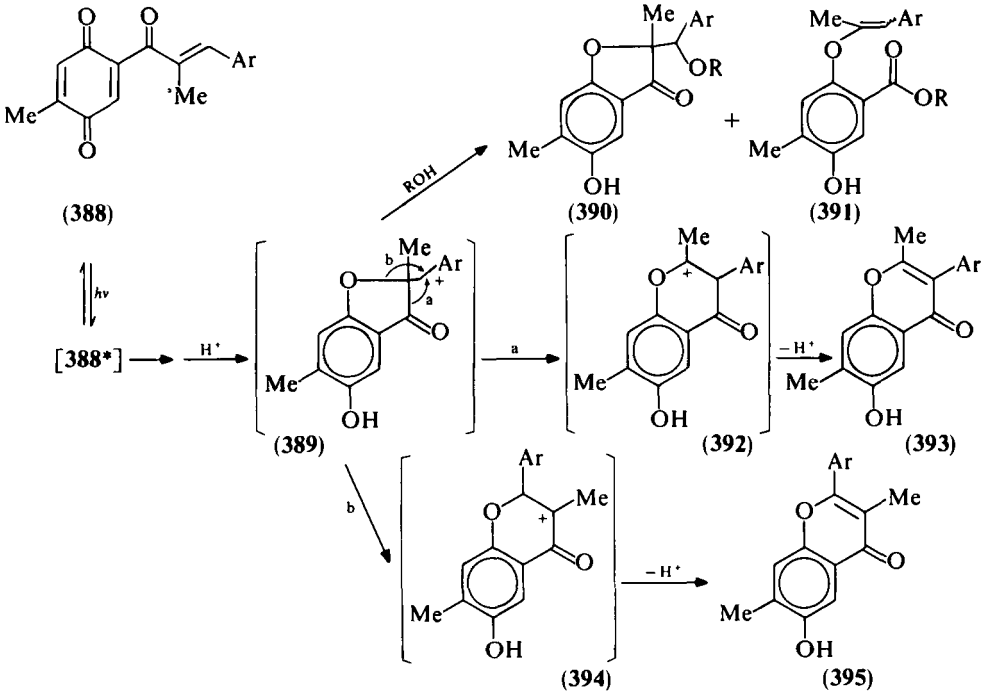


383	R^1	R^2	Isolated yields (%) in ethanol 386	in ethanol 387	in methanol 386	in methanol 387
a	H	Me	9	87	11	86
b	Me	Me	73	21	87	9
c	H	*p*-$MeOC_6H_4$	93	0	97	0
d	H	*p*-MeC_6H_4	97	1	99	1
e	H	Ph	75	23	82	17
f	H	*p*-ClC_6H_4	66	32	77	21
g	H	*p*-$NO_2C_6H_4$	9	84	18	74

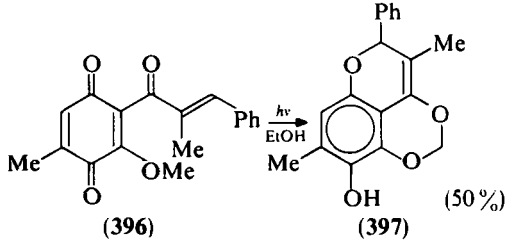
SCHEME 29

of alcohol to the carbocationic center or to ketone carbonyl group may lead to **386** or **387**, respectively. The ratios of **386** to **387** are dependent upon the substituents of R^1 and R^2 as well as on the solvent alcohols. In line with a mechanism involving the intermediacy of **385**, the yields of **386** are raised when the carbocationic center is better stabilized such as in **383c** and **383d**[347]. Another support for the zwitterionic intermediates is provided in the reaction of **388**, where regio-isomeric mixtures of chromene derivatives **393** and **395** are formed in addition to **390** and **391** (Scheme 30)[348]. On the other hand, photolysis of **396** results in hydrogen abstraction from methoxy group, producing a tricyclic compound **397** (equation 120)[349].

When the olefinic moiety is directly conjugated with the quinone chromophore, the photochemical reactivity is greatly altered. Irradiation of isopropenyl-1,4-benzoquinone



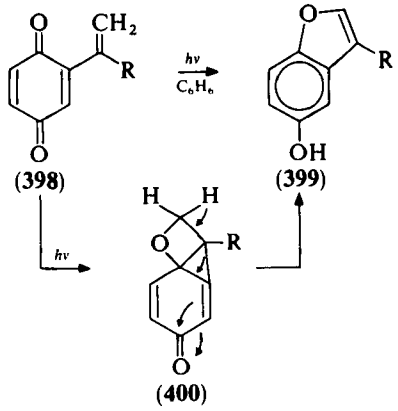
SCHEME 30



(120)

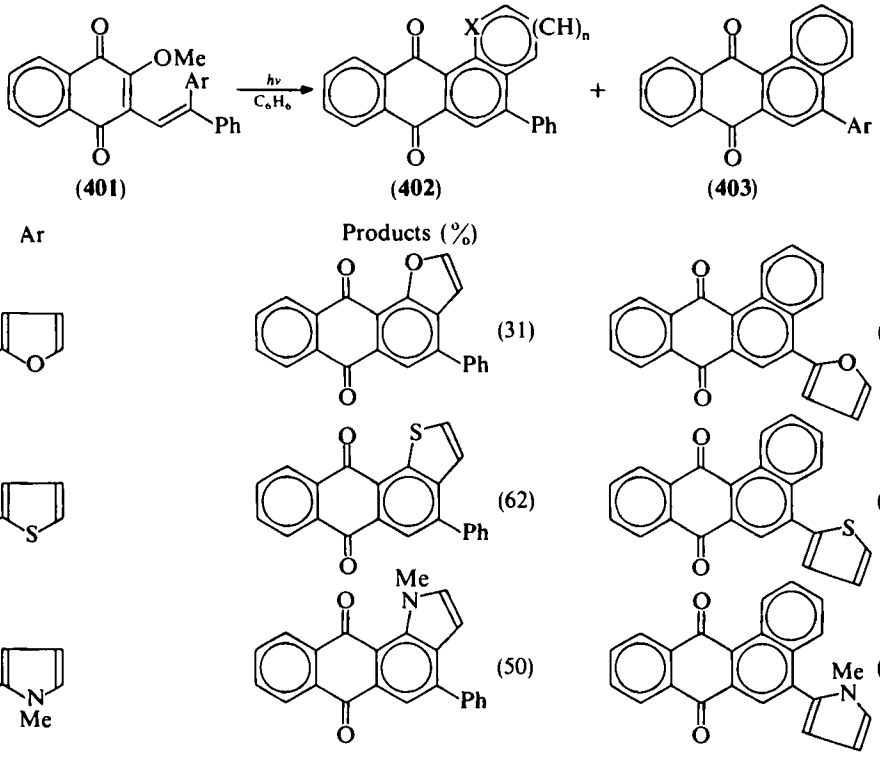
398 (R = Me) gives 5-hydroxy-3-methylbenzofuran 399 (R = Me) (equation 121)[310]. The labeled quinone 398 (R = CD_3) behaves analogously, and the mass and ^{1}H-NMR spectra of the product indicate that there has been neither loss nor scrambling of the label. This rules out a mechanism requiring hydrogen abstraction from the allylic position of the side chain, and therefore indirectly supports a mechanism involving intramolecular addition to the olefinic double bond, possibly to give 400. Phenylvinylquinone 398 (R = Ph) gives the corresponding benzofuran 399 (R = Ph) in 33 % yield, whereas vinyl-1,4-benzoquinone itself affords only amorphous materials[310].

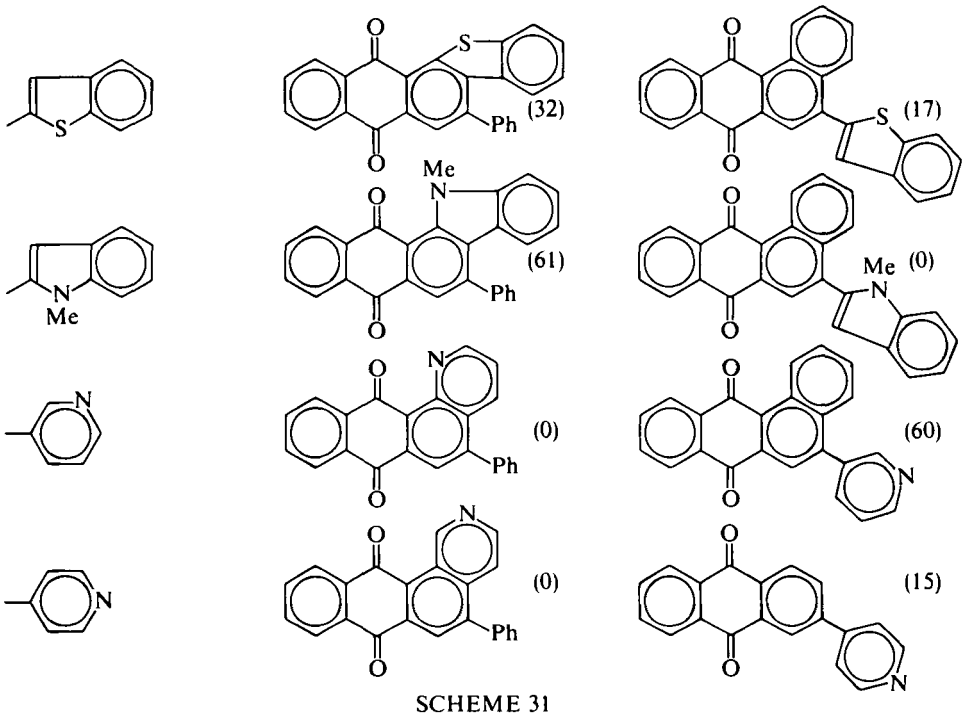
As discussed in Section IV.B, compounds 401 are photochemically cyclized to benz[*a*]anthracene-7,12-dione derivatives. When one of the aryl groups is an electron-rich heterocyclic aromatic ring, the heteroaromatic ring predominantly cyclizes to give a



(121)

product **402** over **403** (Scheme 31)[226b]. Intramolecular charge transfer interaction between the electron-rich heterocyclic ring and the electron-deficient quinone moiety in **401** may induce this selectivity.

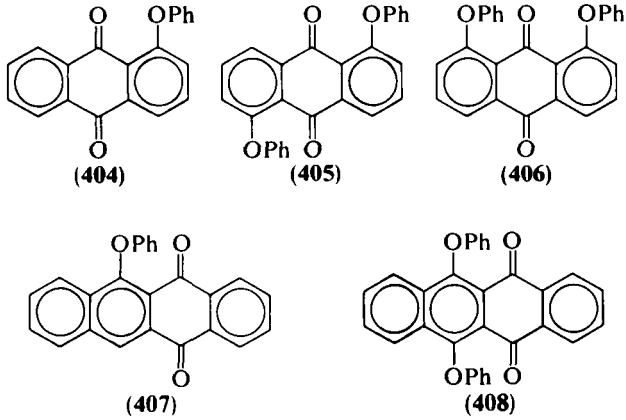




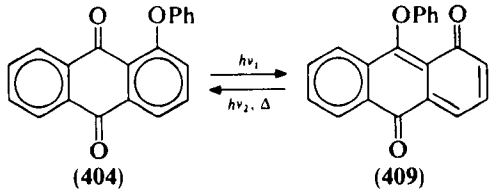
SCHEME 31

C. 'Ana'-quinone Rearrangement

Photochromism is observed in 1-phenoxy- (**404**), 1,5-diphenoxy- (**405**), 1,8-diphenoxy-9,10-anthraquinones (**406**) and in 6-phenoxy- (**407**) and 6,11-diphenoxy-5,12-naphthacenequinones (**408**) on their irradiation in non-polar solvents[350–357]. The spectra of the starting materials are restored when the irradiated solutions are kept in the dark or are re-irradiated with visible light corresponding to the new absorption band

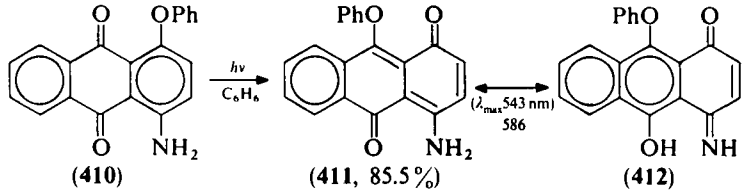


(λ_{max} > 440 nm). This photochromism is due to the photoisomerization to an 'ana-quinone' structure **409**, formed through 1,5-phenyl migration in e.g. **404** (equation 122). In many cases, these 'ana-quinones' are isolated as stable crystals and characterized[350, 356].

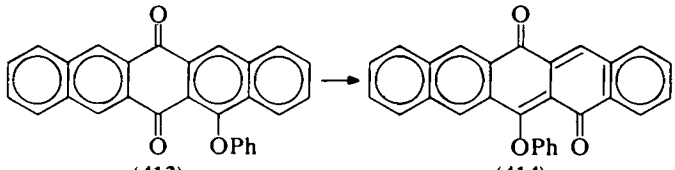


(404) (409) (122)

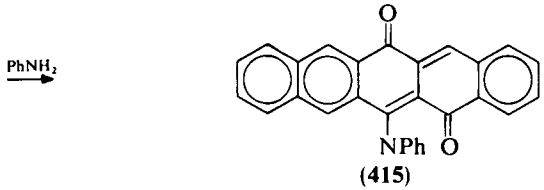
The ability of such 1-phenoxy-9,10-anthraquinones to rearrange to 9-phenoxy-1,10-anthraquinones depends on the position and electronic nature of the substituents[350]. For example, a crystalline 4-amino-9-phenoxy-1,10-anthraquinone (**411**) is isolated on irradiation of 1-amino-4-phenoxy-9,10-anthraquinone (**410**). The unusual absorption spectrum of this compound is likely to be due to the existence of two tautomeric forms (**411** and **412**) (equation 123)[350]. Under UV irradiation, 5-phenoxy-6,13-pentacenequinone (**413**) isomerizes in benzene to 6-phenoxy-5,13-pentacenedione (**414**) (λ_{max} 461, 490 nm), which irreversibly reacts with aniline to give **415** (equation 124). Recently, an analogous photochemical 1,5-acetyl migration was detected upon irradiation of **416** at low temperature matrix (equation 125)[356, 358, 359].



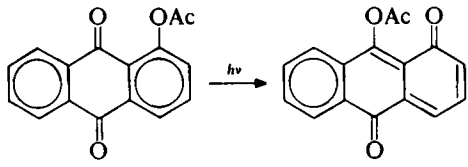
(410) (411, 85.5%) (412) (123)



(413) (414) (124)



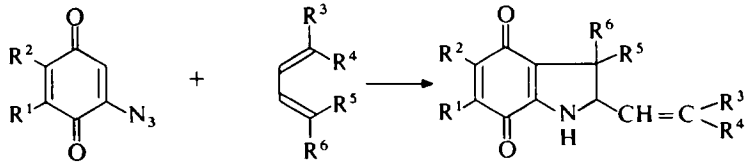
(415)



(416) (417) (125)

D. Photoreaction of Azidoquinones

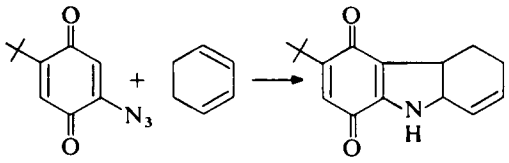
2-Azido-1,4-quinones **418**, **421**, **423**, **425** and **427** react with acyclic and cyclic dienes (e.g. **419**) upon irradiation with 360 nm light to give 2-alkenyl-2,3-dihydroindole-4,7-diones **420**, **422**, **424**, **426** and **428** (Scheme 32 and equations 126–129)[360,361]. This reaction has



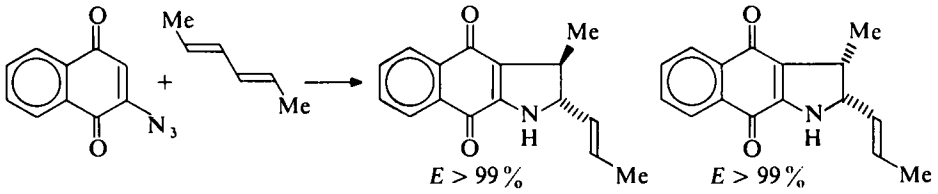
(418) (419) (420)

R^1	R^2	R^3	R^4	R^5	R^6	(%)
H	*t*-Bu	Me	H	H	H	96
H	*t*-Bu	H	Me	H	H	73
H	*t*-Bu	Me	H	H	Me	66
H	*t*-Bu	H	Me	Me	H	53
H	Me	Me	H	H	H	40
H	Me	H	Me	Me	H	72
-CH=CH-CH=CH-		Me	H	H	H	72
-CH=CH-CH=CH-		H	Me	Me	H	82

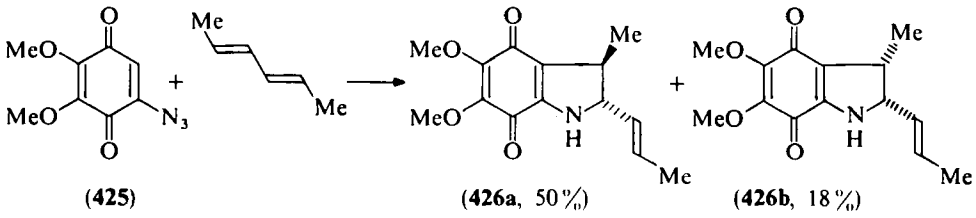
SCHEME 32



(421) (422, 53%) (126)

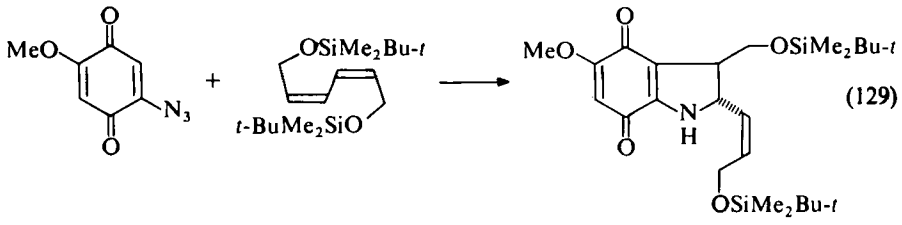


(423) (424a, 60%) (424b, 18%) (127)



(425) (426a, 50%) (426b, 18%)

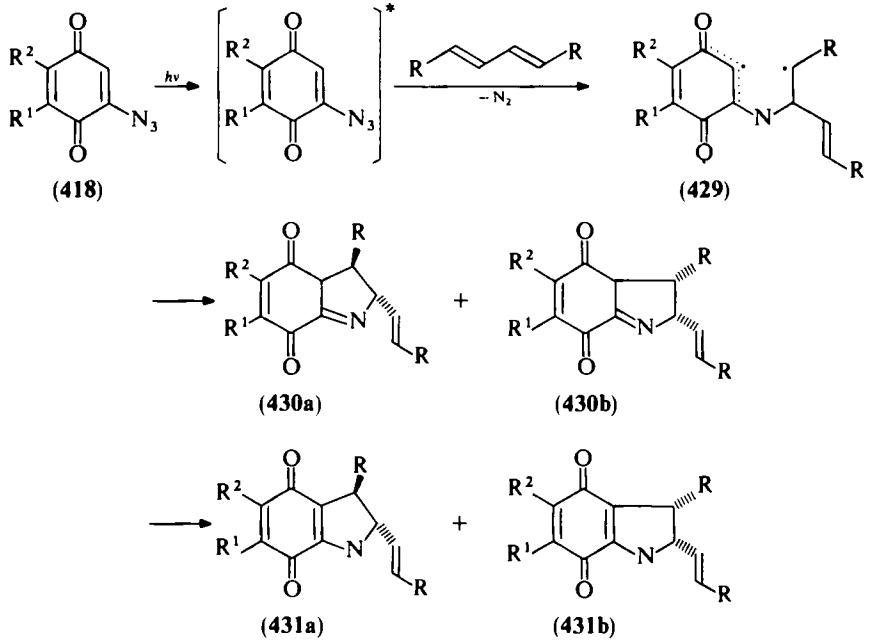
(128)



(427) (428, 43%)

(129)

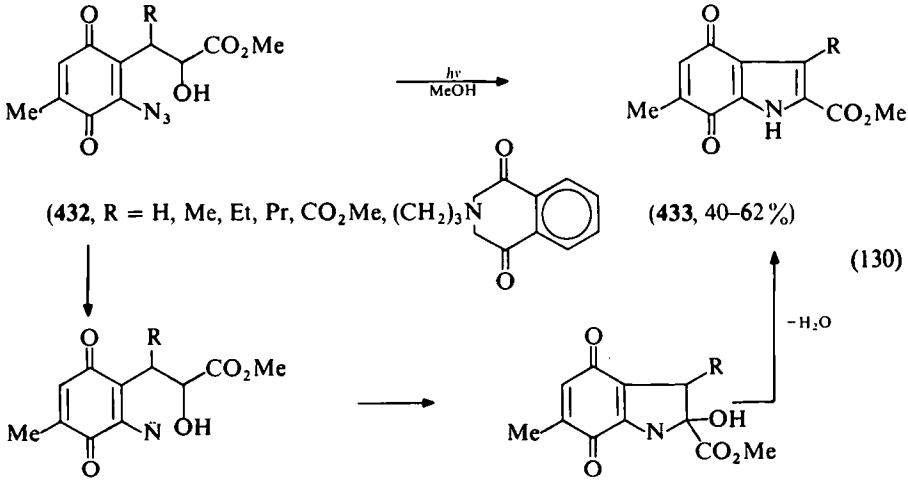
wide applicability and a synthetic utility in relevance to mitomycin synthesis. Contrary to the original report[360], the stereochemical outcomes of this cyclization are as follows: (1) regardless of the stereochemistry of the used diene, the stereochemistry at the 2,3-positions in the cyclized product is predominantly *trans* (equations 127–129), and this

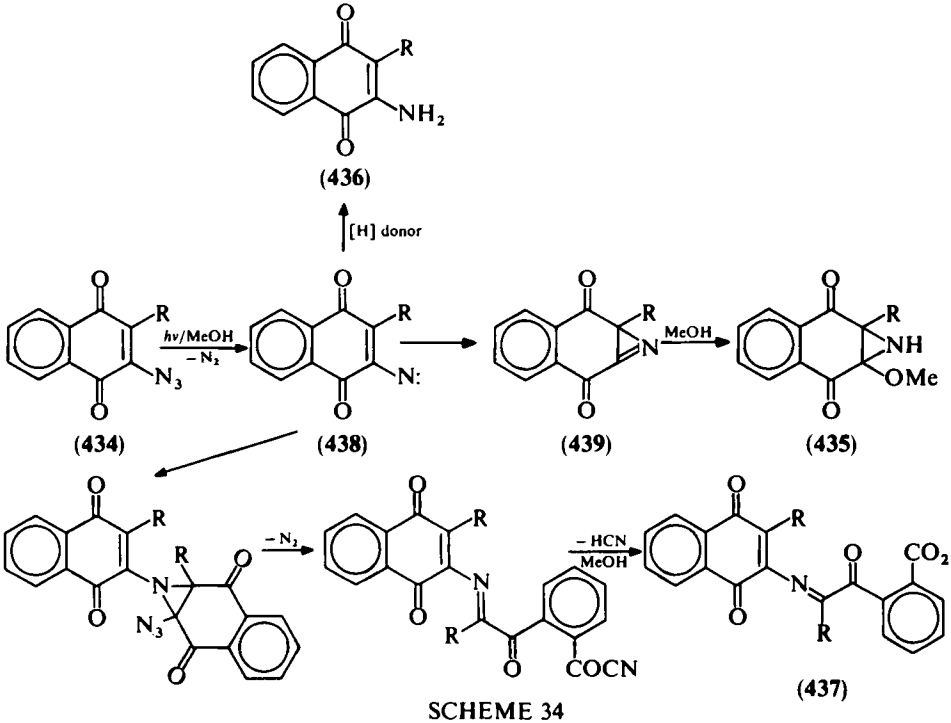


(418) (429) (430a) (430b) (431a) (431b)

SCHEME 33

selectivity is enhanced when both terminals of the diene have bulky groups; (2) the side-chain double bond in the cyclized product shows complete preservation of the original stereochemistry of the diene; and (3) the recovered diene shows no significant isomerization, even after repeated uses in the reaction. Based on these results, the reaction course



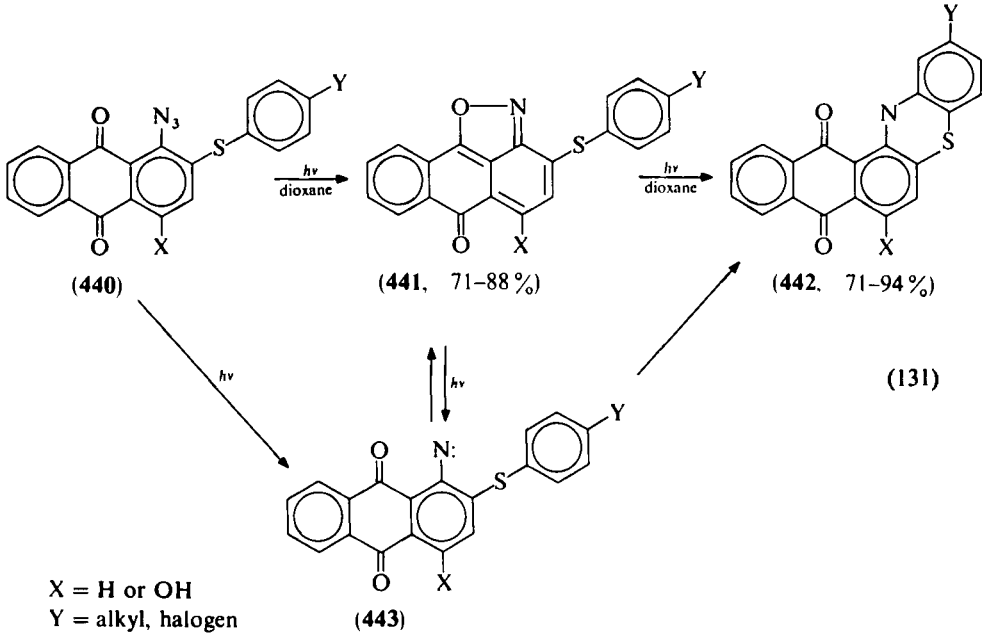


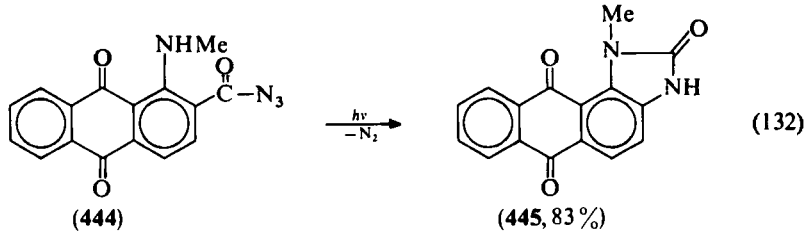
SCHEME 34

shown in Scheme 33 is proposed. Attack of a photoexcited azidoquinone on a conjugated diene with loss of nitrogen affords a biradical intermediate **429**, which will cyclize to **430a** and **430b**. At this stage, the bulky group R will favor the *trans* isomer **430a**[361a].

Irradiation of a methanol solution of azidoquinones (**432**) gives indoloquinones (**433**) in moderate yields. Apparently the reaction proceeds via the nitrene intermediate (equation 130)[362]. On the other hand, irradiation of 2-alkyl-3-azido-1,4-naphthoquinones (**434**) in methanol yields aziridinonaphthoquinones (**435**), aminonaphthoquinones (**436**) and compounds **437**, all of which seem to arise via a nitrene intermediate (**438**) (Scheme 34)[363]. Of these, the formation of aziridinonaphthoquinone **435** is most interesting from both synthetic and mechanistic points of view, since it has a unique aziridine-condensed naphthoquinone structure and is undoubtedly a product of methanol addition to the azirine **439**.

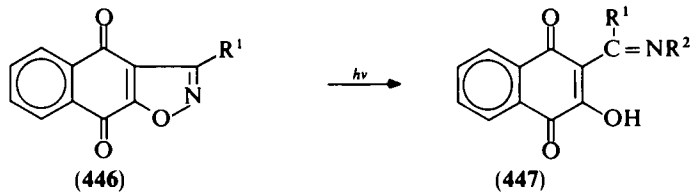
Brief irradiation of 2-azidoanthraquinones (**440**) in dioxane give 3-arylthio[1,9-*cd*]isoxazol-6-ones (**441**) in good yields. These, in turn, are transformed into phenothiazine derivatives (**442**) upon prolonged irradiation. The nitrenes **443** were considered as intermediates in these transformations (equation 131)[364, 365]. Irradiation of 1-alkylamino-2-azidocarbonyl anthraquinone **444** gives **445** in good yield via a photo-induced Curtius rearrangement (equation 132)[366].



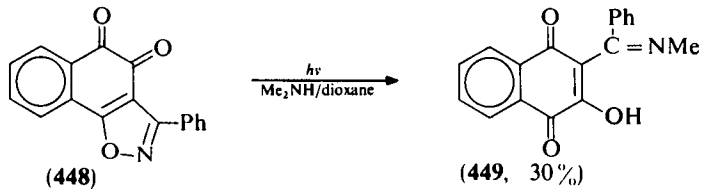


E. Miscellaneous

The heterocyclic naphthoquinone **446** (R^1 = Ph) is photochemically converted to **447** (R^1 = Ph, R^2 = H) in methanol, whereas *N*-methylated product **447** (R^1 = Ph, R^2 = Me) is formed from the same compound upon irradiation in dioxane in the presence of dimethylamine (equation 133)[367]. Photolysis of 1,2-naphthoquinone **448** also results in the cleavage of isoxazole ring to produce **449** (equation 134)[367].



(446) (447) (133)

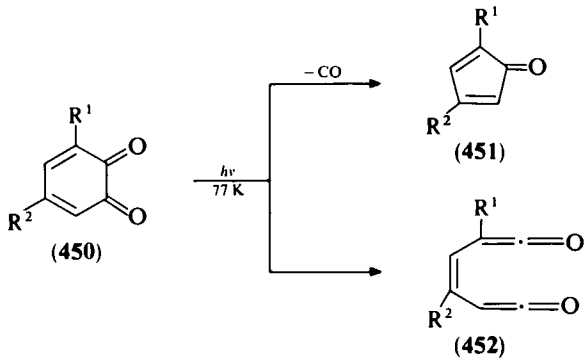


(448) (449, 30%) (134)

The photolysis of BQ in nitrogen matrix at 12 K leads to a slow decomposition of the quinone, which is accompanied by the appearance of the IR bands of acetylene (3268 and 750 cm^{-1}) and CO (2140 cm^{-1}) (equation 135), while NQ and AQ are inert under similar

$$BQ \xrightarrow{h\nu} 2HC \equiv CH + 2CO \qquad (135)$$

conditions. The authors suggest the possibility of a two-photon process for this fragmentation reaction[368]. Photolysis of 1,2-benzoquinone **450** (R^1 = R^2 = *t*-butyl) in nujol at 77 K results in the decarbonylation to cyclopentadienone **451**. With less substituted quinone **450** (R^1 = H, R^2 = *t*-butyl; R^1 = Me, R^2 = H), irradiation brings about the bis-ketene **452** as well as CO and dienone **451** (equation 136)[369–371].



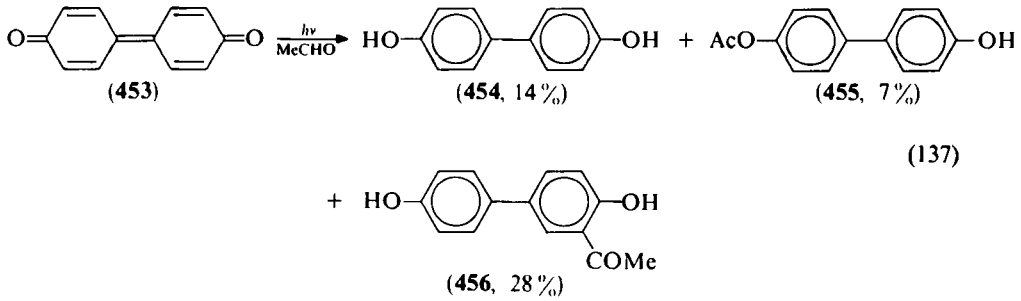
(450) (451) (452) (136)

VII. PHOTOCHEMISTRY OF QUINONE RELATED COMPOUNDS

A. Diphenoquinone

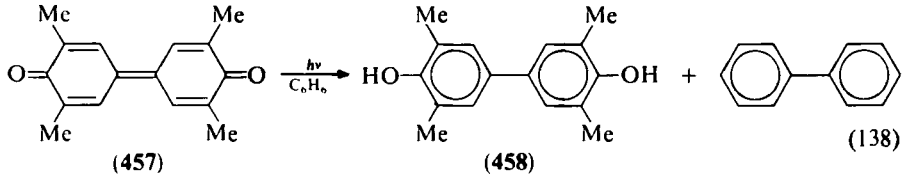
Diphenoquinones are generally strong electron acceptors capable of being reduced to semiquinone radicals. The ion-radical salts of diphenoquinones have been found to be organic conductors[372]. Investigations of the photochemical reactions of diphenoquinones have been stimulated by their expected usefulness in silver-free photography as well as by the molecular level understanding of the degrading effect of light on certain biological substrates. Diphenoquinones are intensively colored compounds that are reduced and decolorized on photoexcitation in the presence of appropriate hydrogen donors[373–377].

Irradiation of parent diphenoquinone **453** itself in acetaldehyde gives 4,4′-dihydroxybiphenyl (**454**), 4-acetoxy-4′-hydroxybiphenyl (**455**) and 3-acetyl-4,4′-dihydroxybiphenyl (**456**) (equation 137)[378]. Under identical conditions, 3,3′,5,5′-tetramethyldiphenoquinone



(**453**) (**454**, 14%) (**455**, 7%) (**456**, 28%) (137)

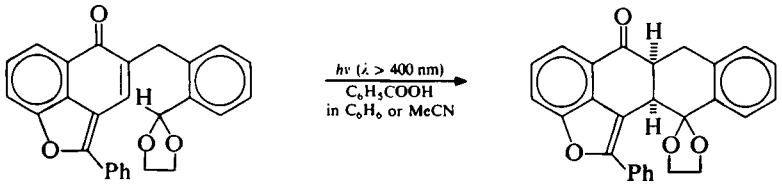
is reduced to the corresponding diphenol but sterically hindered 3,3′,5,5′-tetra-*t*-butyldiphenoquinone is inert[378]. Photoexcited 2,2′,6,6′-tetramethyldiphenoquinone (**457**) abstracts a hydrogen even from benzene to give **458** and biphenyl (equation 138)[376].



(**457**) (**458**) (138)

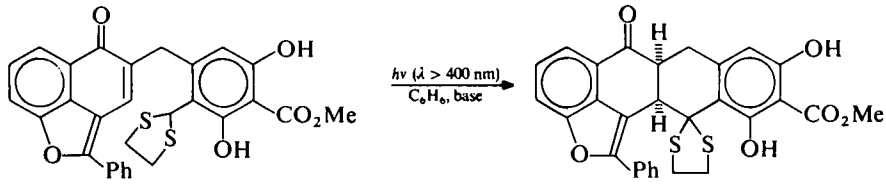
B. Quinone Methide and Quinone Imine

The ethylene acetal of 4-(2-formylbenzyl)-2-phenylnaphtho[1,8-*bc*]furan-5-one (**459**) has been cyclized under acid-catalyzed photolytic conditions to **460** (equation 139)[379].



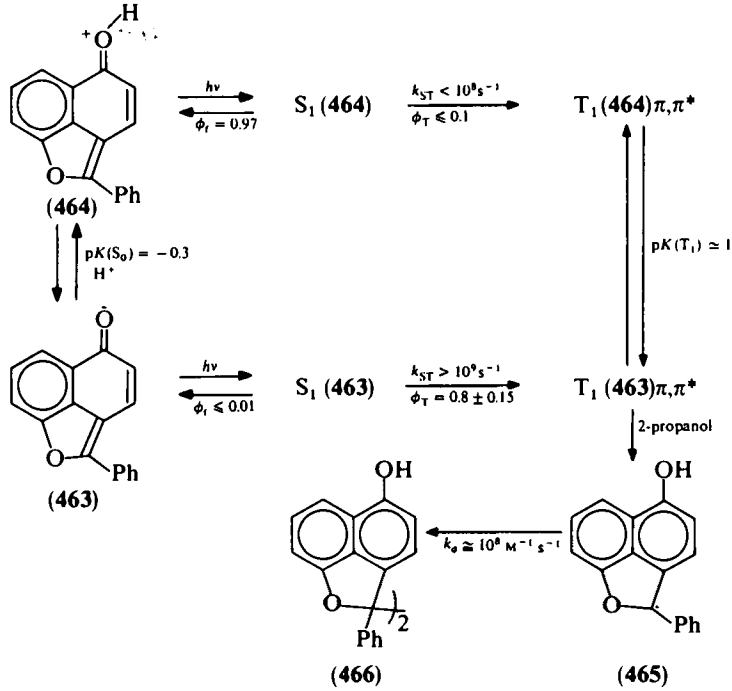
(**459**) (**460**, 78%) (139)

Improved procedure has recently been used for the photocyclization of **461** to **462** (equation 140)[380]. In relation to these reactions, the kinetics of the photophysical decay



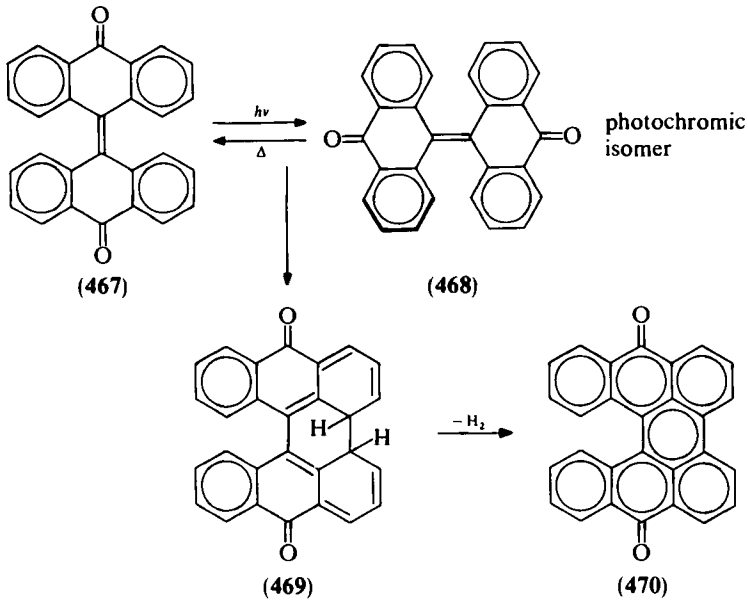
(461) (462, 68%) (140)

and the photochemical reactivity of the parent **463** and its conjugated acid **464** have been investigated (Scheme 35)[381]. The fluorescence of **463** in benzene is very weak, whereas the conjugated acid **464** exhibits an intense green fluorescence ($\phi_f = 0.97 \pm 0.1$)[381]. The lowest (π, π^*) triplet is an intermediate in the photoreduction of **463** in 2-propanol, which leads to the formation of dimer **466** via a semiquinone methide radical **465**[381].



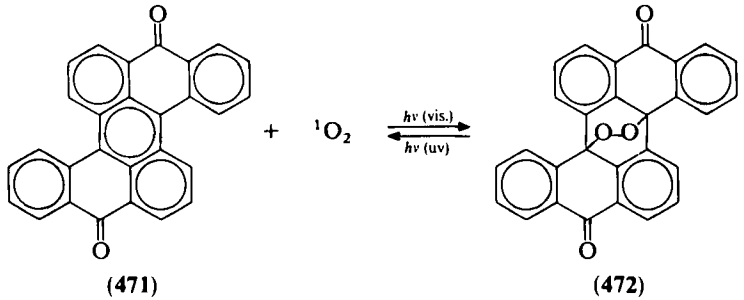
SCHEME 35

The photochromism of bianthrones (e.g. the parent **467**) has long been a subject of extensive study[382,383]. The structure of the photochromic isomer ($\lambda_{max} = 650$ nm) has been established as that of the twisted conformer **468** in which the bianthronyl system is twisted by ca. 57° about the central double bond and each of its anthrone half-moiety is planar[384]. Photochromism takes place via the triplet state of the starting isomer and gives



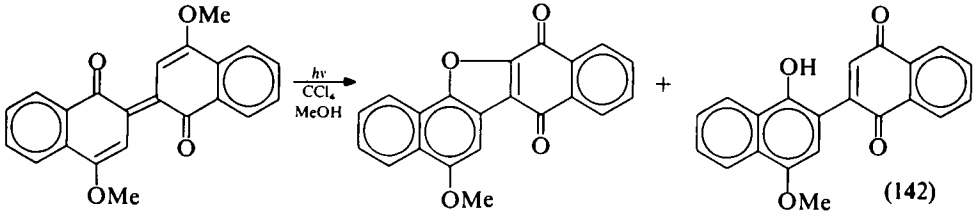
SCHEME 36

470 via **469** (Scheme 36)[385, 386]. A photochromic system which is based on the photoreversible addition of singlet oxygen into an arene derivative has been reported (equation 141)[387, 388]. Photocleavage of **472**, which is reported to occur via the S_2 (π, π^*) state, produces **471** in the ground state and O_2 in an electronically excited singlet state.

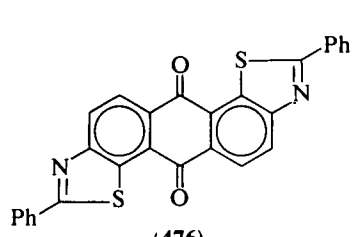


Illumination of a solution of **473** in CCl_4–methanol using a tungsten lamp produces a red quinone (**474**) and a blue quinone (**475**), the latter of which undergoes photocyclization and aerial oxidation to give the former (equation 142)[389]. Primary photochemical processes of phototendering vat dyes **476** and **477** are shown to be H abstraction and electron transfer, respectively[118].

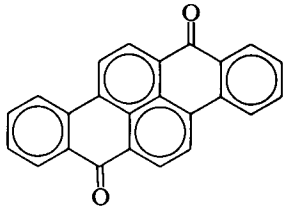
Irradiation (λ_{max} = 365 nm) of benzene solutions of quinone methide **478** produces the benzofuran derivative **479**[390]. The route envisaged is shown in equation 143, whereby the photoexcited carbonyl group adds to the benzene ring, yielding the intermediate spirobiradical **480**. Subsequent bonding to give **481** and ring-opening of the cyclopropane moiety yields **479**[390].



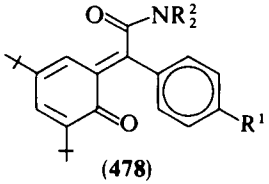
(473, blue) (474, red) (142) (475, blue)



(476)

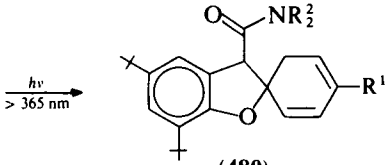


(477)

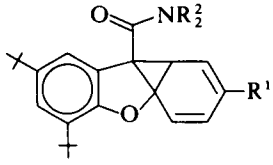


(478)

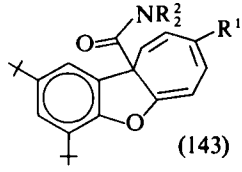
a, R^1 = H, R^2 = Et
b, R^1 = H, R^2 = i-Pr
c, R^1 = Me, R^2 = Et



(480)



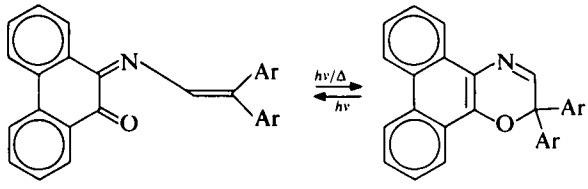
(481)



(143)

(479)
a, 85%
b, 55%
c, 75%

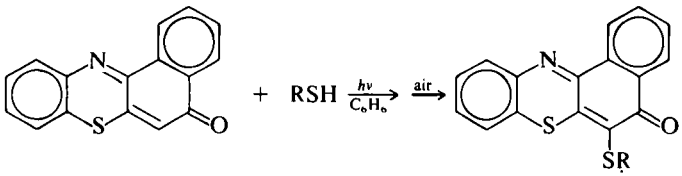
Azamerocyanine (**482**) undergoes a reversible ring-closure on photoexcitation, forming colorless 2*H*-1,4-oxazine (**483**) (equation 144)[391]. Phenothiazine quinone imine (**484**) is



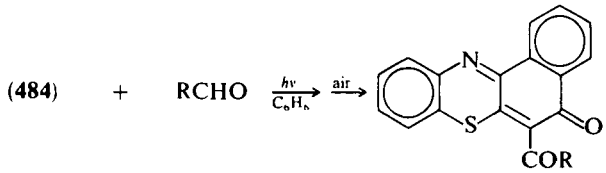
(144)

(482) (483)

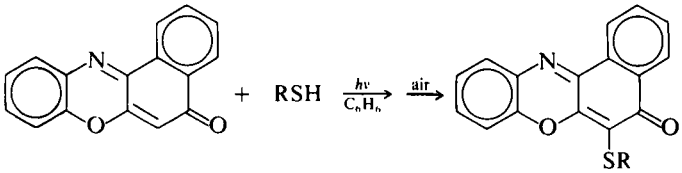
photochemically active toward hydrogen donors such as thiols and aldehydes, giving coupling products **485** and **486**, respectively (equations 145 and 146)[392]. An analogous



(484) (485) (145)

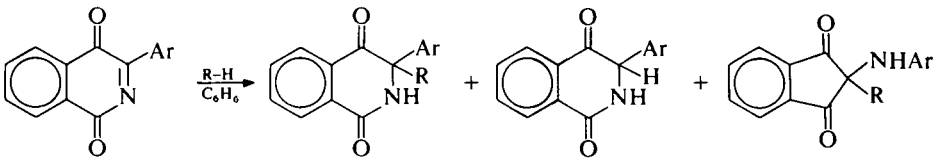


(484) (486) (146)



(487) (488) (147)

reaction of phenoxazine quinone imine (**487**) with thiol gives **488** (equation 147). 2-Aza-3-aryl-1,4-naphthoquinone (**489**) has the lowest excited state of a (n, π^*) character and is photochemically reduced to **490**, **491** and **492** in the presence of hydrogen donors (equation 148)[393].

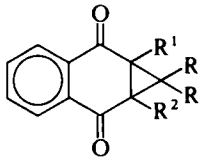


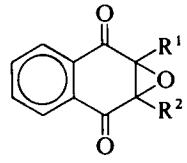
(489) (490) (491) (492) (148)

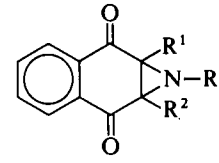
R–H = Xanthene, toluene, and tetrahydrofuran

C. One-atom Homologs of 1,4-Naphthoquinone

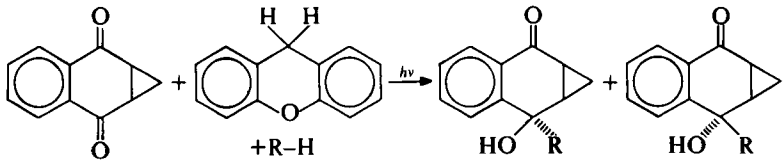
The photochemistry of one-atom homologs of 1,4-naphthoquinone such as methanonaphthoquinone (**493**), epoxynaphthoquinone (**494**) and iminonaphthoquinone (**495**), in which the carbon–carbon double bond of the quinone ring is replaced with cyclopropane, oxirane and aziridine ring, respectively, has been extensively studied.

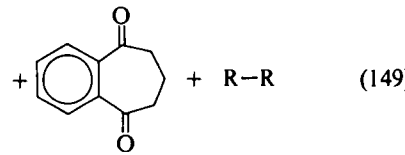

(493)


(494)

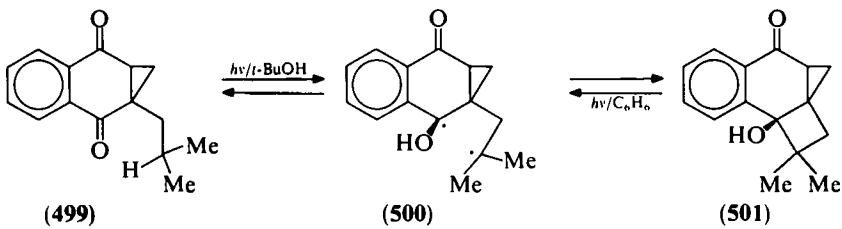

(495)

Methanonaphthoquinone **496** has a usual (n, π^*) reactivity quite similar to that of aromatic ketones. Thus, inter- and intramolecular H-abstraction reactions proceed efficiently (equations 149 and 150)[394-396]. Irradiation of methanonaphthoquinone **499** in

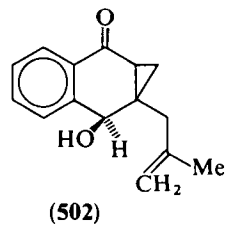

(496) (497a) (497b)


(498)

(149)

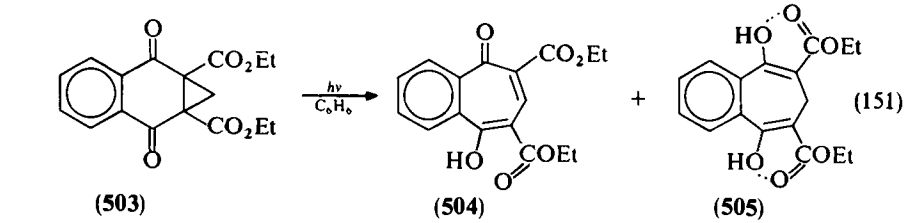

(499) (500) (501)

(150)

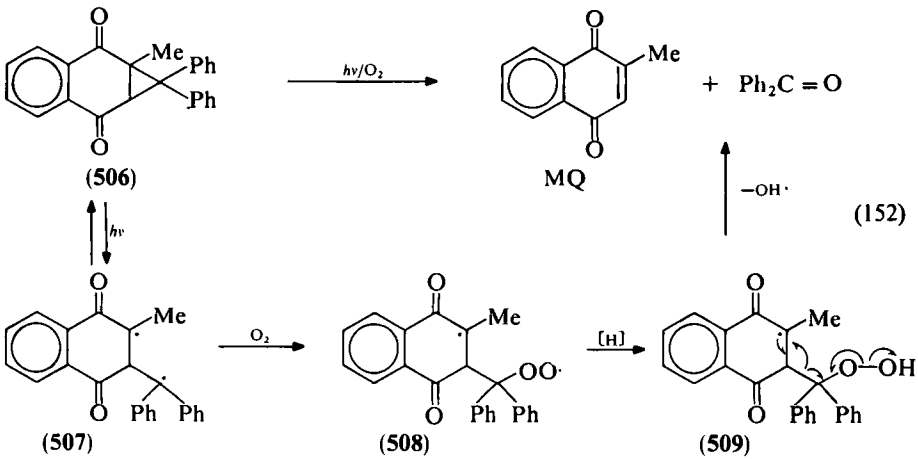

(502)

t-butanol gives cyclobutanol **501** efficiently. Upon irradiation in benzene, **501** is converted back to **499** via a 1,4-biradical **500**[395, 396]. The internal carbon–carbon bond of the

cyclopropane ring of **503** is photochemically cleaved to produce **504** and **505** (equation 151)[394b]. Diphenyl-substituted methanonaphthoquinone **506** is quite stable even in the presence of good hydrogen donors under completely deaerated conditions but it cleaves readily to MQ and benzophenone in the presence of both oxygen and hydrogen donors[394b]. Reversible formation of biradical **507** and its interception by oxygen to form **508** which abstracts hydrogen to form **509** are suggested for this oxidative fragmentation reaction (equation 152).

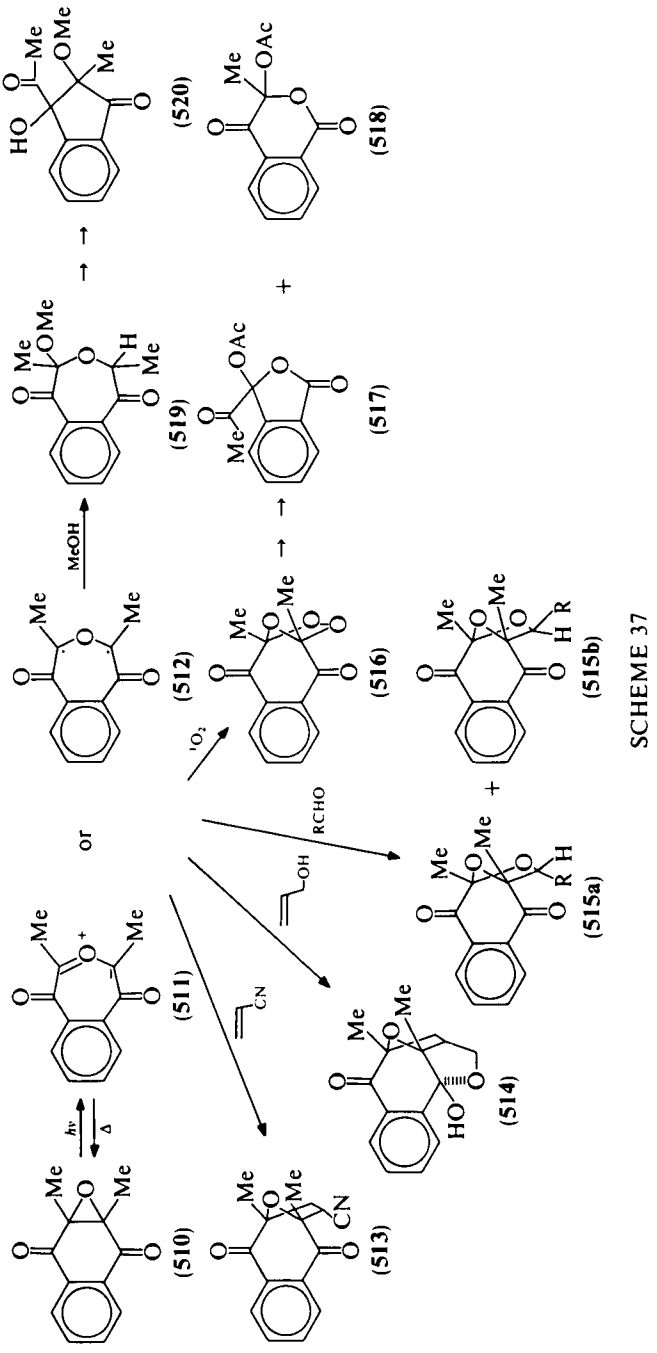


(503) (504) (505)

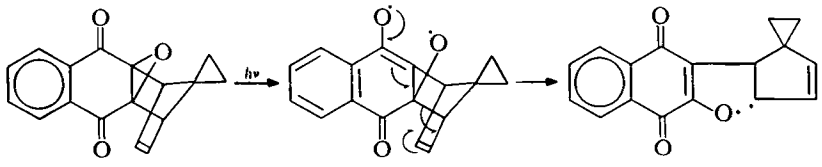


(506) MQ (507) (508) (509)

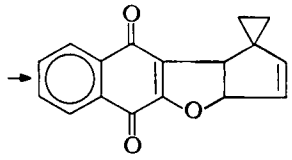
Epoxyquinones are metabolites of biologically important quinones, and thus their photochemical reaction may be related to some photodamaging effect of quinonoid compounds. Since intersystem crossing of epoxynaphthoquinones is very efficient and their lowest triplet state has a characteristic (n, π^*) nature, all photochemical reactions of epoxynaphthoquinone may be considered to start from the lowest triplet (n, π^*) state[397]. Irradiation of dimethyl-substituted epoxynaphthoquinone (**510**) results in a reversible formation of carbonyl ylide **511** or the 1,3-biradical **512**, which are trapped by olefins[398], aldehydes and ketones[399], singlet oxygen[400] and alcohols to form products **513–520** (Scheme 37)[401]. Excited triplet state of **510** is quenched by electron-rich olefins via exciplex deactivation; this quenching competes with the decaying pathway leading to **511** or **512**[398]. Photochemical generation of a carbonyl ylide or a 1,3-biradical is also reported in the photolysis of 2-aryl and 2,3-diaryl substituted epoxynaphthoquinones[402,403]. Photolysis of epoxynaphthoquinones **521** and **524** gives **522** and **525**, respectively[404–406]. These photoisomerizations are explained in terms of a mechanism starting with α-cleavage (equations 153 and 154).



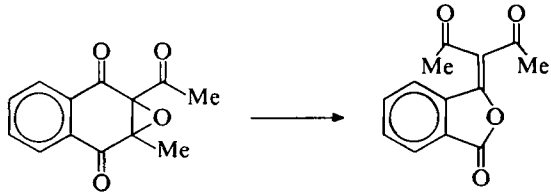
SCHEME 37



(521) (523) (153)

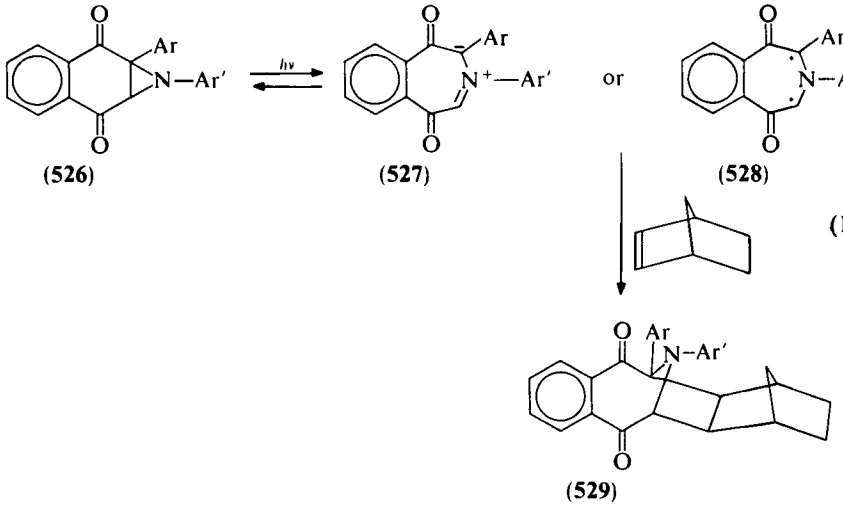


(522)



(524) (525) (154)

The lowest triplet state of iminonaphthoquinone has a mixed (n, π^*) and CT character. Irradiation of **526** in the presence of an olefin gives cycloadduct **529** via intermediate **527** or **528** (equation 155), similarly but much less efficiently compared with epoxynaphthoquinone[407].



(526) (527) (528) (155)

(529)

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CHAPTER 14

Radiation chemistry of quinonoid compounds

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I. INTRODUCTION

Quinonoid compounds have played a major role in radiation chemistry because of their importance in biological systems and industrial applications and in electron transfer

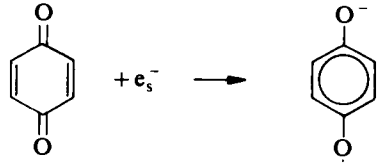
reactions in general. In turn, the techniques of radiation chemistry have proven to be extremely useful for the study of free radical and one-electron transfer reactions of quinones as well as their excited states. Since the publication of the original chapter[1] in this series a large body of data has accumulated on this topic. Various aspects of this information have been partly reviewed[2-6] and recent compilations have summarized the rate constants for reactions of quinonoid compounds with hydrated electrons[7,8], hydrogen atoms[9], hydroxyl radicals[10], perhydroxyl and superoxide[11], organic radicals[12,13], as well as the one-electron redox potentials[14,15].

The majority of the radiation chemical studies on quinones were carried out with solutions at room temperature, in particular aqueous solutions. The effect of radiation on water and other solvents and the manipulation of the primary radicals toward a desired particular reaction have been discussed in detail (see, e.g. Refs 1, 3, 5 and references therein). In this chapter we concentrate on the kinetics and mechanisms of the radiolytic reactions of quinones and on the properties of the intermediate species.

II. REACTIONS OF QUINONES WITH RADICALS

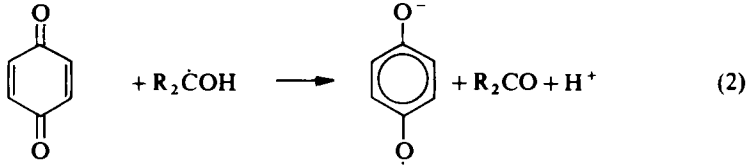
A. Reactions with Solvated Electrons and Reducing Radicals

Quinones and related compounds react with solvated electrons with diffusion-controlled rate constants ($k \sim 10^{10}$ M^{-1}s^{-1})[7,8] to form the semiquinone radical anions. They react with hydrogen atoms nearly as rapidly ($k \sim 10^9$ M^{-1}s^{-1})[9] to form the same radical, unless the molecule contains an additional site where H atoms may react partially to form a different radical.



(1)

Quinones are very readily reduced by a wide variety of organic radicals. Typical reducing radicals are α-hydroxy- or α-amino-substituted alkyls, such as those formed from methanol ($\dot{C}H_2OH$), 2-propanol ($(Me)_2\dot{C}OH$), formate ($\dot{C}O_2^-$), or glycine ($^-O_2C\dot{C}HNH_2$), which transfer an electron to quinones very rapidly ($k \sim 10^9$ M^{-1}s^{-1})[12,13], e.g.



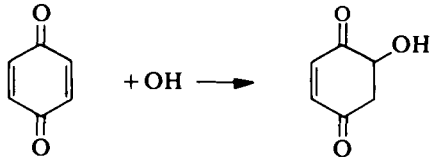
(2)

Many other aliphatic and aromatic radicals reduce quinones by a similar mechanism but with lower rate constants. Consequently, quinones have been used to probe the reducing nature of organic radicals and other species as well. These reactions will be discussed in Section V.

B. Reactions with Hydroxyl, Alkyl and Phenyl

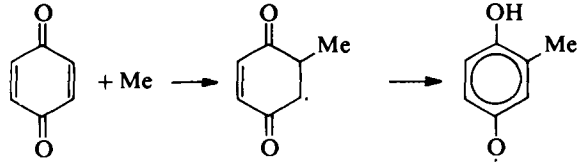
Quinones also react with certain radicals via addition to the double bond. Such was suggested to be the mechanism of their reaction with OH radicals, e.g. reaction 3 for

benzoquinone with $k_3 = 1.2 \times 10^9 \text{M}^{-1}\text{s}^{-1}$ [16]. Similar reactions and rate constants have been reported for various substituted anthraquinones[17–19]. These reactions, followed by disproportionation or oxidation of the radical adducts, result in the radiolytic hydroxylation of the quinones.



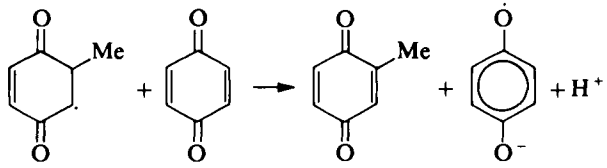
(3)

An addition mechanism was demonstrated also for the reaction of quinones with methyl and phenyl radicals[20], e.g.



(4)

This reaction, with $k = 4.5 \times 10^7\ \text{M}^{-1}\text{s}^{-1}$ for Me and $1.2 \times 10^9\ \text{M}^{-1}\text{s}^{-1}$ for Ph, was found to be followed by a rapid electron transfer from the adduct radicals to benzoquinone. This results in the quantitative formation of methyl- or phenylbenzoquinone from each Me$^{\cdot}$ or Ph$^{\cdot}$ produced in the solution.



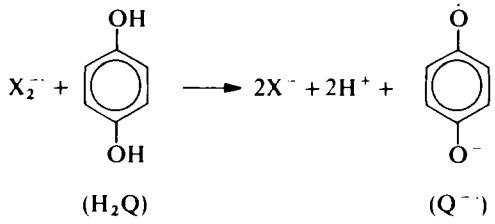
(5)

III. FORMATION OF SEMIQUINONES

Semiquinone radicals are produced by one-electron reduction of quinones as described in Section II. They are also produced by one-electron oxidation of hydroquinones with various radicals and by the reaction of OH radicals with hydroquinones and with certain substituted phenols.

A. One-electron Oxidation of Hydroquinones

Hydroquinones react with a variety of organic and inorganic one-electron oxidizing radicals to yield the semiquinones. The typical oxidants are $X_2^{-\cdot}$ (X = Cl, Br, I, SCN), $N_3^{\cdot}$ and $\dot{C}H_2CHO$. Rate constants for oxidation by $X_2^{-\cdot}$ are moderate in neutral solutions and become very rapid in alkaline solution due to the acid dissociation of the hydroquinone[21].



(H_2Q) $(Q^{-\cdot})$ (6)

$$X_2^{-\cdot} + HQ^- \rightarrow 2X^- + H^+ + Q^{-\cdot} \quad (7)$$

$$X_2^{-\cdot} + Q^{2-} \rightarrow 2X^- + Q^{-\cdot} \quad (8)$$

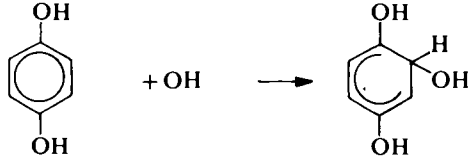
The $N_3^{\cdot}$ radical is a more powerful oxidant which reacts with hydroquinones very rapidly ($k \sim 10^9$ M^{-1} s^{-1}) even in neutral solutions[22,23]. The $\dot{C}H_2CHO$ radical is a weaker oxidant which is useful for his purpose mainly in alkaline solutions[24,25].

$$\dot{C}H_2CHO + H^+ + Q^{2-} \rightarrow CH_3CHO + Q^{-\cdot} \quad (9)$$

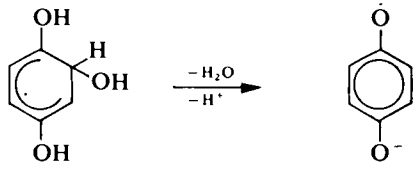
Other radicals which were found to oxidize hydroquinones include $\dot{N}H_2$[26], $\dot{S}O_3^-$ and $SO_5^{-\cdot}$[27], alkoxyl[28] and phenoxyl[25].

B. Reaction of OH Radicals with Hydroquinones

Although the hydroxyl radical is a strong oxidant it tends to react with aromatic compounds by addition to the ring and this mechanism holds for hydroquinones as well. The adduct radicals undergo water elimination to form the semiquinone[16,29–32]. Reaction 11 is a stepwise acid- or base-catalyzed reaction, which in neutral solutions is catalyzed by buffers. The rate of elimination is strongly dependent on the structure of the aromatic compound.



(10)



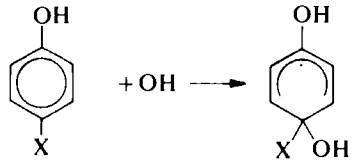
(11)

At very high pH, where the OH radical dissociates to $O^{-\cdot}$ ($pK_a = 11.8$), the reaction becomes a direct electron transfer, as suggested for phenoxide ions[33].

$$O^{-\cdot} + Q^{2-} + H^+ \rightarrow OH^- + Q^{-\cdot} \quad (12)$$

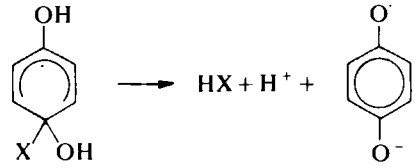
C. Reaction of OH Radicals with Other Substituted Phenols

Addition of OH radicals to substituted phenols takes place at various ring carbons, including those bearing the substituent (*ipso* position)



(13)

Ipso adducts with certain substituents (X = halogen, NH_2, OMe, NO_2) undergo very rapid elimination of HX to form semiquinones[29, 34-37].



(14)

IV. PROPERTIES OF SEMIQUINONES

A. Optical Absorption Spectra

Pulse radiolytic studies on the reduction of quinones or the oxidation of hydroquinones permitted the determination of the optical absorption spectra of the semiquinone radicals. These spectra were used, in turn, to characterize the semiquinones, their rates of formation and reactions, their acid–base equilibria and redox potentials. It is important, therefore, to summarize the absorption spectra. The main parameters are given in Table 1.

TABLE 1. Optical absorption spectra of semiquinones

	λ_{max}	ε_{max}	Reference
p-Benzosemiquinones			
Unsubstituted	430	6100	16, 38, 39
	404	~ 5000	
	(316)	(40 000)[a]	
2-Methyl-	430	6200	38
	405	4500	
2,3-Dimethyl-	430	6700	38
	415	5100	
2,5-Dimethyl-	435	6800	38, 39
	415	5000	
2,6-Dimethyl-	430	6100	38
	405	4900	
2,3,5-Trimethyl-	435	6700	38
	410	4300	
Tetramethyl-	440	7600	38, 39
	420	4700	
2-Carboxymethyl-	430	6000	25
	405	5200	
	310	11 000	

TABLE 1. (*Contd.*)

	λ_{max}	ε_{max}	Reference
2,3-Dimethoxy-5-methyl-6-R-(ubiquinone; R = isoprenoid side chain)	445 425	8600 5300	38
o-Benzosemiquinones			
Unsubstituted	300		16
4-*t*-Butyl-	313 (350)	12200 (2400)	31
4-(2-Amino-2-carboxyethyl)- (from DOPA)	310	5800	25
4-(2-Amino-1-hydroxyethyl)- (from norepinephrine)	310	5400	25
m-Benzosemiquinones			
Unsubstituted	450 ~ 430	~ 2200 ~ 2000	25
1,4-Naphthosemiquinones			
Unsubstituted	390 370	12500 7100	38
2-Methyl-	390 370	12500 9500	38, 39
2,3-Dimethyl-	400 380	11000 7300	38
2-Hydroxy-	390	6300	39
2-Methyl-3-phytyl-(vitamin K_1)	400 380	10200 9900	38
1,2-Naphthosemiquinones			
Unsubstituted	265	40000	39
9,10-Anthrasemiquinones			
Unsubstituted	480 395	7300 7800	39
1-Sulfonate	500 400	8000 8000	17, 39
2-Sulfonate	505 405	7600 8000	17, 40
1-Amino-	490 400	8000 6500	17
1,4-Diamino-	500	14000	41
Miscellaneous semiquinones from[b]			
Gallic acid (ox)	337	3500	25
5-Hydroxydopamine (ox)	315	4800	25
Catechin (ox)	315	5800	25
6-Hydroxydopamine (ox)	440 420 345	3500 2700 7600	25

TABLE 1. *(Contd.)*

	λ_{max}	ε_{max}	Reference
6,7-Dihydroxycoumarin (ox)	530	2400	25
Ellagic acid (ox)	525	6400	25
Quercetin (ox)	520	17000	25
7-Hydroxycoumarin (ox)	575	2700	25
	525	1750	
Quinalizarin (ox)	720	17000	25
Naphthazarin (red)[c]	~ 700		42
	~ 400	~ 10000	
Adriamycin (red)	660	1300	43
	480	12400	
Mitomycin c (red)	510	5500	43
	360	15600	43
Daunomycin (red)	700	7200	43
	500	10500	
Lumazine (red)	~ 450	1000	44
	360	~ 7000	
Lumichrome (red)[c]	450	3900	45
	360	~ 12000	
Riboflavin (red)	570	5000	46
	510	6000	
	340	11000	
Flavin-adenine-dinucleotide (red)	~ 550		47
	340		

[a] Determined by non-radiolytic means by S. Fukuzumi, Y. Ono and T. Keii, *Bull. Chem. Soc. Japan*, **46**, 3353 (1973).
[b] Semiquinones produced from the following compounds by oxidation (ox) or by reduction (red).
[c] Spectral parameters given for neutral solutions. Similar values were found for 1-methyl, 3-methyl and dimethyl derivatives. Spectral changes are observed upon protonation of the radical in acid solutions or deprotonation in alkaline solutions (see Ref. 45).

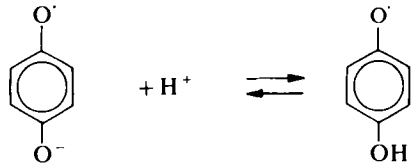
It is seen from Table 1 that *p*-benzosemiquinones exhibit absorption maxima at ~ 430 nm with $\varepsilon \sim 6000$–$7000\ M^{-1}\,cm^{-1}$, a second peak at slightly lower wavelengths, and a third very intense peak around 310 nm. In contrast, *o*-benzosemiquinones absorb only at the lower wavelength region, ~ 310 nm. The *m*-benzosemiquinone radical, produced by one-electron oxidation of resorcinol, exhibits a relatively weak absorption at 450 nm ($\varepsilon \sim 2200\ M^{-1}\,cm^{-1}$). These differences are important in that they permit optical monitoring of reactions, e.g. electron transfer, between different types of semiquinones but not within the same type.

A parallel situation occurs with naphthosemiquinones. The 1,4-isomers absorb at 380–400 nm while the 1,2-isomers only at < 300 nm. The spectra of anthrasemiquinones are red shifted to ~ 500 nm. The miscellaneous semiquinones at the end of Table 1 also conform to the above generalities if their basic structures are not perturbed greatly.

The absorption spectra of the semiquinones given in Table 1 have been determined predominantly in neutral solutions, where all the simple cases exist as the radical anions. The spectra of the simple semiquinones are found to be shifted to lower wavelengths in acid solutions owing to protonation of the O^-. These spectral changes have been utilized for the determination of the acid–base equilibria.

B. Acid–Base Equilibria

The pK_a values for semiquinones are summarized in Table 2.



(15)

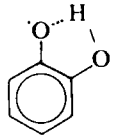
It is seen from Table 2 that most semiquinones have pK_a values around 3–5, i.e. much lower than the values for the same OH group in the parent reduced molecule. Clearly, the

TABLE 2. Acid dissociation constants of semiquinones

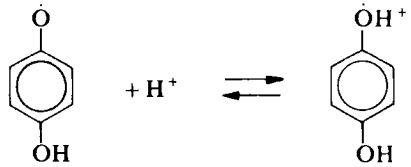
	pK_a	Reference
p-Benzosemiquinones		
Unsubstituted	4.0, 4.1	16, 39
2-Methyl-	4.5	38
2,3-Dimethyl-	4.7	38
2,5-Dimethyl-	4.6	39, 48
2,6-Dimethyl-	4.8	38
2,3,5-Trimethyl-	5.0	38
Tetramethyl-	4.9, 5.1	38, 39, 48
Ubisemiquinone	5.9	38
o-Benzosemiquinones		
Unsubstituted	5.0	34
4-*t*-Butyl-	5.2	31
m-Benzosemiquinone		
Unsubstituted	7.1	49
1,4-Naphthosemiquinones		
Unsubstituted	4.1	39, 48
2-Methyl-	4.4–4.7	38, 39, 48
2,3-Dimethyl-	4.3	38
2-Hydroxy-	4.7	39
2-Methyl-3-phytyl-(vitamin K_1)	5.5	38
9,10-Anthrasemiquinones		
Unsubstituted	5.3	39
1-Sulfonate	5.4	17
2-Sulfonate	3.2	17
2,6-Disulfonate	3.2	48
Miscellaneous semiquinones from[a]		
Adriamycin	2.9, 9.2, > 14	42, 50
Lumazine	2.9, ~ 8.6, ~ 12.6	44
1-Methyllumichrome	~ 3.5, 10.5	45, 51
3-Methyllumichrome	~ 3.5, 7.8	45, 51
Dimethyllumichrome	3.5, 10.2	51
Lumichrome	3.5, 8.8, 12.5	51
Riboflavin	2.3, 8.3	46

[a] Radicals from the following compounds undergo several acid-base equilibria with different pK values. For the possible sites of protonation see original references.

unpaired electron causes a considerable increase in the acidity of phenolic OH groups and the magnitude of this effect is dependent on the relative positions. For example, *m*-benzosemiquinone has $pK_a = 7.1$, *o*-benzosemiquinone 5.0 and *p*-benzosemiquinone 4.0. In the *meta* isomer the pK_a of the radical is about 3 units lower than that of resorcinol while in the *para* isomer it is 6 units lower. This large difference is a result of differences in spin density distributions in the radicals. In *m*-benzosemiquinone most of the spin density is on carbons 4 and 6 with very little on the oxygens, while in the *para* isomer ~60% is on the oxygens. From spin density considerations the *ortho* isomer should have a pK_a value similar to that of the *para* isomer. The value observed is, in fact, higher by 1 unit. The reason for this difference must be intramolecular hydrogen bonding in the *ortho*, which inhibits the proton dissociation. This *ortho* effect is general for other semiquinones (cf. 1,4- vs. 1,2-naphthosemiquinones) and other types of radicals as well.



Semiquinones undergo a second protonation step in strong acid.



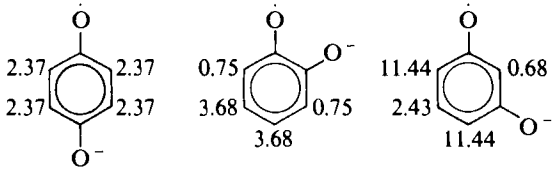
(16)

These equilibria were monitored by ESR in conjunction with non-radiolytic radical production and pK_a values around -2 were determined[52].

C. ESR Spectroscopy

While optical absorption spectroscopy provided most of the kinetic information and acid–base equilibria for semiquinones, ESR spectroscopy allowed the determination of the second protonation step[52] and gave detailed information on the spin density distribution within the radicals. Although ESR spectroscopy of semiquinones was carried out to some extent in conjunction with radiolytic methods of radical production, most of the ESR information was obtained by other techniques. It is, therefore, beyond the scope of this chapter to present a comprehensive summary of the ESR spectroscopy of semiquinones. Only a few points derived from radiolytic studies will be discussed here.

Steady-state *in situ* radiolysis ESR experiments were carried out with solutions of quinones or hydroquinones and the ESR spectra of semiquinones were recorded. The hyperfine splitting constants and *g*-factors are[29, 34, 53]:

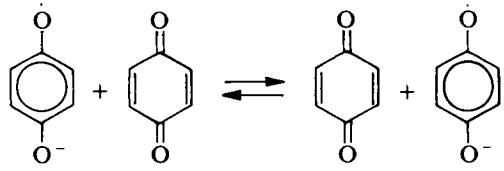


$g = 2.00456$ 2.00455 2.00383

In all cases the two oxygens are equivalent as are all pairs of symmetric carbons. In the case of the *o*- and *p*-semiquinone about 60–65% of the unpaired spin density resides on the oxygens and the rest is distributed over the carbons. The *m*-isomer, on the other hand, has only ~20% of the spin density on the oxygens. This difference is reflected also in the *g*-factors. Protonation of the O^- removes the symmetry and changes the hyperfine splittings considerably. Semiquinones with several substituents have also been studied[29,34] and the ^{13}C hyperfine splitting constants were determined for certain cases[53]. The latter parameters enabled more detailed estimates of spin distributions.

Radiolytic formation of semiquinones was not confined to reduction of quinones or oxidation of hydroquinones. In the ESR study of various phenols[29], reactions with OH radicals were found to yield the corresponding phenoxyl as the main product, but secondary reactions led to the formation of *o*- and *p*-semiquinones as well. With substituents like methoxy or nitro, addition of OH at the *ipso* position was found to be followed by demethoxylation or denitration and production of semiquinone[34,35].

ESR studies of semiquinones are unique in that they permit determination of electron exchange rate constants from line broadening measurements[54].The values for benzoquinone and its methylated derivatives were found to be in the range of $0.5–2 \times 10^8$ $M^{-1}s^{-1}$.



(17)

Another study adapted the radiolysis–ESR technique to the measurement of spin-lattice relaxation times for semiquinones[55]. A value of 2 μs was found for *p*-benzosemiquinone anion and a longer T_1 (11.5 μs) for the 2,5-di-*t*-butyl derivative.

Radiolysis of benzoquinone in frozen $CFCl_3$ solutions gave the radical cation and the ESR spectrum indicated that the radical is localized on one oxygen only[56].

D. Raman Spectroscopy

Recent adaptation of time-resolved resonance Raman spectroscopy to pulse radiolysis has led to several studies on semiquinones[57–61]. Raman frequencies have been ascribed to C–O and C–C stretching modes and C–C–C bending modes. For *p*-benzosemiquinones the frequency assigned to the C–O bond was found to be intermediate between those for the corresponding bonds in hydroquinone and benzoquinone. This led to the conclusion that the C–O bond order in the semiquinone is ~ 1.5[57]. The frequency of the C–O bond increases upon halogenation indicating a higher double bond character[58,60]. On the other hand, deuteration decreases the C–C stretching frequencies with little effect on the C–O frequencies[61].

Raman spectroscopy also yielded information on the excited states of the radicals from examination of the frequencies which are resonance-enhanced. Time-resolved experiments have also been carried out, which allow kinetic measurements on a specific intermediate unmasked by changes in other species.

V. QUINONES AS ELECTRON ACCEPTORS

It has been established in early pulse radiolysis experiments that benzoquinone accepts an electron rapidly from a wide variety of radicals[62]. These radicals include not only typical

reducing species (see reaction 2) but also radicals like O_2^- and NAD. In fact, quinones are such strong electron acceptors that they have been used to detect mild reducing radicals and to distinguish between radicals in a mixture through differences in electron transfer reactions.

2-Methyl-1,4-naphthoquinone has been used to detect reducing radicals in a wide variety of systems[63]. These include radicals produced by hydrogen abstraction from alcohols, sugars, carboxylic acids, amino acids, dipeptides, amines, and amides, by OH addition to aromatic and heterocyclic compounds, and by electron addition to ketones, pyridines, other heterocycles, and metal ions. In most cases reduction of the quinone took place by a certain portion of the radicals and with rate constants of $\sim 10^8$–10^9 $M^{-1}s^{-1}$. Lower rate constants could not be measured because of the competing rapid decay of the radicals under those conditions. Partial yields were rationalized by partial decay of the radical, in competition with electron transfer to the quinone, or by formation of several radicals of which only some are capable of reducing the quinone. By measuring the rate and degree of electron transfer from radicals to several quinones and dyes, an attempt was made to correlate these parameters with the redox potentials of the acceptors[64-67]. The correlation, however, was only qualitative and partially inaccurate.

Because many quinones are reduced by O_2^- to form the easily detectable semiquinones, they have been used to monitor O_2^- formation upon reaction of organic radicals with O_2 [68-71]. This was principally done to distinguish between the two possible mechanisms: electron transfer ($R + O_2 \rightarrow R^+ + O_2^-$) and addition ($\dot{R} + O_2 \rightarrow R\dot{O}_2$). While O_2^- reduces benzoquinone, peroxyl radicals do not. With $\dot{R}$ bearing an OH or NH_2 group in the alpha position the product of reaction with O_2 was also found to be pH dependent. The initial step is always formation of peroxyl radical (e.g. $(HO)R\dot{O}_2$) but at higher pH values these radicals decompose to give O_2^-.

The reaction of O_2^- with benzoquinone was used also as a reference to measure rate constants for other reactions of O_2^- which are not readily monitored[71].

Addition of OH radicals to aromatic and heterocyclic compounds may take place at several positions and thus produce different radicals which may or may not reduce quinones and may react with different rate constants. For example, addition of OH to anisole yields three isomeric radicals, of which the *o*- and *p*- reduce benzoquinone rapidly ($k = 1.2$ and 4.4×10^9 $M^{-1}s^{-1}$, respectively) but the *m*- does not ($k \leqslant 8 \times 10^5$ $M^{-1}s^{-1}$)[72]. These differences helped in the determination of the isomeric distribution of OH adducts. Similar studies were carried out on the OH adducts of phenol and using several quinones as oxidants[73]. Addition of OH to phenol was found to take place 48% at the *ortho* positions, 36% at the *para*, 8% at the *meta* and 8% at the *ipso* position[73].

Addition of OH to pyrimidine bases also yields different radicals which partially reduce quinones[74]. It was established later that 5-OH adducts are the reducing radicals while 6-OH adducts are oxidants[75].

Several studies have utilized quinones to demonstrate the reducing power of unstable metal ions. For example, benzoquinone is reduced very rapidly ($k \sim 3$–5×10^9 $M^{-1}s^{-1}$) by Cd^+, Co^+, Pb^+, Zn^+, moderately rapidly ($k \sim 10^8$ $M^{-1}s^{-1}$) by Ag_3^+, Cr^{2+}, Ni^+ and only very slowly ($k < 10^6$ $M^{-1}s^{-1}$) by Cu^+ [76]. $Ru(bipyridyl)_3^+$ was found to reduce duroquinone extremely rapidly, $k = 4.0 \times 10^9$ $M^{-1}s^{-1}$ [77] and Co(I) complexes with macrocyclic ligands were found to reduce several quinones also with $k \sim 4 \times 10^9$ $M^{-1}s^{-1}$ [78].

The above discussion included representative examples of the utilization of quinones as electron acceptors from various organic and inorganic species. No attempt is made here to cover this topic comprehensively or to tabulate the rate constants. The reader is referred to compilations which give many more rate constants[12,13,79].

Despite the high electron affinity of quinones the semiquinone radicals have been found to donate electrons to nitroxyl radicals[80], superoxide dismutase[81], triphenyltetrazolium[82] and of course to other quinones of higher electron affinity. The latter will be discussed in more detail in the next section.

VI. ONE-ELECTRON REDOX POTENTIALS

Quinones undergo two successive one-electron reduction steps:

$$Q \underset{E^1}{\overset{+e^-}{\rightleftharpoons}} Q^{\cdot -} \underset{E^2}{\overset{+e^-}{\rightleftharpoons}} Q^{2-} \tag{18}$$

The overall two-electron redox potentials have been determined by classical methods and the individual one-electron redox potentials were accessible only under limited conditions where the semiquinone is infinitely stable. Measurement of E^1 and E^2 in aqueous solutions, particularly at neutral pH when $Q^{\cdot -}$ is relatively short-lived, necessitates the use of a fast detection technique. Pulse radiolysis is the most useful method for this purpose. It permits determination of one-electron redox potentials from equilibria such as

$$S^{\cdot -} + Q \rightleftharpoons S + Q^{\cdot -} \tag{19}$$

if E^1 for the $Q/Q^{\cdot -}$ or for the other substrate $S/S^{\cdot -}$ is known, and provided equilibrium 19 is achieved before the radicals decay.

Equilibria between the quinones and oxygen

$$O_2^- + Q \rightleftharpoons O_2 + Q^{\cdot -} \tag{20}$$

have been demonstrated and equilibrium constants derived[38]. $K_{20} = 2.3 \times 10^{-2}$ was determined for duroquinone. E^1 for duroquinone was derived from its two-electron redox potential and its semiquinone formation constant[83, 84]. Thus $E^1(O_2/O_2^-)$ could be calculated from K_{20}[83, 84] and further confirmation obtained from experiments with 2,5-dimethylbenzoquinone[85].

This technique was further developed for determination of E^1 for quinones by equilibria with reference quinones, for example naphthoquinone or anthraquinone versus duroquinone[40, 86]. Using a set of established E^1 values for several quinones it was possible to determine by pulse radiolysis the one-electron reduction potentials for many other compounds. In particular, redox potentials for nitroaromatic and nitroheterocyclic compounds have been measured[40, 87–90] because of the importance of these compounds as radiosensitizers[89]. In addition, several biologically important molecules have been studied by this method (see below).

The values of E^1 for several quinones are summarized in Table 3. A more complete listing is found in Ref. 14. The redox potentials decrease in going from benzoquinone to

TABLE 3. One-electron reduction potentials of quinones at pH 7

Quinone	E^1 (Q/Q^-) (mV vs. NHE)	Ref.
1,4-Benzoquinone	+99	84
2-Methylbenzoquinone	+23	84
2,3-Dimethylbenzoquinone	−74	84
2,5-Dimethylbenzoquinone	−67	84
2,3,5-Trimethylbenzoquinone	−165	84
Duroquinone	−235	86
1,4-Naphthoquinone-2-sulfonate	−60	84
2-Methyl-1,4-naphthoquinone	−203	86
2,3-Dimethyl-1,4-naphthoquinone	−240	84
9,10-Anthraquinone-2-sulfonate	−375	40, 87

naphthoquinone to anthraquinone by ~ 200 mV in each step. Within each series methyl substitution is found to decrease the redox potential substantially. Further generalizations await additional experimental data.

The one-electron reduction potentials have been correlated with rates of electron transfer[54,91] according to the Marcus theory. Table 4 indicates the general trend of increasing rate constant upon increase in driving force (ΔE). Rate constants of ~ 10^9 $M^{-1}s^{-1}$ or above may be diffusion-limited. With no driving force the rate constants of self-exchange were found to be ~ 5×10^7–2×10^8 $M^{-1}s^{-1}$ for several quinones. With negative driving force, i.e. for the less favorable back reactions, the rate constants are ~ 10^{-6} $M^{-1}s^{-1}$ or less. Quantitative correlations have been discussed before[54,91]. Such correlations are important for indicating the outer sphere nature of the electron transfer, for detecting special circumstances (e.g. geometric constraints) and for predicting unknown rate constants.

TABLE 4. Rate constants of electron transfer from semiquinones to quinones

Semiquinone[a]	Quinone[a]	ΔE^1 (mV,pH 7)	$k(M^{-1}s^{-1})$[b]
$DQ^{-\cdot}$	BQ	334	1.1×10^9
2,6-$DMBQ^{-\cdot}$	BQ	179	1.0×10^9
$DQ^{-\cdot}$	2,5-DMBQ	170	1.1×10^9
2,5-$DMBQ^{-\cdot}$	BQ	164	6.5×10^8
$DQ^{-\cdot}$	2,6-DMBQ	155	9.6×10^8
$AQS^{-\cdot}$	DQ	155	4×10^8
$DQ^{-\cdot}$	DQ	0	2.0×10^8
2,6-$DMBQ^{-\cdot}$	2,6-DMBQ	0	1.7×10^8
$BQ^{-\cdot}$	BQ	0	6.2×10^7
2,5-$DMBQ^{-\cdot}$	2,5-DMBQ	0	5.5×10^7
$DQ^{-\cdot}$	AQS	−155	1.6×10^6
2,6-$DMBQ^{-\cdot}$	DQ	−155	2.0×10^6
$BQ^{-\cdot}$	2,5-DMBQ	−164	9.7×10^5
2,5-$DMBQ^{-\cdot}$	DQ	−170	1.2×10^6
$BQ^{-\cdot}$	2,6-DMBQ	−179	8.3×10^5
$BQ^{-\cdot}$	DQ	−334	1.9×10^3

[a] Abbreviations: BQ, 1,4-benzoquinones; DQ, duroquinone; DMBQ, dimethylbenzoquinone; AQS, 9,10-anthraquinone-2-sulfonate.
[b] From Ref. 54 except values for AQS which are from Ref. 40.

Redox potentials for the second one-electron reduction of quinone, E^2, can be calculated from the overall two-electron potential and E^1 (see e.g. Ref. 84) or can be determined experimentally from equilibria with reference pairs.

$$Q_1^{-\cdot} + Q_2^{2-} \rightleftharpoons Q_1^{2-} + Q_2^{-\cdot} \tag{21}$$

Such equilibria for semiquinone/hydroquinone pairs have been determined by pulse radiolysis[25] and are partially summarized in Table 5. These values also correspond to the oxidation potentials of the doubly ionized dihydroxybenzenes. It is seen from Table 5 that catechol is oxidized only slightly less readily than hydroquinone while resorcinol differs by ~ 350 mV. Substitution affects the redox potentials as expected, i.e. the electron-donating substituents methyl, methoxy and hydroxy enhance the oxidation, in that order, while the electron-withdrawing substituents carboxy, sulfonate, vinyl and acetyl exert the opposite effect.

TABLE 5. One electron reduction potentials of semiquinones

Semiquinone	E^2(mV vs. NHE)[a]
1,4-Benzosemiquinones	
Unsubstituted	23
2-Hydroxy-	−110
2-Methoxy-	−85
Tetramethyl-	−54
2-Carboxymethyl-	−50
2-Carboxy-	33
2,5-Disulfonate	116
2-Acetyl	118
1,2-Benzosemiquinones	
Unsubstituted	43
4-Hydroxy-	−110
3-Hydroxy-	−9
4-(2-Amino-2-carboxyethyl)-	18
4-Carboxymethyl-	21
3-Hydroxy-5-(2-aminoethyl)-	42
4-(2-Amino-1-hydroxyethyl)-	44
4-(2-Carboxyvinyl)-	84
3-Carboxy-	118
4-Carboxy-	119
1,3-Benzosemiquinone	385

[a] From Ref. 25 except the value for the 2,5-disulfonate which is from Ref. 27. Determined at 0.5 M KOH.

The redox potentials E^1 and E^2 are pH dependent due to the acid–base equilibria of the semiquinones and the hydroquinones. From known pK_a values, redox potentials at different pHs have been calculated[25, 40, 84, 86].

The rate constants leading to equilibrium 21 (k_{21} and k_{-21}) were also found to be in the range of 10^5–10^9 $M^{-1}s^{-1}$ and to depend on the driving force[25]. These rate constants are strongly dependent upon pH since, in general, the rate of oxidation of QH_2 is much slower than that of QH^- or Q^{2-}. Consequently, equilibrium 21 could not be monitored in neutral solutions.

VII. QUINONES OF BIOLOGICAL IMPORTANCE

Naturally occurring quinones are important in electron transport, in photosynthesis and as vitamins. Other quinones have biological importance as drugs. Radiation chemical studies of these quinones have helped in characterizing the chemical behavior of these compounds, especially their electron transfer rates and redox potentials, and often contributed to the understanding of their biological action.

Quinones have been shown to act as sensitizers of radiation damage to hypoxic cells and thus may serve as drugs to enhance tumor radiotherapy (see e.g. Refs 92–94). Their efficiency as radiosensitizers is related to their ability to oxidize or trap radiation-produced free radicals and thus 'fix' the radiation damage[95–97]. Their efficiency has been correlated with their one-electron reduction potentials determined by pulse radiolysis[93, 94]. Although other pharmacological properties are obviously very important, the reduction potential serves as a preliminary test to predict the radiosensitization efficiency of a drug. It should be pointed out, however, that the majority of research on radiosensitizers has concentrated

on nitroheterocyclic compounds and not on quinones. The redox potentials for the nitro compounds have been determined in most cases by reference to a quinone using pulse radiolysis[14].

Several studies dealt with anthracycline drugs, such as adriamycin and mitomycin, in an attempt to understand their cancer chemotherapeutic effect from pulse radiolytic observations on their semiquinone radicals[43, 50, 98-101]. To help in the interpretation of those results additional information was obtained on model compounds[42, 102]. In these studies the absorption spectra, acid dissociation constants and redox potentials of the semiquinones have been determined. More importantly, their reactions with oxygen and iron complexes have been monitored. Based on the rates of these reactions, a mechanism has been proposed to account for the enhanced free radical damage caused by these drugs[98, 99, 102]. The main reactions appear to be those of the semiquinones with O_2 to give O_2^- (which disproportionate to yield H_2O_2) and with Fe^{3+} to give Fe^{2+}. This enhances the probability of a Fenton reaction ($Fe^{2+} + H_2O_2 \rightarrow OH$) which forms the damaging OH radicals.

For the drug daunorubicin, reaction of its doubly reduced form with H_2O_2 has been suggested[100, 101]. Furthermore, radiolytic reduction of this drug was found to result in cleavage of the glycosidic bond.

The effect of radiation on another drug, tetracycline, in the solid state was found to result in cleavage of the dimethylamino group[103]. Significant cleavage was detected only at doses much higher than those used for sterilization purposes.

Pulse radiolysis studies on other semiquinones of biological importance have been discussed in previous sections. These include rates of electron transfer to vitamin K and ubiquinone and the spectra and pK_a values of their semiquinones[38]. Other studies dealt with the semiquinones produced by oxidation of catecholamines and related compounds, including their spectra and redox potentials (see e.g. Refs 25, 30). Disproportionation of the semiquinone derived from 3,4-dihydroxyphenylalanine (DOPA) was found to form dopaquinone which cyclizes to yield dopachrome and eventually polymerizes to melanin[23].

Other researchers were concerned with the involvement of plastoquinone and ubiquinone in the reaction centers of photosynthesis. Pulse radiolysis studies[104] on plastoquinone in methanolic solutions showed that the spectrum of the semiquinone is similar to that observed after photoexcitation of Photosystem II of plants, where plastoquinone serves as an electron acceptor. Experiments with ubiquinone found similarity between its semiquinone spectrum and that observed upon photoexcitation of bacterial reaction centers, thus suggesting that ubiquinone may be the electron acceptor in these systems[104]. That quinones are good electron acceptors from excited chlorophyll and porphyrins has been shown by many photochemical studies. Pulse radiolytic experiments demonstrated that quinones accept electrons rapidly ($k \sim 10^8$–10^9 $M^{-1}s^{-1}$) from the radical anions of chlorophyll and porphyrins[105].

VIII. FLAVINS AND RELATED COMPOUNDS

The main biological function of flavins is electron transport. Therefore, they were frequently studied by pulse radiolysis. Rate constants for electron transfer to flavins and from flavin semiquinones to other acceptors, as well as one-electron redox potentials, have been determined. Studies were carried out on riboflavin, FMN (flavinmononucleotide) and FAD[46, 47, 106-111] (flavin adenine dinucleotide) and on simpler model compounds, lumiflavin[112, 113], lumichrome[45, 51, 114] and lumazine[44].

Flavins are reduced by hydrated electrons and by organic radicals such as CO_2^- and $(Me)_2\dot{C}OH$ very rapidly to produce the semiquinones. These radicals exhibit intense absorptions in the 300–600 nm region (see Table 1) which are dependent on pH. From this

dependence pK_a values for the semiquinones were determined and found to be in the region of ~ 3 and ~ 8 (see Table 2). The acid form of the radical is very stable while the neutral and basic forms are short-lived[46, 108]. They decay by disproportionation to form flavin and dihydroflavin.

The one-electron reduction potentials for flavins have been determined from equilibria with several reference quinones and pyridine derivatives. The values at pH 7 for riboflavin, FMN and FAD were $E^1_7(\text{Fl}/\text{Fl}^-) \sim -310$ mV[47, 106, 107] and for the lumichromes ~ -520 mV[51]. These values change with pH according to the acid–base equilibria of the radicals (mentioned above) and of the parent flavins. From the known two-electron potential $E^\circ_7(\text{Fl}/\text{FlH}_2) = -219$ mV the value of the second one-electron reduction potential $E^2_7(\text{Fl}^{-\cdot}/\text{FlH}_2) \sim -120$ mV was calculated[107].

Flavins are reduced also by α-aminoalkyl radicals, e.g. those derived from glycine and EDTA[113]. $\text{RSSR}^{-\cdot}$ radicals also reduce flavins very rapidly[110, 111], while RS radicals

$(\text{RS} + \text{RS}^- \rightleftharpoons \text{RSSR}^-)$ oxidize dihydroflavin, as do other typical oxidizing radicals[115].

Electron transfer from the semiquinone of FMN to cytochrome c also was examined by pulse radiolysis and found to have a rate constant of 4×10^7 M^{-1}s^{-1} [109]. This value is about an order of magnitude higher than the rate constant for reduction of cytochrome c by cytochrome reductase.

Rates of electron transfer to flavins were examined by pulse radiolysis also for flavins bound to proteins[116–119]. It is interesting to note that much of the initial reduction occurs on protein sites and subsequently an intramolecular electron transfer leads to formation of the flavin semiquinone. The flavin semiquinone anion is first produced and is then stabilized by accepting a proton from other sites of the protein[119].

IX. EXCITED STATES

The above sections dealt with radiolytic studies of quinones involving free radicals. In certain solvents, however, it is possible to form the excited states of quinones by radiolysis. Thus pulse radiolysis has been utilized also for monitoring spectra and kinetics of quinones in their excited states, predominantly in benzene solutions[120–127].

Triplet–triplet extinction coefficients were determined by pulse radiolysis by monitoring energy transfer processes[120]. This method has an advantage over earlier techniques in that it permits interconnecting a large number of triplets as donor–acceptor pairs[120]. The rate constants for energy transfer were near $\sim 10^{10}$ M^{-1}s^{-1} [120].

The triplet excited states of anthraquinones were also characterized by the energy transfer method[121]. Their lifetimes in benzene and their rate of reaction with O_2 and isopropanol were determined. No interaction was detected between the triplets and their ground states[121].

It is noted, however, that anthraquinones 1,4-disubstituted with amino or hydroxyl groups were suggested to exist in benzene solutions in an associated form even at very low concentrations[124]. This suggestion was based on the observation that triplet energy transfer from biphenyl to the anthraquinone appears to remove more than one ground state molecule. No aggregation was indicated for the triplets of these quinones.

Pulse radiolysis permitted the first observation of the triplet excited state of ubiquinone[122]. Various derivatives of ubiquinones were subsequently studied[123]. The results with these derivatives led to the conclusion that the low triplet energy and quantum yield of triplet ubiquinone is due to the methoxy groups on the ring and not the isoprenoid side chain[123]. These results further suggested that the ubisemiquinone observed in bacterial photosynthesis is most likely formed by electron transfer from excited chlorophyll rather than via triplet ubiquinone[123].

X. MISCELLANEOUS TOPICS

Quinones, being efficient traps for electrons, have been used frequently to probe various effects on the reactivity of solvated electrons and on electron transfer reactions[128-136]. In a study on the kinetics of electron attachment to benzoquinone in non-polar solvents an unusual dependence on solvent and temperature has been noted[130]. In pentane and similar solvents the reaction was found to be fast and with a positive activation energy but in solvents like neopentane and tetramethysilane the reaction is much slower and has a negative activation energy. These results have been rationalized by suggesting that an electron reacting with benzoquinone leads to an excited benzoquinone anion. In pentane this product relaxes rapidly to a stable semiquinone anion but in tetramethylsilane the excited anion detaches its electron rapidly because the energy level of the electron in this liquid is much lower[130].

Quinones have been used to study the effect of exothermicity on rates of electron transfer reactions in order to test electron transfer theories. By measuring the rates in rigid organic glasses the problems of diffusion control and reactant complexation were avoided. The rates of electron transfer were slow for reactions with low driving force and became faster upon increasing exothermicity. However, at very high exothermicities the rates were found to decrease, as predicted by the theories[135]. Further confirmation of this 'inverted region' was obtained from measurements of intramolecular electron transfer rates[136]. A series of electron acceptors, including several quinones, were attached to one end of a rigid molecular spacer (androstane skeleton) which was bound to biphenyl at its other end. Rates of intramolecular electron transfer from the biphenyl anion to the acceptor were measured by pulse radiolysis. They were found to increase from $10^6\ s^{-1}$ to $> 10^9\ s^{-1}$ upon increasing ΔG° from 0.05 to 1.2 eV. Further increase in ΔG° to 2.4 eV was accompanied by a gradual decrease in rate constant to $< 10^8\ s^{-1}$ [136].

Bianthrone, because of steric interactions, assumes two distinct conformations. The anion radicals of bianthrones were found to undergo conformational changes. The rate constants for these processes were also monitored by pulse radiolysis[137]. A rate of $7 \times 10^4\ s^{-1}$ was found for bianthrone anion but only $1.1 \times 10^3\ s^{-1}$ for the 1,1'-dimethyl derivative, in which the conformational change is sterically hindered.

Several studies examined the radiation-induced bleaching of anthraquinone dyes in solution[138-140] and in the solid state[141]. Bleaching was found to result from the reactions of electrons and other reducing radicals as well as by addition of OH to the ring. The effects of O_2 and H_2O_2 concentrations were examined. The interest in these systems was primarily for their application in radiation dosimetry and no detailed mechanistic studies were carried out.

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CHAPTER 15

Chemistry of quinone bis- and monoketals

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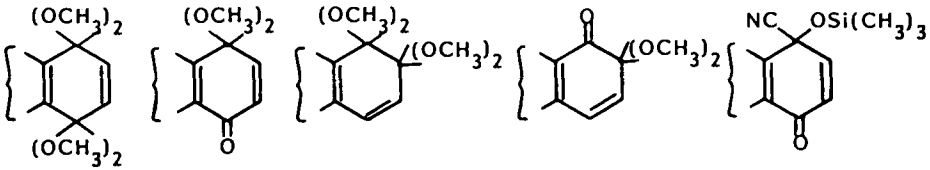
I. INTRODUCTION

Quinone and quinone-related natural products have occupied a pivotal position in organic chemistry throughout the years; thus, methods for the preparation of quinones and the chemistry of the quinone moiety have been well-studied[1]. The simple quinone unit is quite reactive toward nucleophiles and is easily reduced via electron transfer to form the corresponding radical anion. Thus, in the synthesis of functionalized quinones, the usual approach is to perform many of the synthetic operations on the corresponding hydroquinone ether. The quinone unit is then introduced at one of the later stages of the synthesis by oxidation of the functionalized hydroquinone ether. Aside from the high reactivity of the quinone linkage, 1,4 additions to unsymmetrical quinones often afford mixtures of regioisomeric products. This complicates synthetic processes initiated by addition at the β position of the quinone, one example being the preparation of certain indoles via the reaction of quinones with enamines—the Nenitzescu reaction[2].

In the past ten years two types of protected quinone derivatives—*p*-quinone bisketals (**1**) and quinone monoketals (**2**)—have become readily available, leading to increased use of the compounds in synthesis[3]. The quinone bisketal and monoketal serve as valuable



protected quinone derivatives since they possess the quinone oxidation state; yet, they often circumvent reactivity and regiochemical problems encountered in reactions of the quinone entity itself. This review will discuss first the preparation and chemistry of quinone bisketals, followed by an analogous treatment of the preparation and chemistry of quinone monoketals. Sufficient literature has appeared in the past several years to establish the chemical utility of these compounds. A comparison of this chemistry with that of the analogous quinones will be made where possible. Although less chemistry of the *o*-quinone analogs (**3**) and (**4**) has been published, a brief survey of this chemistry is also given. Excluded from this detailed coverage is the chemistry of trimethylsilyl cyanide-blocked quinone derivatives[4], e.g. **5**, although this chemistry will be noted wherever a direct comparison can be made with reactions reported for quinone monoketals.

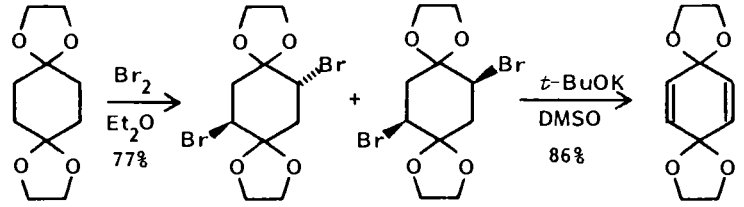
Several conventions will be observed throughout the chapter. Chemical Abstracts and IUPAC rules no longer use the term ketal, favoring the term acetal for all such structural

units; nevertheless, the term bisketal will be used when describing a molecule such as **1**. Furthermore, although bisketals of both *p*- and *o*-quinones are known, much more chemistry has been published on the former series of compounds. Thus, the *p*-quinone bisketals will be referred to simply as quinone bisketals while similar derivatives of *o*-quinones will explicitly be called *o*-quinone bisketals. Finally, the symbol Ⓔ used in equations denotes electrochemical oxidation.

II. PREPARATION OF QUINONE BISKETALS

A. Anodic Oxidation of 1,4-Dimethoxyaromatic Systems

Although reaction of a quinone with alcohol would be the most direct route to quinone bisketals, this method is usually unsatisfactory. Presumably, 1,4 addition of the alcohol to the quinone system followed by irreversible aromatization dominates the reversible 1,2 addition required for ketal formation. The one non-electrochemical[5] preparation of the quinone bisethylene glycol ketal **9** involved bromination of the 1,4-cyclohexanedione



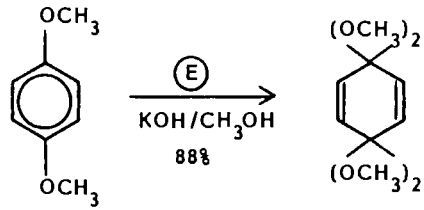
(1)

6 7 8 9

bisethylene glycol ketal **6** followed by dehydrobromination of **7** and **8** (equation 1). The yields for this reaction were good; however, the generality of the method as a route to substituted benzoquinone bisketals rests on the availability of the requisite 1,4-cyclohexanedione. As will be discussed below, the high yields of quinone bisketals from anodic oxidation of readily available 1,4-dimethoxybenzene derivatives make the above chemistry of historical interest only. Furthermore, this bromination/dehydrobromination sequence does not appear to be directly applicable to the preparation of naphthoquinone bisketals.

1. Anodic oxidations in a single cell

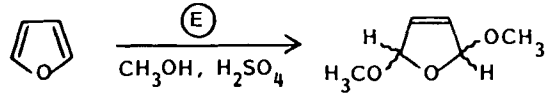
A route that has proved to be the most general for the preparation of quinone bisketals was first reported by Weinberg and Belleau in 1963[6]. Thus, anodic oxidation of 1,4-dimethoxybenzene (**10**) at constant current in a single cell (anode and cathode not separated) using 1% methanolic potassium hydroxide as both solvent and electrolyte afforded the benzoquinone dimethyl ketal **11a** in 88% yield (equation 2). Apparently, this



(2)

10 11a

unique route was inspired by anodic oxidation studies of furans in the early 1950s by Clauson-Kaas and coworkers[7a-d] who showed that a wide variety of furans (e.g the parent **12**) could be electrochemically oxidized to the bisketals of structure **13** (equation 3). This transformation was initially conducted with ammonium bromide[7a] as electrolyte in methanol and involved electrogenerated bromine as the reactive species. Subsequent work demonstrated that electrochemical oxidation performed on furans with non-halogen electrolytes[7b-d] also afforded products analogous to **13** in good yield.



12 13 (3)

This anodic oxidation provided a unique and efficient route to a totally protected quinone derivative in one step from 1,4-dimethoxybenzene; however, the reaction attracted little attention in the intervening years. Several papers of a mechanistic nature appeared in 1973–5[8], but little synthetic use was made of the chemistry. Shortly thereafter, however, the potential utility of the reaction for the preparation of functionalized quinones was recognized[9]. This electrochemical oxidation was originally envisioned as a method for the preparation of functionalized protected quinone derivatives which subsequently could be transformed into anthraquinone natural products[10].

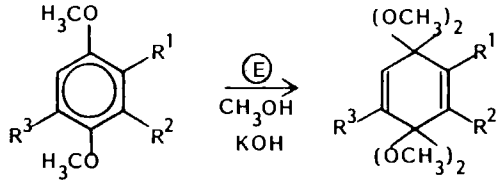
Of particular concern was the generality of the anodic oxidation to produce quinone bisketals. The concern was that oxidation of substituents on the benzenoid system would compete with the desired ring oxidation[11a-d]. In fact, under conditions similar to those employed for the anodic oxidation to form **11a**, oxidation of benzylic methylene groups, benzylic secondary and tertiary alcohols, dimethyl acetals, aldehydes, amides and conjugated esters had been reported[11d]. However, as illustrated in Table 1, this particular oxidation occurs in a single cell without potential control for a wide range of substituted 1,4-dimethoxybenzene and 1,4-dimethoxynaphthalene[11,12] systems as well as for some heterocyclic compounds[13,14]. Furthermore, some highly functionalized 1,4-dimethoxy-aromatic systems were oxidized to the respective quinone bisketals in good yields[15-17]. Some representative examples are given in Table 2.

The majority of these reactions were performed in 1 % methanolic potassium hydroxide; the presence of the water in the potassium hydroxide and adventitious water in the methanol had little effect on the reaction. However, the efficiency of the anodic oxidation decreased with increasing concentration of potassium hydroxide (Figure 1)[18]. For cases wherein base hydrolysis of a functional group is a problem (e.g. methyl esters), sodium methoxide in anhydrous methanol can be employed as the electrolyte and solvent system. Certain easily oxidized functional groups in an unprotected form such as amines, aldehydes and primary and secondary alcohols undergo competing oxidation and complicate the product mixture. However, amino groups not directly attached to the ring can be protected from oxidation by conversion to their trifluoroacetates[19]. Likewise, aldehydes and alcohols can be converted to their corresponding acetals and ethers. The latter linkages are stable to these electrochemical oxidation conditions.

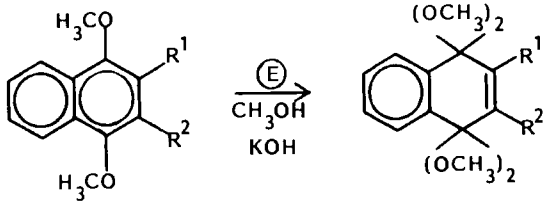
2. Anodic oxidations in a divided cell

The single-cell oxidations described above are conducted with the compound in contact with both the anode and the cathode. This arrangement is acceptable for anodic oxidations in which the substrate is not easily reduced at the cathode. However, for compounds which

TABLE 1. Anodic oxidation in single cell[11d]



R^1	R^2	R^3	Yield (%)
Br	H	H	78
Br	H	Br	58
CH_3	H	H	80
$Si(CH_3)_3$	H	H	93
CH_3	CH_3	CH_3	63
$CH(OCH_3)CH_3$	H	H	92
1, 3-dioxolan-2-yl	H	H	88
$CH(OH)CH_3$	H	H	50[a]
$(CH_2)_3OH$	H	H	48[a]
$CH_2CH{=}CH_2$	H	H	81
SCH_3	H	H	54[b]



R^1	R^2	Yield (%)
H	H	74
CH_3	H	75
OCH_3	H	83
CH_3	OCH_3	82
CH_3	$Si(CH_3)_3$	80

[a] Other products characterized from the reaction mixture.
[b] Yield of quinone monoketal from direct hydrolysis of the reaction mixture.

TABLE 2. Some representative anodic oxidations of functionalized 1,4-dimethoxyaromatic and heterocyclic systems in CH_3OH/KOH

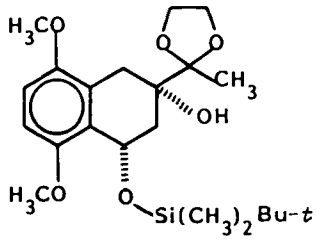
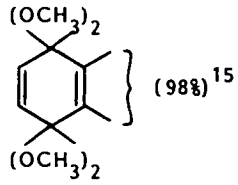
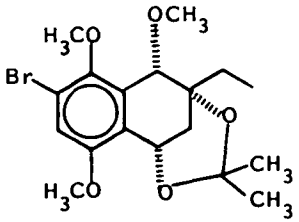
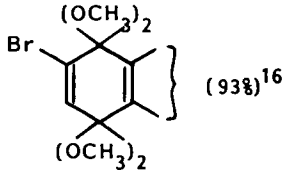
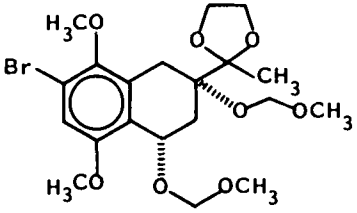
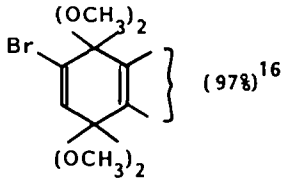
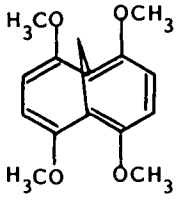
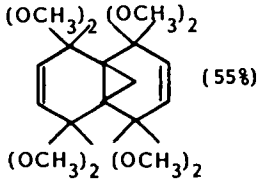
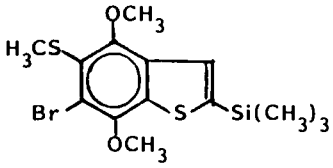
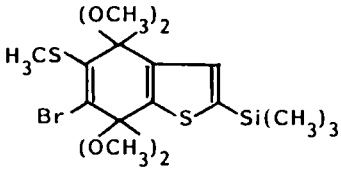
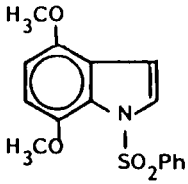
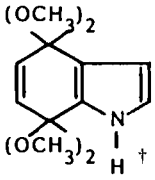
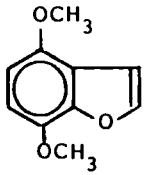
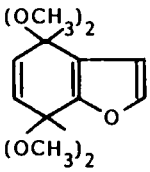
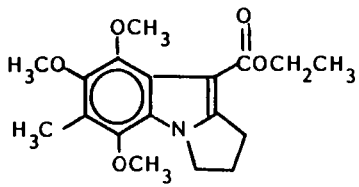
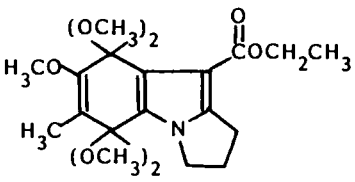
Starting aromatic compound	Product (Yield)
	 (98%)[15]
	 (93%)[16]
	 (97%)[16]
	 (55%)[17]

Table 2. (continued)

Starting aromatic compound	Product (Yield)	
		(85%)[13]
	 †	(76%)[14a]
		(74%)[14b]
		(50%)[14a]

† The phenylsulfonyl group is lost either during the reaction or in the workup.

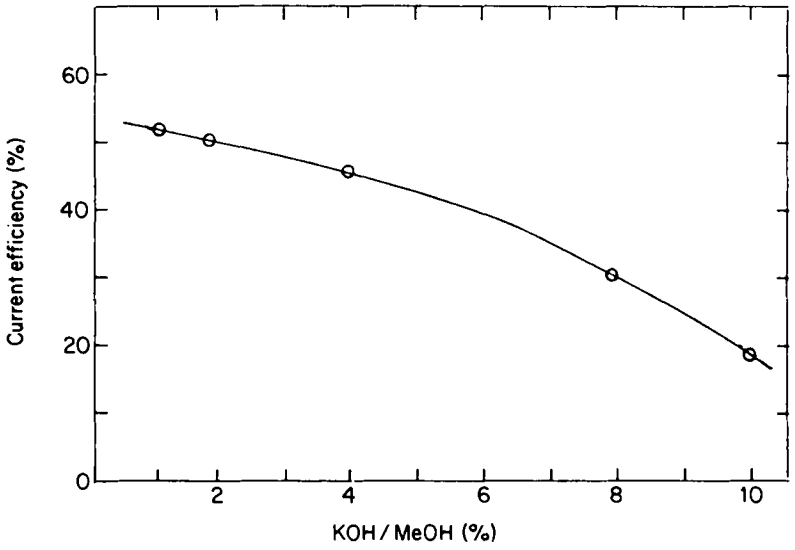


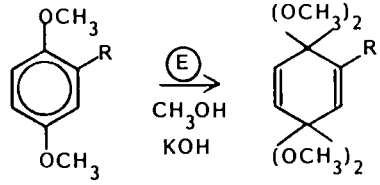
FIGURE 1. Current efficiency for anodic oxidation of 1-methoxynaphthalene as a function of base concentration

have reducible functional groups, this cell design can lead to undesired reduction processes of the substrate. In these cases successful oxidation of the compounds to quinone bisketals can be performed by conducting the electrochemical experiment in a cell which allows current to flow between the electrodes but keeps the substrate from coming into contact with the cathode. A simple method of conducting divided-cell oxidations is to employ an H-type cell with the anode and cathode compartments separated by a glass frit. More elaborate cell designs have the anode and cathode separated by a variety of membranes. Simple alkyl, chloro and bromo groups (in the benzenoid series only), non-conjugated double bonds, acetals and ethers are stable to the aforementioned anodic oxidation conditions in a single cell[11d]. However, other substituents undergo a competing reduction at the cathode under these conditions. Table 3 lists a series of anodic oxidations which, while giving complex mixtures of products in a single-cell system, usually gave acceptable yields of quinone bisketals in divided-cell electrolyses[11d]. In some cases the lower yields for anodic oxidations in divided cells may be attributed to diffusion of the compound into the cathode chamber during the course of the electrolysis and do not reflect any inherent inefficiency in the electrolysis reaction itself.

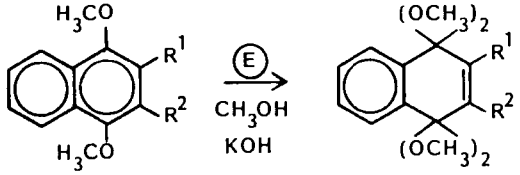
3. Mechanistic and experimental aspects of the anodic oxidation of other 1,4-oxygenated aromatics to quinone bisketals

Although anodic oxidation studies have been performed mainly on 1,4-dimethoxybenzene systems, it would seem that other simple 1,4-dialkoxybenzenes should also undergo smooth oxidation to the corresponding quinone bisketals[20]. Anodic oxidation of 1,4-diethoxybenzene **14** in 1% methanolic potassium hydroxide afforded in high yield an approximate 1:1 mixture of stereoisomeric bisketals **15** (equation 4) as determined by ^{13}C-NMR analysis at 125 MHz in these laboratories. Furthermore, quinone bisketals were formed in good yield from anodic oxidation of the compounds shown in Table 4. For the

TABLE 3. Anodic oxidations in a divided cell[11d]

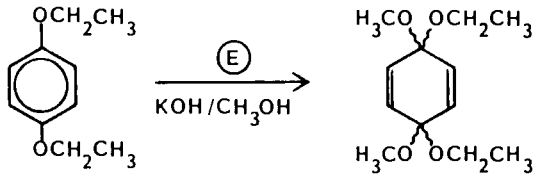


R	Yield (%)
$NHCOCH_3$	17
$(CH_2)_2CO_2CH_3$	61
$(CH_2)_2CON(CH_3)_2$	68
$(CH_2)_2CONH_2$	50
$CH{=}CHCO_2CH_3$	46
CHO	26, 59[a]



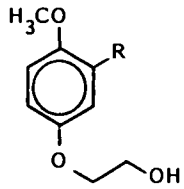
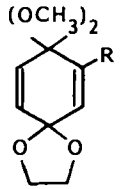
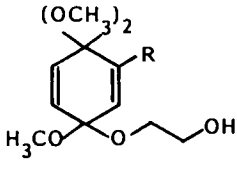
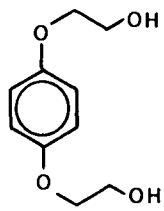
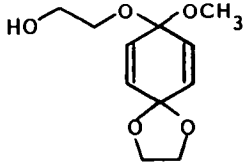
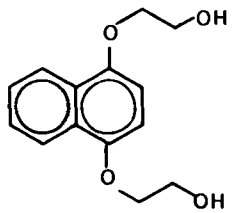
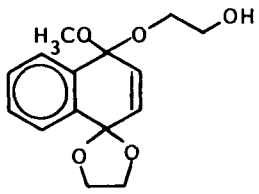
R^1	R^2	Yield (%)
Br	H	84
Br	CH_3	85
Br	Br	50

[a] Reaction at a vitreous carbon electrode.
The product is the bis(ketal) ester ($R = CO_2CH_3$).

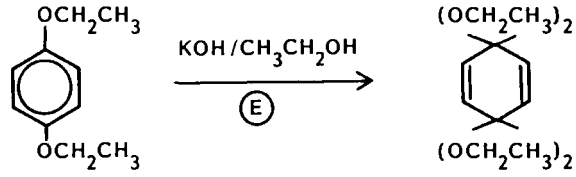


14 15 (78%) (4)

TABLE 4. Anodic oxidations to form ethylene glycol ketals of benzo- and naphthoquinone in CH_3OH/KOH

Entry	Reactant	Product(s) (Yield)	
		 + 	
1	R = H	(66%)	(15%)[21]
2	R = CH_3	(83%)	(7%)[21]
3	R = Br	(81%)	(13%)[21]
4	R = OCH_3	(86%)	—
5			(93%)[8c]
6			(85%)[21]

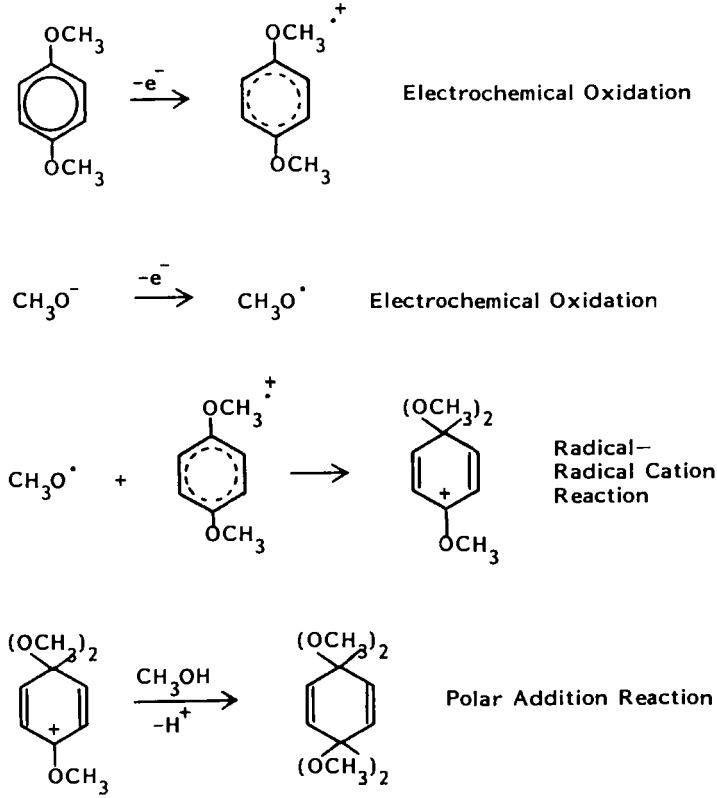
reactions cited in Table 4, anodic oxidation produced the mixed methanol–ethylene glycol ketal—a result of mechanistic significance[8c, 18]. Although not extensively studied, the nature of the alcohol component in the bisketal formation appears to have a bearing on the yield and current efficiency of the reaction, judging from the results of anodic oxidation of **14**. Electrolysis of **14** in ethanolic potassium hydroxide did form the analogous bisketal **16** (equation 5) but in lower isolated yield (63%) and current efficiency (21%) than the



14 16 (5)

analogous reaction in methanol[11d]. Furthermore, the crude reaction mixture appeared much more complex as compared to analogous anodic oxidations done in methanol. This limitation on the reaction is not serious since the bisketals from other alcohols may often be prepared by performing exchange reactions on the readily available tetramethyl bisketal (*vide infra*).

An important, yet unanswered, mechanistic question is the detailed steps in the anodic oxidation of 1,4-dimethoxybenzenes to quinone bisketals. Several mechanisms have been offered for the process, but only the most recent proposal[18, 22] will be illustrated for 1,4-dimethoxybenzene (Scheme 1). The key feature of this mechanism is that two electrochemical intermediates are generated at the anode. The first is the radical cation of the



SCHEME 1. EEC_rC_p mechanism for anodic oxidation of 1,4-dimethoxybenzene[18]

aromatic substrate, and the second is the methoxyl radical. Reaction of these two transients on the electrode surface affords a cationic intermediate which then reacts with methanol to produce the observed quinone bisketal. These steps were termed the EEC_rC_p mechanism[18], denoting that two electrochemical steps (EE) were followed by a radical combination step (C_r) and a polar-addition step (C_p). Although the detailed arguments supporting this mechanistic proposal will not be covered in this review, interested readers are referred to the original papers[18,22] for further details.

In summary, anodic oxidations of 1,4-dimethoxybenzene and naphthalene systems are usually high-yield routes to their respective quinone bisketals. The current efficiencies of the oxidations are in the 20–80% range, most simple systems having current efficiencies of greater than 50%. Experimentally, the reactions require only a source of direct current and electrodes. Only in some highly functionalized systems has controlled potential electrolysis markedly improved the yield of the reaction. Platinum anodes and cathodes were used in the majority of the studies because of their convenience: however, inexpensive vitreous carbon anodes gave comparable—in some cases better—yields than platinum anodes[11d].

The reactions are usually conducted at 0°C but have been performed at temperatures as high as the boiling point of the solvent and as low as −25°C. The progress of the reaction is conveniently followed by UV spectroscopy since the product absorbs light at a considerably shorter wavelength than the starting material, although thin-layer chromatography can also be used if a UV spectrometer is not available. In fact, for many of the systems studied, an isosbestic point is observed as the reaction progresses: at the completion of the reaction, the optical density of the starting material at its absorption maximum is less than 5% of its initial value. Although it is more efficient to oxidize a homogeneous solution, compounds only partially soluble in methanol can be successfully electrolyzed as a slurry and/or with some tetrahydrofuran added as cosolvent. This works acceptably provided that the product is soluble in the reaction media so it does not precipitate onto the electrode.

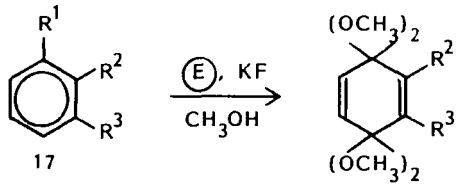
The bisketals of quinones are usually quite stable in the absence of acid. However, for extended storage the bisketals should be handled with and stored in glassware which has been washed with dilute ammonium hydroxide. Magnesium sulfate should never be used as a drying agent for solutions of bisketals since hydrolysis to the monoketal will occur for some systems.

B. Quinone Bisketals from Anodic Oxidation of Other Aromatic Compounds

The anodic oxidation of 1,4-dialkoxyaromatic derivatives (hydroquinone ethers) is a very convenient method for preparation of quinone bisketals in the laboratory. However, this method requires the respective hydroquinone or the quinone as starting material. If the starting hydroquinone ethers are prepared from the quinone itself, the three-step reaction sequence—quinone reduction/alkylation/anodic oxidation—does not change the oxidation state of the compound and is a circuitous route to quinone bisketals. Furthermore, the availability of the hydroquinone ether determines the convenience of the electrochemical oxidation. Often, more readily available starting materials for the preparation of quinone bisketals are aromatic compounds below the hydroquinone oxidation state. Direct conversion of such systems to quinone bisketals also couples the oxidation step with the formation of the bisketal and involves efficient use of oxidation equivalents.

The anodic oxidation of benzene and simple benzene derivatives has been studied by the Hoechst group[23]. Although anodic oxidation of benzene does not appear to proceed satisfactorily in methanolic potassium hydroxide, this oxidation can be conducted in

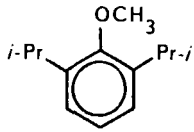
methanol at a platinum anode using a variety of other electrolytes. Most of the reported anodic oxidations were conducted only to partial conversion, the current efficiency for the formation of quinone bisketals being about 40%. This reaction has been conducted successfully for benzene (**17a**), anisole (**17b**), *o*-chloroanisole (**17c**), and *m*-methoxytoluene (**17d**) (equation 6).



	R^1	R^2	R^3
a,	H	H	H
b,	OCH_3	H	H
c,	OCH_3	Cl	H
d,	OCH_3	H	CH_3

(6)

Oxidation potentials for benzene and its simple alkyl derivatives are apparently too high for their efficient oxidation to quinone bisketals in methanolic potassium hydroxide. Even anodic oxidations of anisole, 2,6-di-*i*-propylanisole (**18**) and 2,6-di-*t*-butylanisole (**19**) give only low yields (20–40%) of their respective quinone bisketals in addition to other oxidation products[22]. However, anodic oxidation of 1,3-dimethoxybenzene (**20**) in methanolic potassium hydroxide gives the bisketal (**11e**) in 66% yield (equation 7)[6].



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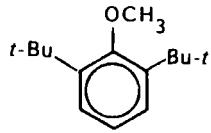
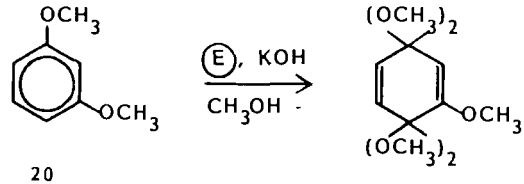
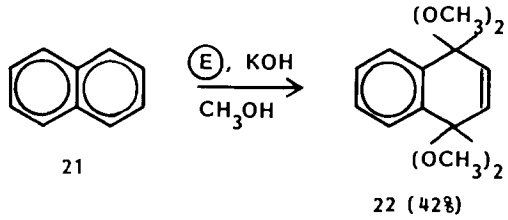


19



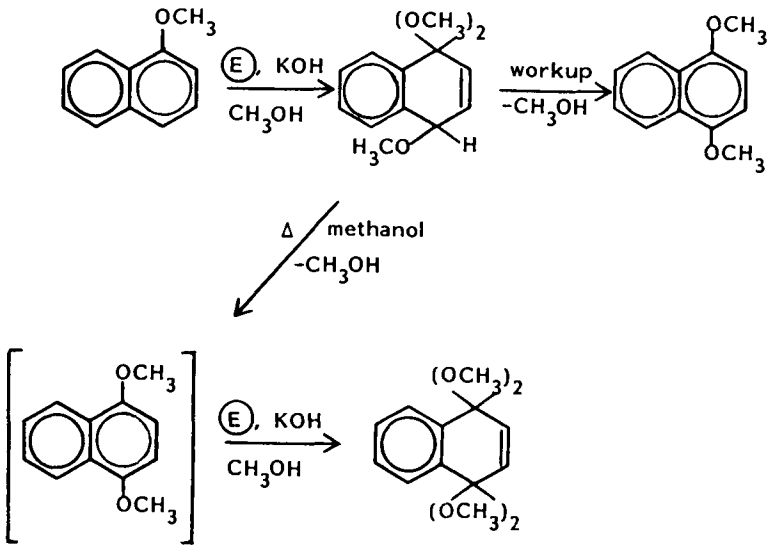
(7)

Naphthalene (**21**) is more easily oxidized than benzene: thus, conversion of a methoxylated naphthalene[11c, e, 12, 18] to a 1,4-naphthoquinone bisketal should be more facile than the analogous reaction of anisole. Anodic oxidation of naphthalene itself in methanolic potassium hydroxide heated to reflux gave the bisketal **22** in 42% isolated yield (22% current efficiency, equation 8)[18]. At the time the work was performed, the investigators were unaware of the Hoechst work[23]; presumably, the efficiency and yield of the reaction could be markedly improved by conducting the reaction in methanol with potassium fluoride as the electrolyte.



21 22 (42%) (8)

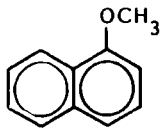
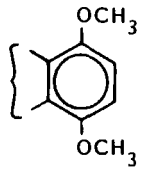
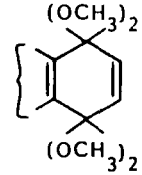
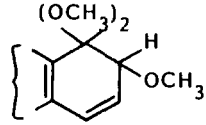
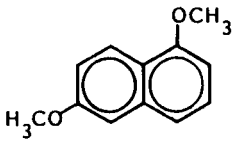
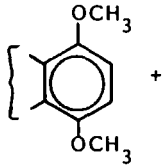
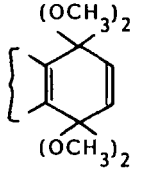
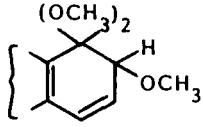
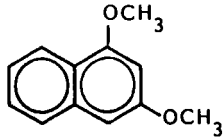
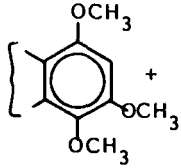
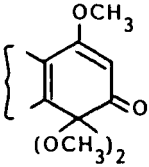
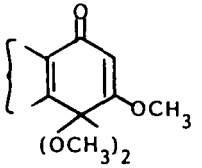
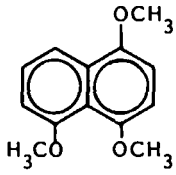
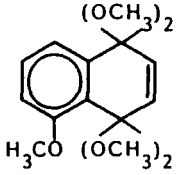
An extensive investigation of the products and their mechanisms of formation for anodic oxidation of 1- and 2-methoxynaphthalene and 1,2-, 1,3-, 1,4-, 1,5-, 1,6-, 1,7-, 2,3-, 2,6- and 2,7-dimethoxynaphthalene in methanolic potassium hydroxide has been reported[18]. Table 5 summarizes the reactions relevant to the present discussion. Interested readers are referred to the original article[18] for other electrochemical processes and the mechanistic discussion of these reactions; however, several general points concerning the synthetic utility of the reactions are noteworthy. The ratio of two- and four-electron oxidation products was dependent upon the particular compound being oxidized and the temperature of the oxidation. The origin of the temperature dependence of the products from anodic oxidation of 1-methoxynaphthalene is outlined in Scheme 2. Thus, the major process is two-electron oxidation and 1,4 addition of methanol to give 1,1,4-trimethoxy-1,4-dihydronaphthalene. At low temperature this product is moderately stable toward 1,4 elimination of methanol, but elimination occurs during workup of the reaction mixture to give 1,4-dimethoxynaphthalene. When the reaction is conducted in methanolic potassium hydroxide heated to reflux, an *in situ* 1,4 elimination of methanol occurs, followed by further oxidation to produce the bisketal.



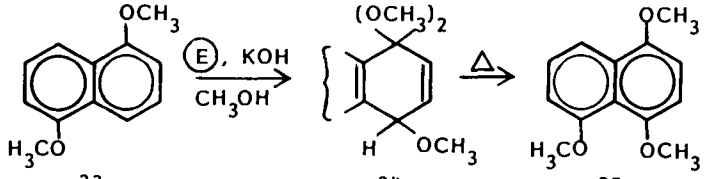
SCHEME 2. Rationalization of the temperature dependence of the anodic oxidation of 1-methoxynaphthalene

Due to the temperature-dependent nature of the electrochemical oxidation, this chemistry can also serve as a valuable method for the preparation of methoxylated

TABLE 5. Anodic oxidation products of selected methoxylated naphthalenes[18]

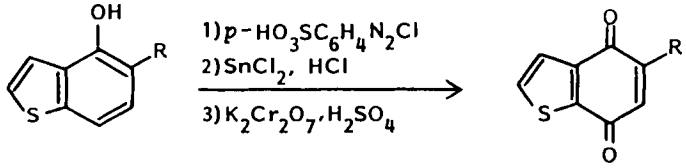
Reactant (Temperature)	Products (Yields)		
			
(0 °C)	(66%)	(21%)	(8%)
(reflux)	--	(83%)	(9%)
			
(reflux)	(10%)	(45%)	(14%)
			
(reflux)	(14%)	(59%)	(20%)
			
(25 °C)	(> 80%)		

naphthalene derivatives. This is illustrated by the preparation of 1,4,5-trimethoxynaphthalene (**25**)—a valuable intermediate for production of juglone methyl ether (5-methoxy-1,4-naphthoquinone)—by anodic oxidation of readily available 1,5-dimethoxynaphthalene (**23**) (equation 9)[12,16].



23 24 25 (9)

Anodic oxidation can be the most advantageous method for conversion of methoxylated aromatic systems to the quinone oxidation state. The preparation of benzo[*b*]thiophene quinones is illustrative of this point. Conversion of the phenols **26a,b** to their respective quinones (**27**) by classical chemical methods was effected in overall

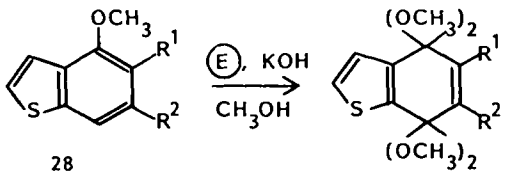


(10)

26a, R = H — 27 (44%)

b, R = CH_3 — (15%)

yields of 44%[24a] and 15%[24b] (equation 10). Anodic oxidation of the corresponding methoxyl derivatives **28** afforded the quinone bisketals **29a–d** in yields of 76–85% (equation 11)[13]. These compounds can be hydrolyzed with aqueous acid to the corresponding quinones in excellent yields. Thus, this four-electron oxidation procedure



28 29

	R^1	R^2	%
a,	H	H	78
b,	CH_3	H	85
c,	Br	H	79
d,	H	Br	76

(11)

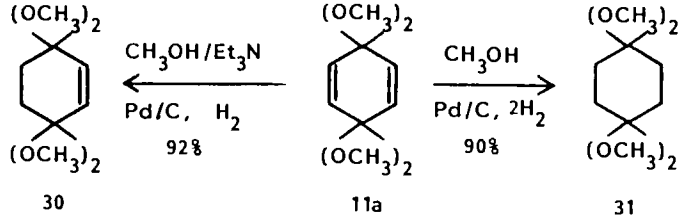
more than complements the classical method for preparation of benzo[*b*]thiophene quinones and quinone bisketals.

III. REACTIONS OF QUINONE BISKETALS

A. General Considerations

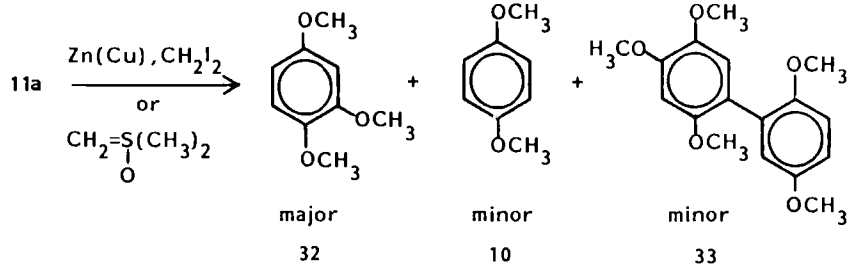
Many quinone bisketals are easily hydrolyzed by adventitious acid and moisture in the air to quinone monoketals—the source of acid catalysis is most often found on the surface

of glassware. As noted earlier, all glassware which is to come in contact with these molecules should be rinsed with dilute ammonium hydroxide and dried in an acid-free environment. Furthermore, chromatography is best conducted on neutral alumina or silica gel which has been washed with ca. 5% methanolic ammonia and then dried *in vacuo* at ca. 100°C overnight. Ordinary silica gel often causes hydrolysis of quinone bisketals to quinone monoketals. With this acid lability in mind, quinone bisketals can be handled and reacted in an otherwise normal fashion. The bisketals are reasonably stable thermally since benzoquinone bisketal **11a** can be isolated by vacuum distillation (b.p. 85–89 °C/0.3 mm). Electrophilic additions to the double bond of quinone bisketals have not been studied extensively. However, hydrogenation[25] of benzoquinone bisketal **11a** to the bisketals of 1,4-



30 11a 31 (12)

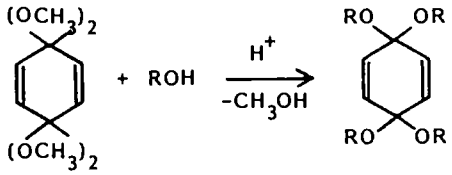
cyclohexanedione (**31**) and 1,4-cyclohex-2-ene-1,4-dione **30** has been reported (equation 12). Interestingly, reaction of the Simmons–Smith reagent or dimethylsulfoxonium methylide and **11** led to **10**, **32** and **33** (equation 13)[26].



(13)

B. Exchange Reactions with Quinone Bisketals

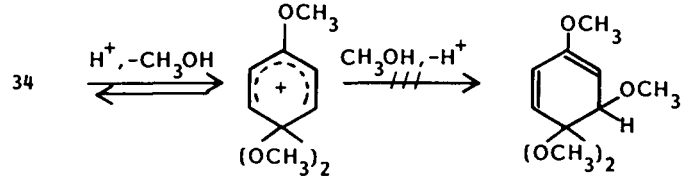
As was noted previously, anodic oxidation of 1,4-diethoxybenzene in ethanolic potassium hydroxide was not a clean reaction. Although the anodic oxidations of



11a (14)

34a, R = Et (91%)
b, R = *n*-Bu (90%)
c, R = $PhCH_2$ (96%)

hydroquinone ethers in solvents other than methanol and ethanol have not been extensively studied, many of the bisketals that can be potentially derived from these types of reactions may be prepared from the readily available tetramethoxy compound, **11a**. Thus, the acid-catalyzed reaction of **11a** with an alcohol as solvent at room temperature gave good yields of the bisketals **34a–c** (equation 14)[27]. This chemistry suggests that the cation **35** reacts under kinetic control at the 1-position with oxygen nucleophiles since heating **11a** in methanol with an acid catalyst affords 1,2,4-trimethoxybenzene, presumably via **36** (equation 15).



35 36 (15)

C. Metalated Quinone Bisketals

One of the early uses of quinone bisketals in synthesis was as a metalated quinone equivalent[9]. Brominated benzoquinone and naphthoquinone bisketals, readily available from anodic oxidation of corresponding 1,4-dimethoxy bromoaromatic derivatives, undergo rapid metal–halogen exchange reactions at −78 °C. The lithio derivatives react with selected electrophiles to give good yields of the corresponding functionalized quinone bisketals and thence the functionalized quinone by acid hydrolysis. Table 6 shows the results from reaction of the organolithium derived from the parent benzoquinone bisketal. Several general points are noteworthy.

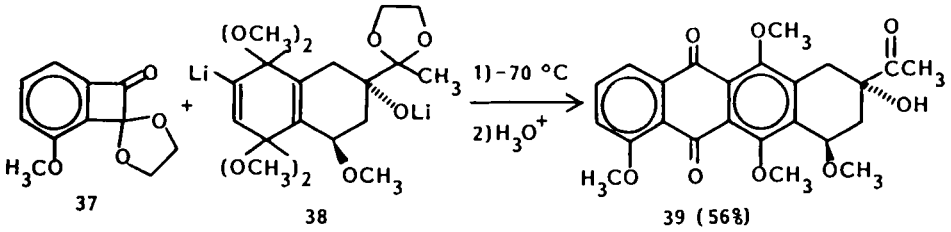
(1) The reagent reacts with difficultly enolizable ketones to give adducts in good yields while protonation of the bisketal is a problem with substrates that are more readily enolized.

(2) This hindered reagent reacts cleanly with aryl esters to give ketones.

(3) Hydrolysis of the adducts from aldehydes and ketones affords the parent quinones in high yields.

(4) Low yields of adducts are obtained from reactions with simple alkyl and allylic halides.

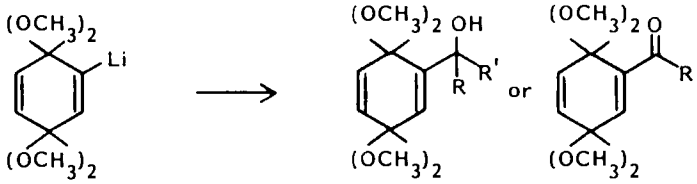
The problem of competing enolization observed in the reaction of the lithiated quinone bisketal with aldehydes and ketones might have been less serious if the recently developed organocerium derivatives[28] had been employed for the reaction. The functionalized lithiated quinone bisketal (**38**) was employed in one of the first regiospecific routes to anthracyclinones (e.g. **39**, equation 16)[29].



37 38 39 (56%)

(16)

TABLE 6. Functionalization chemistry of the 2-lithio derivative of benzoquinone bisketal[9a,b]



Reactant	Yield (%)	Yield (%)	R	R'
cyclohexanone	80	--	$(CH_2)_4$	
cycloheptanone	40	--	$(CH_2)_5$	
benzaldehyde	68	--	Ph	H
benzophenone	72	--	Ph	Ph
methyl benzoate	--	78	Ph	
N-benzoylpiperidine	--	68	Ph	
dimethyl phthalate	--	70*	$2\text{-}CO_2CH_3(C_6H_4)$	
dimethyl 3-methoxyphthalate	--	70	$3\text{-}OCH_3\text{-}2\text{-}CO_2CH_3(C_6H_3)$	

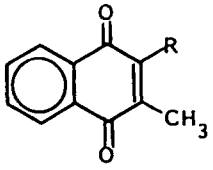
No/low yield of products with: CH_3I, CH_3CH_2I, CH_3CHO, CH_3COCH_3, $PhCH_2Br$, $PhCH_2Cl$, CH_3COCl

* Product was mixture of ester and pseudo ester.

Although introduction of allylic substituents by reaction of the lithiated quinone bisketal with allylic halides was unsuccessful, the reaction proceeded satisfactorily when the corresponding cuprate of the bisketal was employed[30]. Functionalization of quinone bisketals via the cuprate was a key aspect in the synthesis of **40a**, menaquinone-2 (**40b**), phylloquinone (**40c**), cympol (**41a**) and cympol methyl ether (**41b**)[30].

D. Bisketals as Synthons for Nucleophilic Substitution Reactions of 1,4-Dimethoxyaromatic Systems

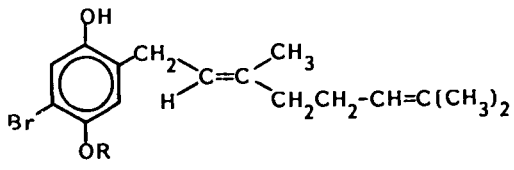
Nucleophilic substitution reactions of quinone bisketals give rise to products in the hydroquinone oxidation state, and this has been exploited by the Hoechst group for the preparation of a variety of 1,4-dimethoxybenzene derivatives[31]. Table 7 illustrates the range of nucleophilic reagents which afforded substitution products under acid-catalyzed conditions with benzoquinone bisketals. Although analogous substitution reactions have not been studied extensively for substituted quinone bisketals, the regiochemical outcome of such reactions should show good selectivity based on the regiochemistry of the



40 a, R = $-CH_2-CH=C(CH_3)_2$

b, R = $-H_2C-CH=C(CH_3)-CH_2CH_2CH=C(CH_3)_2$

c, R = $-H_2C-CH=C(CH_3)-[CH_2CH_2CH(CH_3)]_3CH_3$



41 a, R = H

b, R = CH_3

monohydrolysis of the quinone bisketals (*vide infra*). Much useful aromatic substitution chemistry could result from further studies in this area.

IV. PREPARATION OF QUINONE MONOKETALS

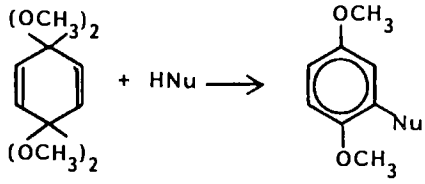
A. Chemical Oxidation of Phenols

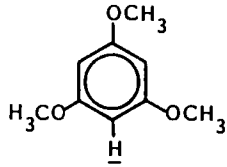
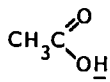
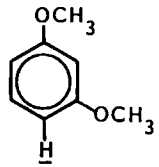
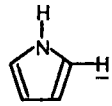
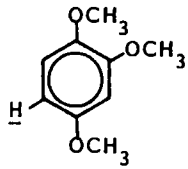
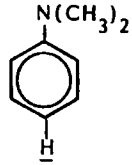
Monoprotected quinones have been known for many years and have been prepared by a variety of methods. Compounds in which one of the quinone carbonyl groups is masked as a dihalide derivative (see Table 8) are well characterized. Although these compounds might permit selective reaction at the unprotected carbonyl group of the quinone, their preparation is not general and often proceeds in low yield. More recently, the trimethylsilyl cyanide blocked quinone derivatives, e.g. 5, have been used in synthesis[4]; however, in general, they appear to be less versatile than the quinone monoketals described below, and their chemistry will not be presented.

There is an extensive body of literature on the formation of quinone monoketals via oxidation of functionalized phenols with a variety of reagents: ferric chloride[35], potassium hexacyanoferrate (III)[35, 36], ceric ammonium sulfate[37], tetrachlorobenzoquinone[37], *N*-bromosuccinimide[37], manganese dioxide[38], dichlorodicyanobenzoquinone[38], silver oxide[38], copper (II) pyridine complex and oxygen[39], periodic acid[40], thallium (III) nitrate[41] and mercuric oxide with iodine[42]. In some cases, the yields of quinone monoketals are low, and in other cases they are not reported. Furthermore, many of these reactions are unique to a particular molecule because they possess structural features which lead to intramolecular formation of the quinone monoketal. Thus, an extensive discussion of this area is beyond the scope of the present review. However, Table 9 shows some of the unique quinone monoketals obtained from these studies, and readers are referred to the original papers for further examples and details.

Although a number of simple quinone monoketals were known in the literature, there was not a reasonably general method for their preparation until the work of McKillop, Taylor and coworkers[41]. These investigators found that thallium trinitrate, in either methanol or a mixture of methanol and trimethyl orthoformate, smoothly converted a number of *p*-alkoxyphenols to quinone monoketals in good yields. Table 10 lists a representative number of oxidations successfully performed using thallium trinitrate. Aside from the toxicity of thallium, which is not a small consideration for the large-scale preparation of monoketals, this is a good procedure for the preparation of these

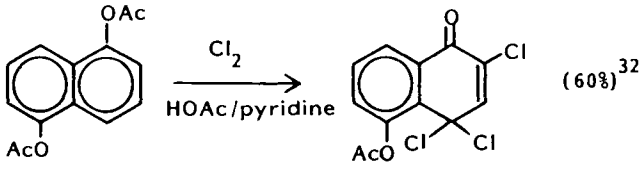
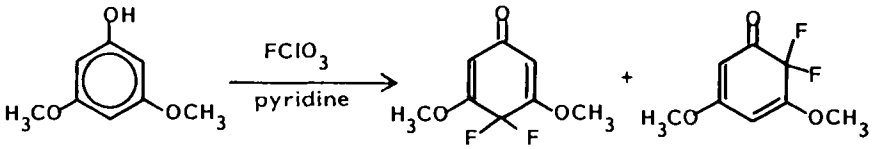
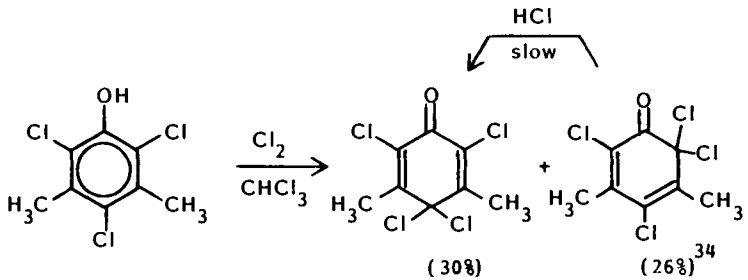
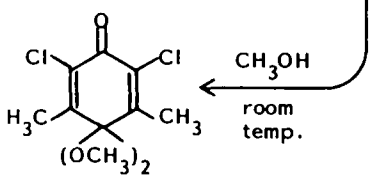
TABLE 7. Benzoquinone bisketals in the synthesis[31] of substituted 1,4-dimethoxybenzenes



H-Nu	Yield (%)	H-Nu	Yield (%)
$CH_3O\underline{H}$	90		50
	92		20
$\underline{H}N_3$	87[a]		
$C_2H_5S\underline{H}$	69		51
$\underline{H}SCH_2CO_2Et$	61		
	61		48

[a] Characterized as the amine after reduction.

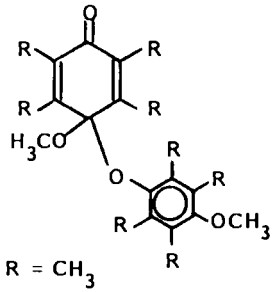
TABLE 8. Some quinone derivatives in which one carbonyl group is masked as a dihalide

Compound	Product(s)
	(60%)[32]
	(1:1 mixture, good yield)[33]
	(30%) (26%)[34]
	

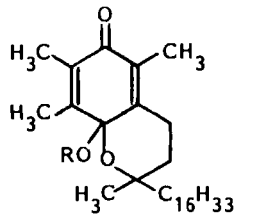
synthetically interesting quinone derivatives. The availability of quinone monoketals via the thallium trinitrate oxidation undoubtedly played a role in the subsequent increase in the use of these compounds in synthesis.

Further work has refined the preparation of quinone monoketals using thallium trinitrate as an oxidant by using suspended potassium bicarbonate in the reaction media—

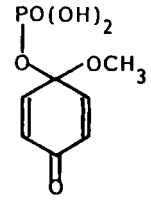
TABLE 9. Selected examples of quinone monoketals and an aminal obtained via phenol oxidations



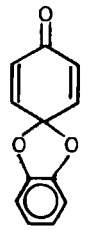
(ref 35)



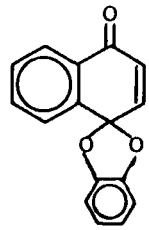
(ref 36)



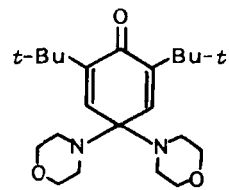
(ref 37b)



(ref 38c)



(ref 38d)



(ref 39)

presumably to neutralize acid generated in the reaction[43]. This synthetic expedient improved the yield of acid-sensitive quinone monoketals. In addition, a comparison was made of the efficiency of the three most common oxidizing agents: dichlorodicyanoquinone (DDQ), ferric chloride and thallium trinitrate[43]. The results, summarized in Table 11, illustrate the complementary nature of these oxidizing agents in the conversion of phenols to quinone monoketals. In many cases, DDQ and ferric chloride gave yields of quinone monoketals comparable to those of the toxic thallium trinitrate.

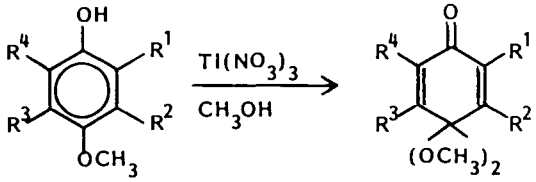
These investigations have made available a variety of quinone monoketals for use in synthesis subject to the availability of the requisite *p*-alkoxyphenol. Although many quinone monoketals are best prepared—especially on a large scale—by hydrolysis of quinone bisketals, for some compounds, chemical oxidation may still be the method of choice.

B. Electrochemical Oxidation of Phenols

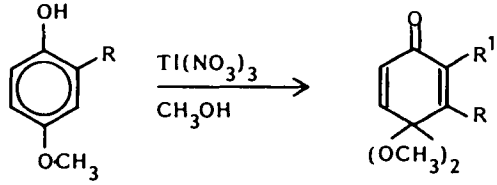
As is apparent from Section IV.A, quinone monoketals are conveniently available by chemical oxidation of *p*-alkoxyphenols. However, in some cases relatively expensive and toxic oxidizing agents are required. Ronlan and coworkers have extensively studied the anodic oxidation of phenols in methanol as a function of anode material (platinum vs. carbon), anode potential, concentration, supporting electrolyte and temperature[47].

TABLE 10. Anodic oxidation of *p*-alkoxyphenols with thallic(III) nitrate

Phenol	Monoketal

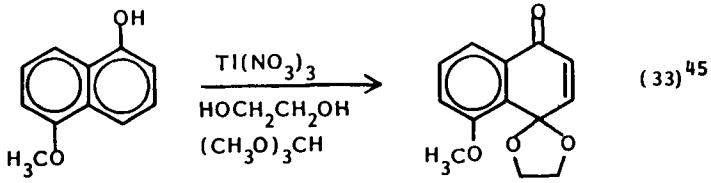


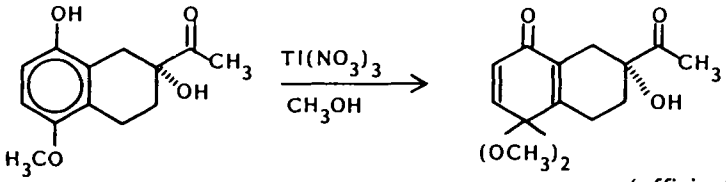
R^1	R^2	R^3	R^4	Yield (%)[41]
H	H	H	H	97
CH_3	H	H	H	89
CH_3	H	H	CH_3	87
t-Bu	H	H	*t*-Bu	96
H	OCH_3	OCH_3	H	95
H	OCH_3	OCH_3	$\overset{O}{\overset{\|}{C}}CH_3$	92
Cl	H	H	H	97
Br	H	H	H	91



R = $\overset{O}{\overset{\|}{C}}H$ R = H, $R^1 = CH(OCH_3)_2$

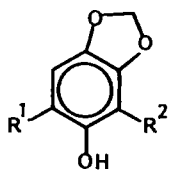
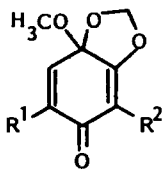
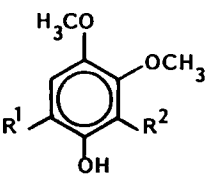
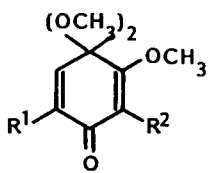
R = CO_2CH_3 R = OCH_3, $R^1 = CO_2CH_3$ (90)[44]



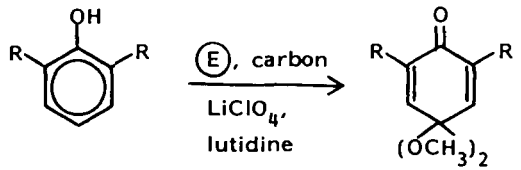


(efficient)[46]

TABLE 11. Comparison of various oxidizing agents for oxidation of *p*-alkoxyphenols to quinone monoketals in methanol[43]

Phenol	Quinone monoketal	R^1	R^2	Yield (%) DDQ	$FeCl_3$	$Tl(NO_3)_3$
		H	H	< 5	< 5	83
		$CH_2CH{=}CH_2$	H	88	84	78
		H	$CH_2CH{=}CH_2$	31	0	21
		H	OCH_3	57	0	68
		OCH_3	H	50	50	70
		H	H	< 5	< 5	66
		$CH_3CH_2CH_2$	H	85	88	80
		H	$CH_2CH{=}CH_2$	75	0	0
		OCH_3	H	< 5	78	0

Although phenol **42** underwent anodic oxidation in methanol to form the quinone monoketal **43** in 46% yield, the authors noted it was quite difficult to separate the product from the oxidation mixture. However, for the more hindered 2,6-di-*t*-butylphenol (**44**) the corresponding quinone monoketal **45** was obtained in 77% yield from a 10-gram electrolysis (equation 17).



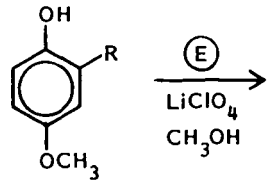
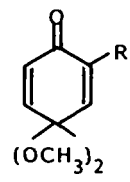
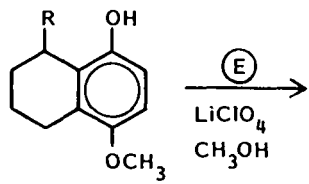
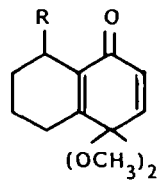
(17)

42, R = H — 43 (46%)

44, R = *t*-Bu — 45 (77%)

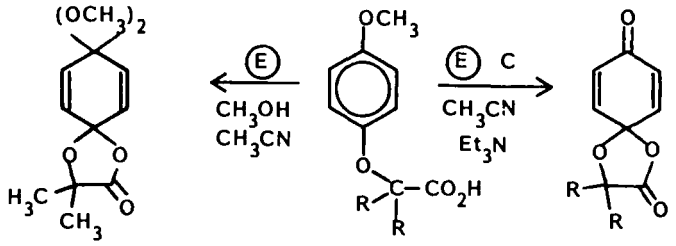
These workers also published a procedure for the preparation of the parent quinone monoketal **43** by oxidation of *p*-methoxyphenol in methanol using lithium perchlorate as supporting electrolyte[25b]. Although this electrochemical oxidation is an excellent method[48] most investigators have preferred to use chemical oxidants for the conversion of *p*-alkoxyphenol to quinone monoketals. However, this electrochemical oxidation was the method of choice for conversion of functionalized *p*-alkoxyphenols to their respective quinone monoketals (Table 12)[49].

TABLE 12. Anodic oxidation of *p*-methoxyphenols to quinone monoketals[49]

Phenol	Quinone Monoketal	R	Yield (%)
		CH_3CH_2	(82)
		t-$BuCH_2$	(83)
		H	(97)
		CH_3	(82)
		CH_3CH_2	(85)
		t-Bu	(82)

One variant of the above phenol oxidation is the electrolysis of the corresponding silyl ether of the phenol[50]. Thus, anodic oxidation of the silyl ether of *p*-methoxyphenol in methanol–acetonitrile using lithium perchlorate as the electrolyte in the presence of lithium carbonate affords benzoquinone monoketal **43** in 99% yield[50].

Another electrochemical method to furnish quinone monoketal systems is the oxidation of phenol ethers in a non-nucleophilic solvent—although the yields in these cases are usually not high. Thus, while anodic oxidation of **46** in acetonitrile/methanol gave **47b**[51a,b], anodic oxidation of **46** in the absence of methanol in the presence of Et_3N afforded the quinone monoketal-like compounds (**47a**) in modest yield (equation 18) in addition to other products[52].



(18)

R	R	Yield (%)
CH_3	CH_3	(41)
CH_3	H	(22)
$(CH_2)_5$		(40)

In summary, the preparation of quinone monoketals via electrochemical oxidation of *p*-methoxyphenols is an excellent alternative to the chemical oxidations discussed above. The reactions have been conducted at constant current on a moderate scale (ca. 0.2 mol) using simple apparatus and afford good yields of product. While the scope of these anodic oxidations has not been extensively studied, this method of phenol oxidation allows preparation of quinone monoketals without the use of toxic and expensive oxidizing agents.

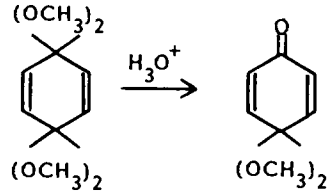
C. Quinone Monoketals via Hydrolysis of Quinone Bisketals

1. Background and general comments

Provided that the required *p*-methoxyphenol is available, the oxidation methods discussed above serve as excellent preparations of the corresponding quinone monoketal. However, for compounds in which the ring is substituted, the 1,4-dialkoxy ether (typically the dimethoxy ether) is often a more readily available starting material since it is prepared by reduction of the quinone and alkylation of the resulting hydroquinone. Since quinone bisketals can be prepared in high yields by anodic oxidation of 1,4-dimethoxy benzene and naphthalene derivatives, hydrolysis of one of the two ketal groups would afford quinone monoketals via a route complementary to that discussed above. Furthermore, some quinone bisketals are available by direct oxidation of aromatic compounds having oxidation states lower than the hydroquinone: this would then serve as a more efficient preparation of quinone monoketals.

The monohydrolysis of the bis(ethylene glycol) ketal of benzoquinone was one of the first routes employed for preparation of quinone monoketals[5]. Even though a kinetic study had reported that the acid-catalyzed hydrolysis of the second ketal of quinone

bisketal (**11a**) was 300 times slower than the first ketal[53], apparently some difficulty was encountered in taking advantage of this difference in rate preparatively[26]. Thus, hydrolysis of **11a** under the conditions[8a] reported to give the monoketal **43** (equation 19) gave only



11a 43 (19)

benzoquinone when repeated by a second group[26]; however, the **11a** to **43** conversion could be conducted by hydrolysis with warm water. The contradictory results reported in these studies probably arose from the presence of adventitious acid catalyzing hydrolysis of the quinone monoketal to the quinone during the reaction.

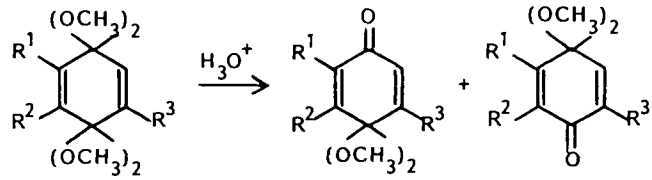
The hydrolysis of quinone bisketals to quinone monoketals is usually a routine preparative procedure when attention is given to the items noted below[54]. It is advantageous to use a weakly acidic media and to mix a cooled solution of the quinone bisketal in acetone with the cooled acid solution. This is advisable even in cases wherein the actual hydrolysis is conducted at room temperature. Most of the quinone bisketal hydrolyses have been conducted in 1–8% aqueous acetic acid–acetone at temperatures from −20 °C to 35 °C, depending upon the particular compound. Ordinarily, the quinone monoketals obtained from standard workup of the reaction mixture are suitable for most preparative purposes. If chromatographic separation of regioisomeric quinone monoketals is required, neutral alumina or silica gel are suitable adsorbents. However, the silica gel should be washed with ca. 5% methanolic ammonia and dried overnight under vacuum above 100 °C for quinone monoketals which are especially labile toward hydrolysis to the quinone. Most quinone monoketals are indefinitely stable when stored in base-washed glassware in the absence of light at 0 °C, although this low temperature is probably not critical to their stability.

2. Stereoelectronic considerations for the regiochemistry of bisketal hydrolysis

A major synthetic advantage of quinone monoketals over quinones is the regiochemistry inherent in nucleophilic additions at the carbon β to the carbonyl group. Thus, the regiochemical outcome of the monohydrolysis of quinone bisketals is of major concern. Tables 13 and 14 illustrate some major points concerning the regioselectivity of quinone bisketal hydrolysis as a function of the substituents on the vinylic carbons. Several general comments about the regiochemistry are noteworthy. First, in both benzene and naphthalene derivatives, the major monoketal arises from hydrolysis of the ketal having the smaller adjacent vinyl substituent. In monosubstituted naphthalene derivatives, virtually one regioisomer is formed since one of the vinylic substituents is hydrogen. In benzoquinone bisketals monosubstituted with an acetamido, bromo, methoxy, benzoyl, or thiomethyl group the regioselectivity of the hydrolysis is very high, the alternate hydrolysis product not being characterized. A simple methyl substituent in benzoquinone bisketal leads to a 64:11 mixture of regioisomers while a trimethylsilyl group gives nearly a 1:1 mixture of the regioisomeric monoketals.

The effect of substituents on the regiochemistry of quinone bisketal hydrolysis undoubtedly results from both the steric and electronic effects of the substituents.

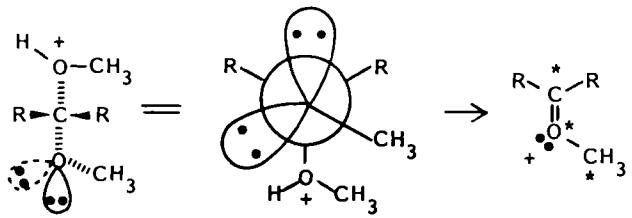
TABLE 13. Monohydrolysis of benzoquinone bisketals[54]



R^1	R^2	R^3	Yield (%)	Yield (%)
H	H	Br	88	3
H	H	CH_3	64 [a]	11 [a]
H	H	$Si(CH_3)_3$	29 [a]	38 [a]
H	H	$CH(CH_3)(OCH_3)$	58 [a]	19 [a]
H	H	$NHCOCH_3$	79	[b]
CH_3	CH_3	CH_3	90	[b]
H	H	OCH_3	66 [a]	[b,c]
H	H	SCH_3	60 [a]	[b]
H	H	COPh	42	[b]

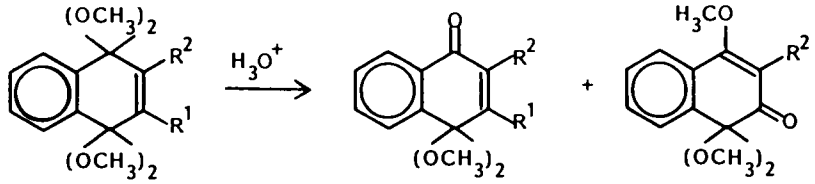
[a] Overall yields of purified monoketals, based on the aromatic precursor to the bisketal.
[b] Alternate hydrolysis product not seen.
[c] Other products observed.

Extensive studies of ketal and orthoester hydrolysis and on the breakdown of tetrahedral intermediates have been reported [55,56] and a discussion of these principles as applied to the regiochemistry of quinone bisketal hydrolysis is instructive. A major point of the previous mechanistic work is that in the transition state for breakage of the carbon–oxygen bond of a protonated ketal, the remaining oxygen should orient one of its lone pairs of electrons in such a way as to stabilize the resultant positive charge. Thus, as the oxonium ion is formed, the starred atoms pictured in Scheme 3 must be coplanar with the C–R bonds to achieve the best overlap of one pair of the oxygens' non-bonding electrons with the cationic center. Any steric effects encountered in achieving this planar intermediate should raise the activation energy for ketal hydrolysis.



SCHEME 3. Stereochemical outcome of ketal hydrolysis

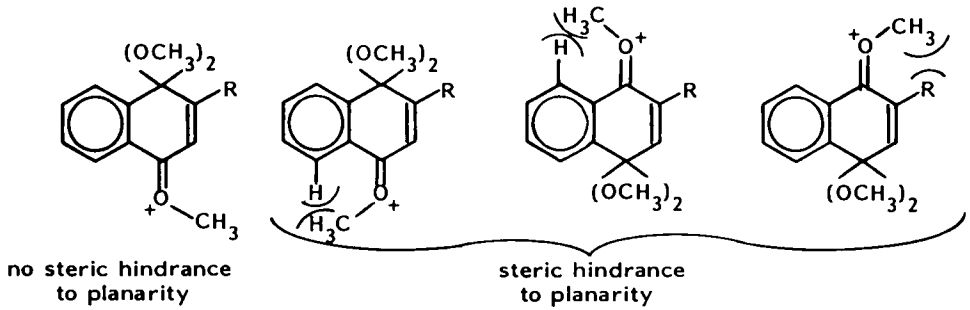
TABLE 14. Monohydrolysis of naphthoquinone bisketals[54]



R^1	R^2	Yield (%)	Yield (%)
H	H	93 [a]	
CH_3	H	90 [a]	
Br	H	85 [a]	
SCH_3	H	56 [a,b]	
CH_3	$Si(CH_3)_3$	57 [b,c]	
OCH_3	H	27	64
OCH_3	CH_3	36 [d]	24
SCH_3	CH_3	58	
Br	CH_3	94 [a]	

[a] Alternate hydrolysis product not seen.
[b] Yield is based on aromatic precursor.
[c] Other isomer not isolated; NMR of Raney Ni reduction products indicated a ratio of ca. 9:1.
[d] Isomeric monoketal formed in 19% yield.

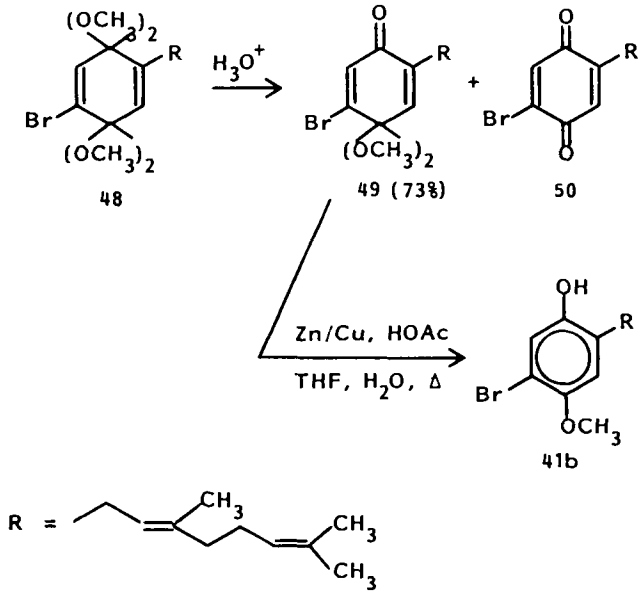
A brief discussion of the higher regioselectivity of ketal hydrolysis in similarly substituted naphthoquinone versus benzoquinone systems illustrates the above discussion. In monosubstituted naphthalenes only one of the four possible intermediates is relatively free of steric interaction as the transition state is approached. Two of the other intermediates for ketal hydrolysis have methoxy–peri hydrogen interactions while the third has a methoxy–R interaction (Scheme 4). This rationale would account for the higher regioselectivity of bisketal hydrolysis observed for naphthoquinone bisketals.



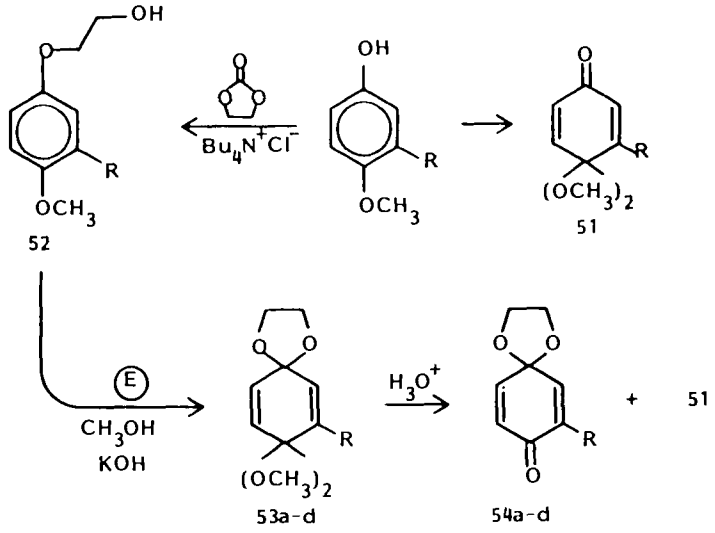
SCHEME 4. Intermediates for hydrolysis of naphthoquinone bisketals

In addition to steric considerations, the effect of the vinyl substituent in stabilizing or destabilizing a carbonium ion center will also influence the direction of ketal hydrolysis. Thus, vinylic substituents such as methyl and methoxy would be expected to stabilize positive centers because of allylic resonance and this would favor hydrolysis of the more distant ketal function. In disubstituted systems such as those listed at the bottom of Table 14, neither ketal can achieve the ideal planar geometry discussed above, and the effect of these substituents on carbonium ion stability may be a primary factor in the regiochemical outcome of the hydrolysis. In summary, as long as steric and electronic effects are complementary, the monohydrolysis of quinone bisketals will be highly regioselective. Where the effects are opposed, the regioselectivity is less predictable. The importance of steric as well as inductive effects in bisketals having more remote functionalities is discussed below.

The generalizations on regiochemistry of bisketal hydrolysis derived from the results of Tables 13 and 14 can be used to predict the regiochemical outcome of the monohydrolysis of bisketals of more synthetic interest. For example, hydrolysis of the bisketal **48** afforded a mixture of **49** and the quinone **50**[30]. The quinone decomposed during alumina chromatography, facilitating the separation of **49** and **50**, thus giving **49** in 73% yield. Reduction with zinc–copper couple afforded pure cymopol monomethyl ether (**41b**, equation 20). A number of tetralin bisketals possessing vinylic bromine substituents have been hydrolyzed to quinone monoketals with high regioselectivity[16,29].



The convenience of preparing substituted quinone monoketals by oxidation of *p*-methoxyphenols is dependent upon availability of the phenol, while the monoketal obtained from bisketal hydrolysis is determined by substituents on the ring. A study has been made using *p*-methoxyphenols as the common intermediates to two alternate quinone monoketals, **51** and **54** (Scheme 5)[21]. In many reactions, **51** and **54** would effectively serve as regioisomeric quinone monoketals. The basis of the strategy for obtaining **51** and **54** from the same *p*-methoxyphenol was the expected slower rate of



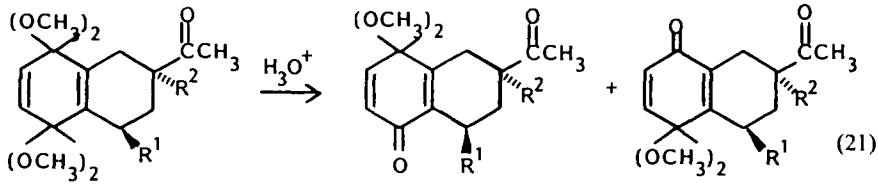
	R	Yields (%) from 53 54	51
a	H	(94)	--
b	CH_3	(93)	--
c	Br	(78)	--[a]
d	OCH_3	--[a]	(68)

SCHEME 5. Strategy and results for preparation of alternate monoketals from a common *p*-methoxyphenol. [a]The alternate monoketal was detected but not isolated

hydrolysis of the ethylene glycol ketal vs. a dimethyl ketal in compounds such as **53**. The electrolysis of mixed ethylene glycol–methanol ethers of substituted hydroquinones proceeds in good to excellent yield (Table 4) to afford the quinone bisketals, **53**. This approach is successful when the substituents on the quinone bisketal are bromo and methyl, since the monoketals of type **54** were obtained in good yield. However, the results with **53d** were disappointing since the influence of a methoxyl group overrides the lower hydrolytic reactivity of the ethylene glycol ketal, affording the same monoketal as that obtained directly from phenol oxidation; thus, the method has limited utility. A general route to both quinone monoketal regioisomers of a given system is yet to be developed.

3. Inductive effects of allylic substituents on the regioselectivity of bisketal hydrolysis

Finally, an interesting effect of an allylic oxygen functionality on the regiochemistry of hydrolysis of bisketal **55b** was noted in connection with synthetic studies of anthracyclinones[15,57]. Although **55a** shows no selectivity in its monohydrolysis, giving a 1:1 mixture of **56a** and **57a**, bisketal **55b** shows a synthetically useful preference for **56b** (equation 21). The products and kinetics for a series of bisketals with different allylic groups was



55a, $R^1 = R^2 = H$
b, $R^1 = OCH_3$, $R^2 = OSi(CH_3)_2Bu\text{-}t$

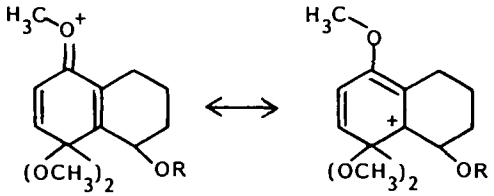
56a (1 part) b (∿ 9 parts)

57a (1 part) b (∿ 1 part)

(21)

studied[58] and the results are shown in Table 15. The kinetic data illustrate the interplay of steric and inductive effects on the regiochemistry of quinone bisketal hydrolysis. While the ether- (entries 3, 4) and fluoro- (entry 5) substituted systems give the same major regioisomer as the alkyl-substituted systems (entries 6 and 7), they do so for different reasons. The selective formation of monoketal **59** from the ether- (entries 3, 4) and the fluoro- (entry 5) substituted systems is not due to an increased rate of formation of **59**, but rather to a decreased rate of formation of **60**. For the alkyl-substituted systems (entries 6 and 7), the overall rate of bisketal hydrolysis increases, and the selective formation of monoketals of type **59** are due largely to the increased rate of formation of **59**. Thus, the similar regioselectivities observed for entries 2–5 and entries 6 and 7 are due to entirely different reasons. Furthermore, the vinyl-substituted systems (entries 8 and 9) favor the formation of regioisomer **63**, not because its formation is increased by the presence of the double bond but largely due to the retarding effect of the double bond on the rate of formation of **62**.

The accelerated rate of hydrolysis for the alkyl-substituted systems (entries 6 and 7) is best attributed to relief of steric interaction in the ionization step. For the bisketals having allylic oxygen and fluoro substituents, the rate of formation of the intermediate leading to

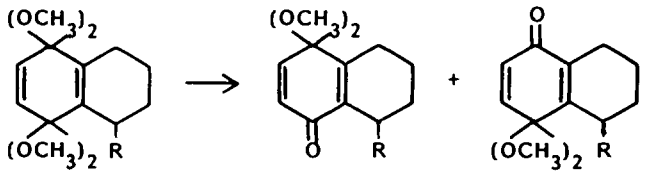


64

64 would be decreased by the inductive effect of the substituent on the allylic cation being formed. Likewise, the decreased rate of formation of monoketal **62** for the triene systems (entries 8 and 9) must be due partly to the inductive effect of the added sp^2 centers. For the intermediate leading to formation of **63**, the inductive effect of the sp^2 center is counterbalanced by the benefit of allylic resonance leading to little change in overall rates. However, for the intermediate leading to the formation of **62**, only the inductive effect of the sp^2 center is operative.

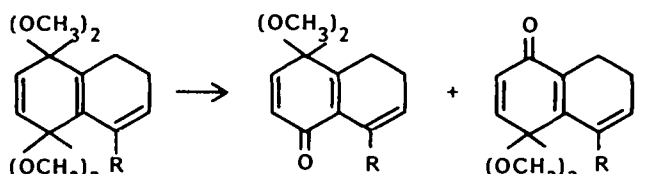
As can be ascertained from the above discussion the regiochemistry of hydrolysis of a given bisketal is an interplay of steric, stereoelectronic and inductive effects. While the individual importance of these effects changes with the compound of interest, sufficient information is available to allow one to make a reasonable prediction as to the regiochemical outcome of the hydrolysis of a functionalized quinone bisketal.

TABLE 15. Effect of allylic substituents on rates and regioselectivity of bisketal hydrolysis[58]



58 59 60

Entry	R	Relative Rate[a]	Relative Rate[b]	Relative Rate[b]	Ratio 59:60
1	H	7.7	3.85	3.85	1:1
2	OH	2.9	2.6	0.3	8.6:1
3	OCH_3	4.6	3.9	0.7	5.6:1
4	$OSi(CH_3)_2Bu\text{-}t$	3.6	2.6	1.0	2.6:1
5	F	1.0	0.9	0.08	11.2:1
6	CH_3	10.0	6.0	4.0	1.5:1
7	Bu-t	20.1	17.5	2.6	6.7:1



61 62 63

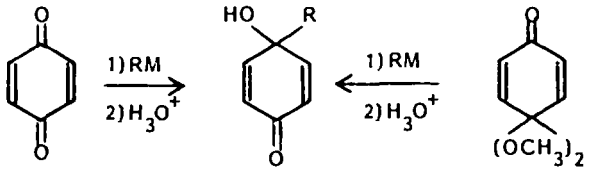
8	H	5.1[c]	0.8	4.3	1:5.3
9	CH_3	2.9[c]	0.3	2.6	1:8.6

[a] For disappearance of 58.
[b] For formation of product.
[c] These relative rate data are on the scale as for entries 1–7.

V. REACTIONS OF QUINONE MONOKETALS

A. 1,2 Additions to Quinone Monoketals

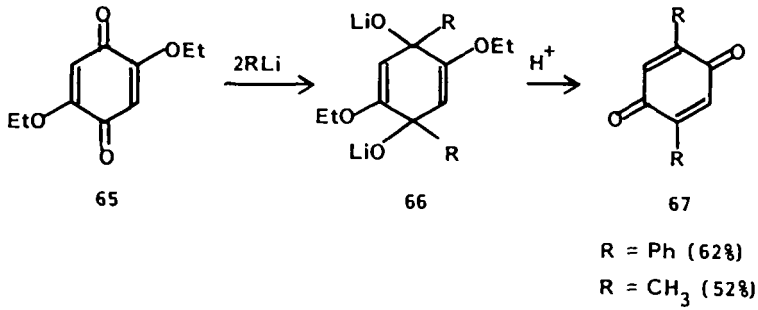
The 1,2 addition of Grignard and organolithium reagents to the carbonyl group of quinone monoketals comprises a synthetically useful approach to a variety of functionalized, protected *p*-quinol derivatives. Since the resultant *p*-quinol ketals can often be hydrolyzed under mild acidic conditions to the respective *p*-quinol, it is interesting to briefly compare analogous additions to quinone monoketals and quinones (Scheme 6). In



SCHEME 6. Routes to *p*-quinols from quinones and quinone monoketals

addition, the trimethylsilyl cyanide derivaties of quinones[4a-f] react with Grignard and organolithium reagents to give *p*-quinol derivatives after deblocking[3d,4]. Thus, additions to both quinone monoketals and the trimethylsilyl cyanide derivatives of quinones serve as viable routes to *p*-quinol derivatives.

The early literature reports variable results for reactions of Grignard reagents with simple quinones. In a 1952 paper[59] it is stated, 'In general, the reactions between quinones and Grignard reagents do not give good yields'. However, direct addition of organometallic reagents to quinones to produce mono- and bisaddition products can be synthetically useful for appropriate substrates and reaction conditions. Thus, reaction of quinones such as **65** with organolithium and Grignard reagents gives the functionalized quinones **67** in 50–60% overall yields after direct hydrolysis of the bisaddition adducts **66**



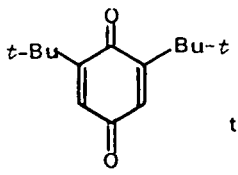
(22)

(equation 22)[60]. It is also possible to selectively perform monoadditions of organolithium reagents to quinones, especially if the reaction is conducted at low temperature (− 78 to − 120°C)[62]. The regioselectivity of these monoadditions is influenced not only by the substituents on the quinone but also by the organometallic reagent (Grignard vs. alkyllithium), the solvent and the presence of tetramethylethylenediamine (TMEDA) in the reaction[62,63]. Thus, reaction of simple alkyllithium and Grignard reagents with

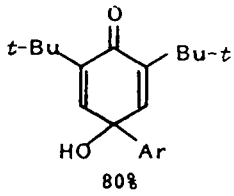
quinones at low temperatures constitutes a synthetic route to *p*-quinols with some regiochemical control (Table 16). However, these reactions can be complicated by electron transfer processes and bisadditions of the organometallic reagents to the quinone.

The formation of *p*-quinols by reaction of quinone monoketals with alkyllithium reagents followed by acid hydrolysis has the advantage of affording only one regioisomeric product (Table 17). However, as would be expected from the extensive studies of organometallic additions to *p*-quinol derivatives[64], reduction of the quinone monoketal to

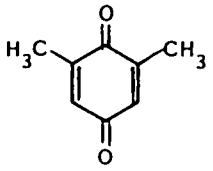
TABLE 16. Selected monoadditions of organometallic reagents to quinones



ArMgBr
room temperature
ref 61



80%



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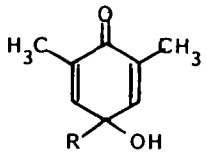
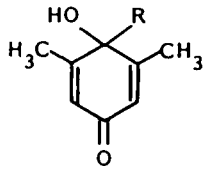
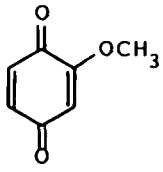


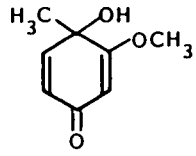
+



Conditions	R	Yield (%)	Yield (%)
CH_3MgBr, -78 °C	CH_3	60	10
CH_3Li, TMEDA, -107 °C	CH_3	10	87
n-BuLi, -78 °C	*n*-Bu	60	15
n-BuLi, TMEDA, -107 °C	*n*-Bu	12	66

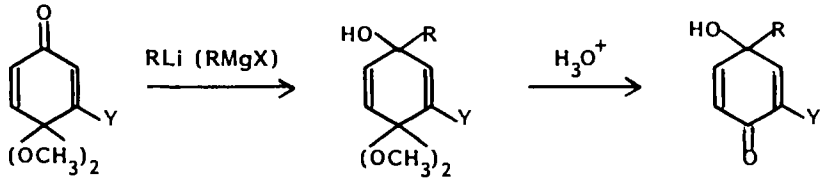


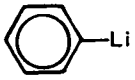
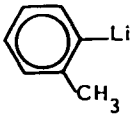
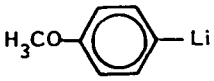
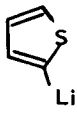
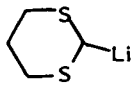
ref 63



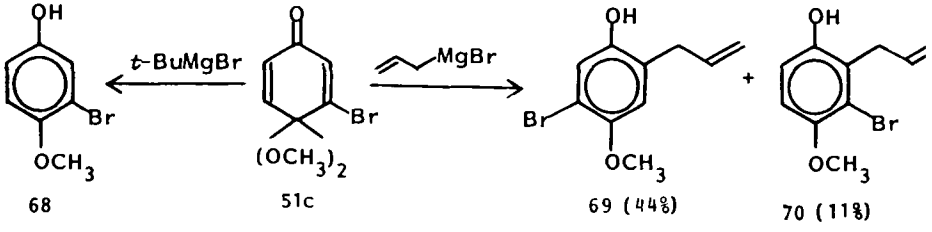
Conditions	
CH_3Li, TMEDA, -107 °C	80%
CH_3MgBr, -78 °C	complex mixture

TABLE 17. Selected examples of *p*-quinol ketals and *p*-quinols prepared from quinone monoketals



RLi(RMgX)	Y	Yield (%)	Yield (%)	Ref
	H	85	81	14a
	H	84	77	14a
	H	90	75	14a
	H	79	--	14a
CH_3MgBr	Br	84	--	14a
	OCH_3	90	--	3b
$LiCH_2CO_2CH_3$	H	91	54	3b
$PhSO_2CH_2Li$	OCH_3	86	--	3b

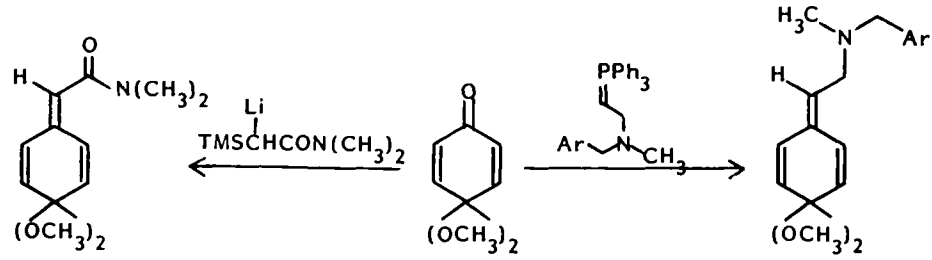
the respective phenol by electron transfer[65] from the organometallic reagent can complicate some of these reactions. In general, primary (methyl, *n*-butyl, etc.) and aryl organometallic reagents react with quinone monoketals at low temperature to afford excellent yields of the corresponding *p*-quinol ketals (Table 17). The 1,2-addition process is favored for a given system if the quinone monoketal is reacted with the alkyllithium reagent at −78°C. However, even under these conditions, reduction of the quinone monoketal to the respective phenol can compete with the 1,2 addition for the case of secondary organolithium and Grignard reagents. While the reaction of tertiary and allylic organometallic reagents with quinone monoketals has not been extensively studied, the reaction of *t*-butyl and allyl Grignard reagents with monoketal **51c** afforded major products that were derived from reduction (**68**) and rearrangement (**69, 70**, equation 23)[54].



68 51c 69 (44%) 70 (11%)

(23)

While there are only a limited number of examples, Peterson[4c] (**43** → **71**) and Wittig[3c,66] (**43** → **72**) reactions of quinone monoketals produce the corresponding protected quinone methides in good yields (equation 24). These compounds have proven to be valuable intermediates in the synthesis of several natural products[3,4] and have recently been employed in the synthesis of aryltetralin lignans[66].

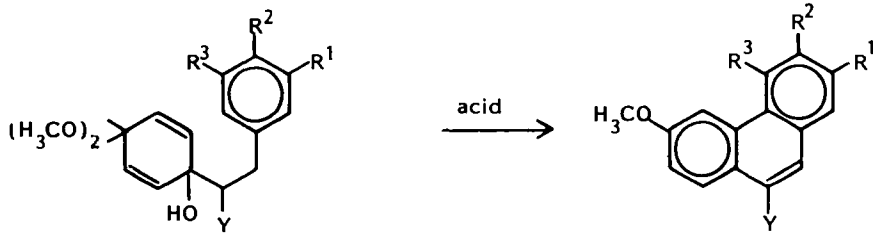


71 (77%) 43 72 (47%)

(24)

With the limitation of reduction as a competing reaction, the 1,2 addition of organometallic reagents to quinone monoketals is a useful approach to certain *p*-quinol ketals and *p*-quinols. The major advantage of additions to quinone monoketals relative to quinones is the well-defined regiochemical outcome of the reaction and the formation of the *p*-quinol in a protected form. The *p*-quinol ketals formed in these reactions can not only be hydrolyzed to *p*-quinols but can also be useful synthetic intermediates in their own right. A recent example is the acid-catalyzed rearrangements of the aryl-substituted *p*-quinol ethers to substituted phenanthrenes (Table 18). A similar cyclization (compound not shown) produced a substituted fluorene derivative.

TABLE 18. Acid-catalyzed cyclization of *p*-quinol ketals to substituted phenanthrenes[4b]



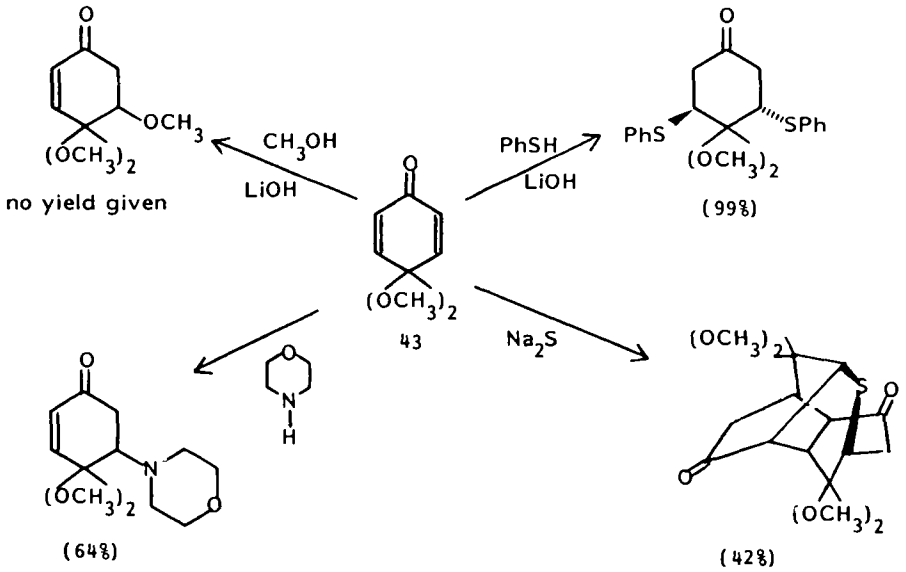
Y	R^1	R^2	R^3	Acid	Yield (%)
CO_2CH_3	OCH_3	OCH_3	OCH_3	P_2O_5/CH_3SO_3H	77
CO_2CH_3	OCH_3	OCH_3	H	$SnCl_4$	74
SO_2Ph	OCH_3	H	H	$BF_3 \cdot Et_2O$	62
CO_2CH_3	H	H	H	$BF_3 \cdot Et_2O$	64

B. Simple Michael Additions to Quinone Monoketals

The high reactivity of simple quinones in 1,4-addition reactions is well-documented. Although the replacement of one carbonyl group of the quinone with a ketal linkage would afford some steric hindrance toward nucleophilic attack at the β position of the monoketal, the inductive effect of the ketal linkage would not markedly alter the electron-deficient character at this position. Thus, as might be expected, quinone monoketals are efficient Michael acceptors and undergo a wide variety of transformations initiated by 1,4 addition of nucleophiles at the β carbon. In contrast to the corresponding quinones, Michael additions to quinone monoketals are regiospecific and the resultant adducts are much less likely to undergo aromatization under the reaction conditions and subsequent adventitious oxidation or reduction. Although virtually unexplored until recently, conjugate additions to quinone monoketals and the subsequent elaboration of the adducts provides a facile method for the preparation of interesting synthetic intermediates. This section will highlight some of the simple 1,4-addition reactions of quinone monoketals. The following sections will present reactions of quinone monoketals initiated by 1,4 addition but having ring formation as the final result.

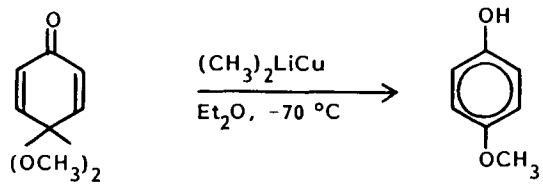
Some early examples of 1,4 additions of oxygen, nitrogen and sulfur nucleophiles to the parent quinone monoketal **43** are outlined in Scheme 7[25a,48]. Especially interesting is the novel caged compound formed from reaction of **43** with sodium sulfide. Likewise, the additions of soft carbon nucleophiles such as diethyl malonate and ethyl cyanopropionate to quinone monoketals (Table 19) afford good yields of 1,4-addition products[67]. These compounds may be aromatized in a second step by heating with acid to afford the functionalized hydroquinone ethers in high yield (Table 19). This sequence provides an excellent two-step procedure for effecting overall nucleophilic substitution on a quinone, regiospecifically producing a functionalized hydroquinone monoether.

Although of reasonable generality, the 1,4 additions to quinone monoketals are not without limitation, especially when the addition involves the transfer of simple alkyl



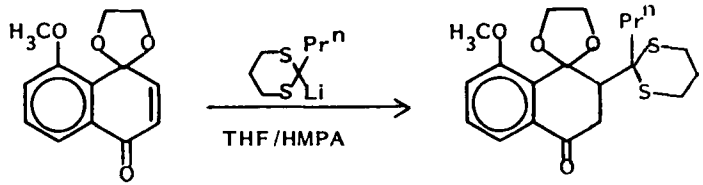
SCHEME 7. Selected examples of Michael addition reactions of nitrogen, oxygen and sulfur nucleophiles to quinone monoketals[48]

groups. Attempted conjugate addition of lithium dimethyl cuprate to quinone monoketals results in reduction of the quinone monoketal to the corresponding phenol, presumably via an electron transfer process as illustrated by the formation of **73** from **43** (equation 25)[25a,65]. Michael addition of simple carbon nucleophiles except cyanide ion) to



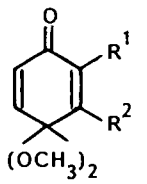
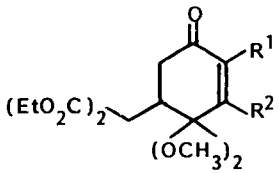
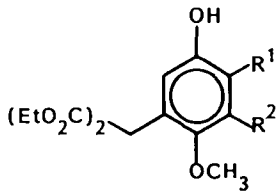
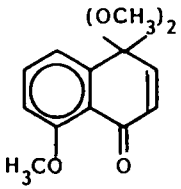
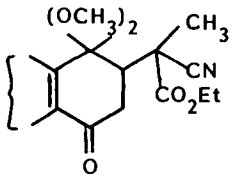
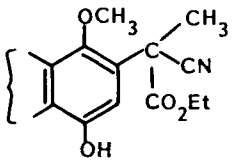
(25)

quinone monoketals is often not a trivial matter, judging from some reports in the literature. In general, quinone monoketals react with 2-lithio-2-alkyl-1,3-dithianes, lithio trimethylsilyl cyanide derivatives of aldehydes and 1-lithio-1-[(methoxymethyl)oxy] butane to give low yields of 1,4-addition products, a mixture of 1,2-addition products and reduction processes usually being observed[68]. However, in one instance, the use of HMPA led to a useful addition of a dithiane anion to the naphthoquinone monoketal **74** to form **75** (equation 26)[68]. The anions from nitromethane and nitroethane have been reported to afford 1,4-addition products in good yield with certain naphthoquinone monoketals, but the scope of the reaction was not studied[68].



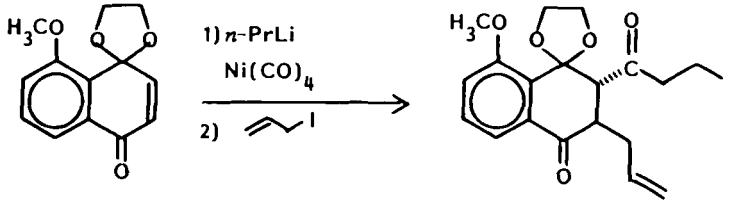
74 75 (86%) (26)

TABLE 19. Diethyl malonate and ethyl cyanopropionate additions to quinone monoketals using sodium ethoxide in ethanol

Monoketal		1,4-Adduct	Hydroquinone Ether
			
R^1	R^2	Yield (%)	Yield (%)
H	H	91	88
OCH_3	H	83	63
OCH_3	CH_3	70	86
			 (84% overall)

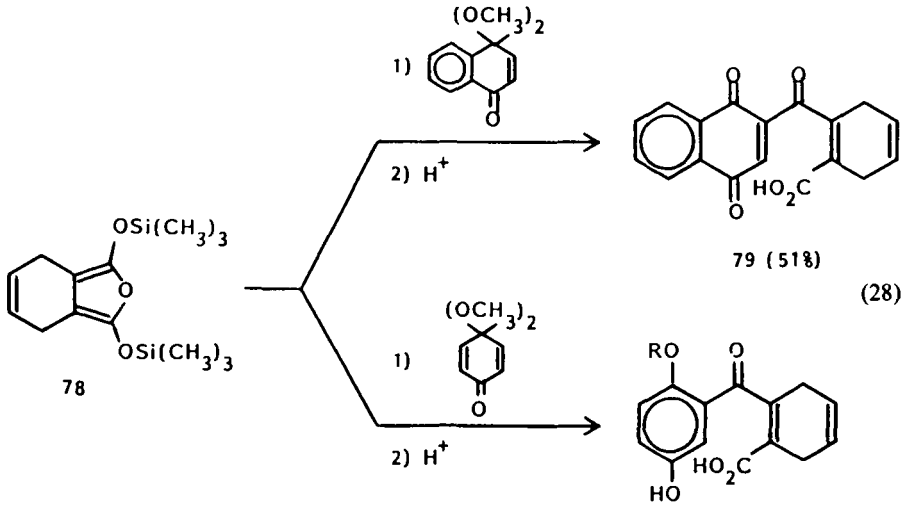
Somewhat more successful 1,4 additions to selected naphthoquinone monoketals were found with acyl nickel complexes of simple alkyllithium compounds formed from the alkyllithium and nickel tetracarbonyl[68]. This reagent reacted with **76** to afford **77** in good

yield (equation 27); however, reduction was the major reaction pathway when benzoquinone monoketals were used as reactants. Thus, this chemistry does not serve as a general method for introduction of acyl groups to the β position of quinone monoketals.



76 77 (81%) (27)

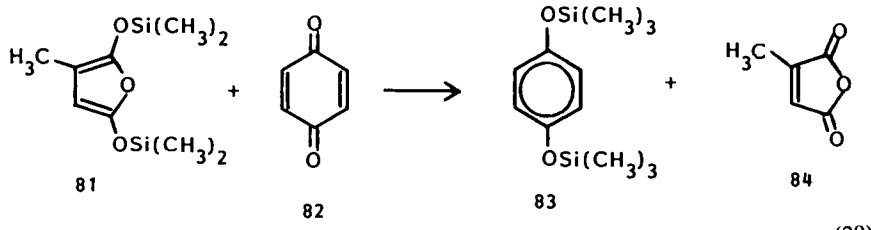
A special type of formal 1,4 addition of acyl groups to quinone monoketals involves reaction of the bis-silyl ether **78** with both benzo- and naphthoquinone monoketals to give 1,4-addition products[69]. For the case of the naphthoquinone monoketal, the reaction afforded **79** via air oxidation of the initially formed hydronaphthoquinone. The benzoquinone monoketal reacted with **78** to give after acidic workup a mixture of **80a** and **80b** (equation 28). In both systems the keto acid moiety was in equilibrium with its



respective cyclic lactol form. Although these products formally derive from a 1,4-addition reaction, they may be formed via an initial Diels–Alder reaction followed by a reverse aldol-type cleavage. Interestingly, **81** reacts with benzoquinone **82** in a rapid redox process to form **83** and **84** with no 1,4-addition product reported (equation 29).

C. Annelations of Quinone Monoketals via Nucleophilic β,β' Addition

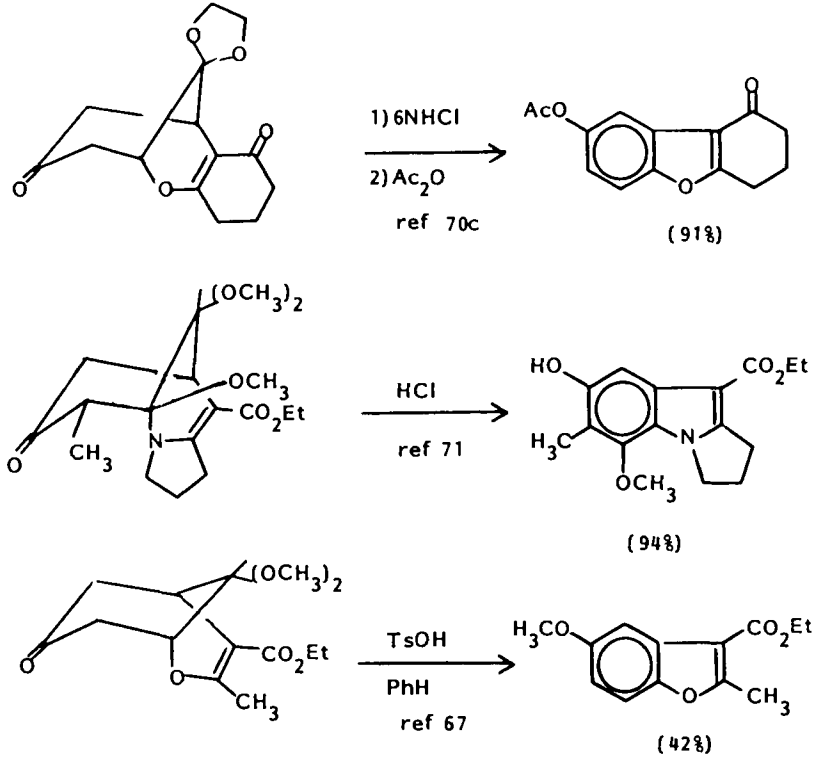
The previous section illustrated the high reactivity of quinone monoketals in Michael addition reactions. Nucleophilic addition at the reactive β position is also the initial step in



(29)

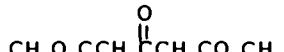
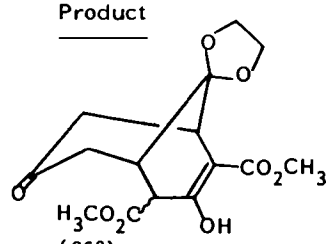
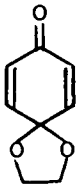
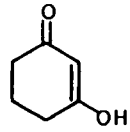
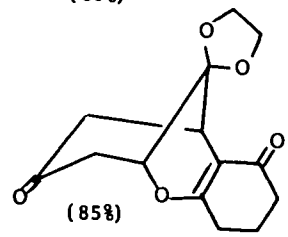
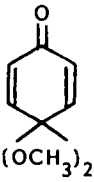
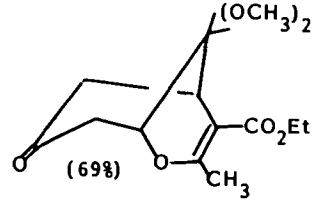
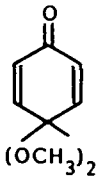
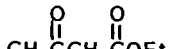
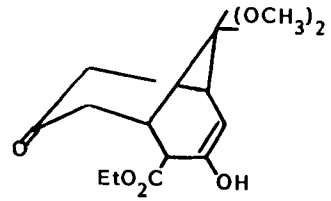
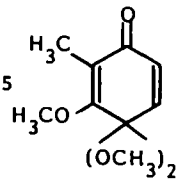
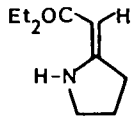
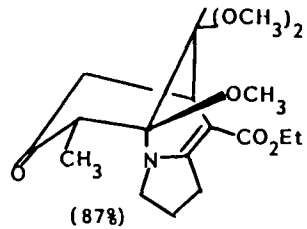
a number of efficient annelation reactions of quinone monoketals. These reactions have been grouped into two categories: β,β' additions, wherein a bimolecular nucleophilic addition to the β carbon of the quinone monoketal is followed by a second intramolecular addition to produce a bicyclo [3.3.1] ring system; and β, α-additions, which involve initial addition to the β carbon, followed by intramolecular reaction of the nucleophilic center generated at the α position with an electrophilic center.

A number of different active methylene compounds have been reacted with quinone monoketals to give β,β'-annelation products in good to excellent yields (Table 20). In reactions with unsymmetrically substituted quinone monoketals, the product is formally



SCHEME 8. Transformations of β,β'-annelation products of quinone monoketals to benzofurans and indoles

TABLE 20. Selected annelations derived from β,β' additions to quinone monoketals

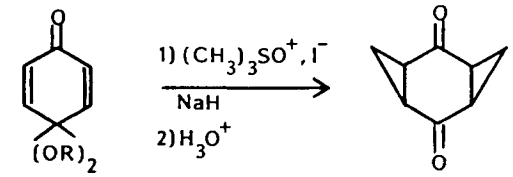
Entry	Monoketal	Anion Precursor Conditions	Product
1		 NaOEt (catalytic) ref 70a	 (86%)
2		 t-BuOK, t-BuOH ref 70c	 (85%)
3		 NaOEt, EtOH ref 67	 (69%)
4		 NaH, THF ref 67	 (66%)
5		 1) NaH 2) H_2O ref 71	 (87%)

derived from initial addition at the less hindered, more reactive β' position (entry 5), followed by cyclization at the more substituted β position. An interesting dependence on reaction conditions was noted for the reactions of quinone monoketals and ethyl acetoacetate (entries 3 and 4). Thus, with sodium ethoxide in ethanol, the second step involves bond formation between the oxygen of the ambident anion and the β' carbon while the sodium enolate in tetrahydrofuran gives the product derived from bonding of the carbon to the β' position.

These β,β'-annelation products can often be converted to functionalized benzofuran and indole ring systems in high yield as illustrated in Scheme 8. These heterocyclic products are formally derived from acid-catalyzed ionization of the ketal followed by 1,2 migration of the heteroatom and subsequent aromatization. Thus, the products from β,β' addition of 1,3-cyclohexanedione and ethyl acetoacetate with quinone monoketals under acidic conditions afford benzofurans, whereas products from the anions of enaminoesters and monoketals give indoles. This latter reaction is only one of several examples and constitutes a regiospecific variant of the Nenitzescu indole synthesis. However, conversion to indoles apparently is limited to adducts derived from quinone monoketals having a β-methoxy group.

D. Annelations of Quinone Monoketals via Nucleophilic β Addition, Followed by Electrophilic α Functionalization

Annelation reactions of quinone monoketals analogous to those of conjugated ketones should be especially facile as long as the nucleophilic species is a poor reducing agent. Fortunately, with many of the common annelating reagents, reduction is seldom observed, and high yields of annelation products are formed. The cyclopropanation of **43** and **54a** by dimethylsulfoxonium methylide was one of the first examples of this process and was a key step in the synthesis of bishomoquinone **85** (equation 30)[5,26]. A similar annelation



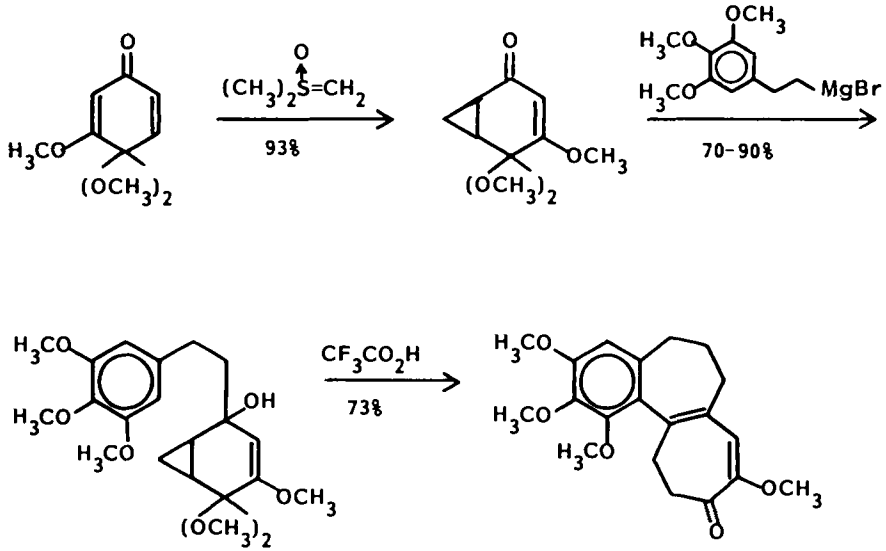
(30)

43, R = CH_3
54a, $(OR)_2$ = OCH_2CH_2O

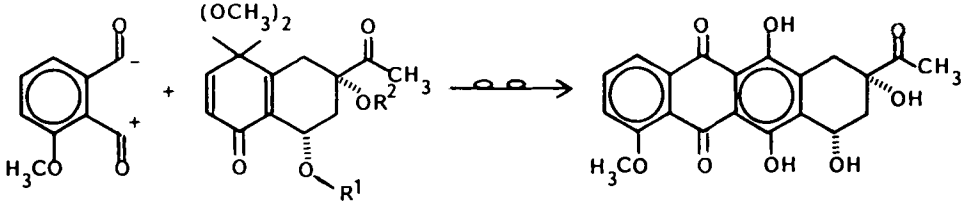
85 (56% overall from **54a**)

product of **54d** was employed as a key intermediate in a synthesis of (±)-deacetamidoisocolchicine (Scheme 9) and (±)-colchicine[72].

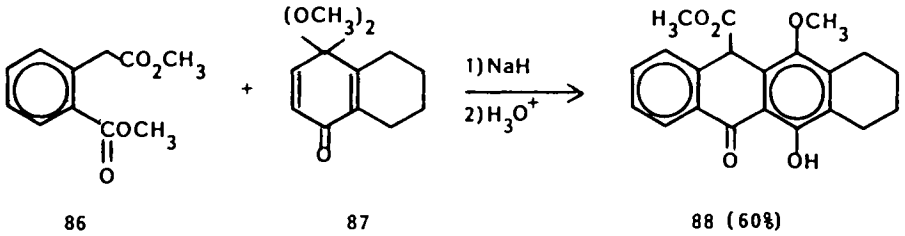
The recent interest in anthracyclinone chemistry has brought about a resurgence in the chemistry of anthraquinones[73]. Thus, an attractive convergent and regiospecific approach to tetracyclic quinone systems would involve β,α annelation of 1,4-dipole equivalents to quinone monoketals (Scheme 10). Initially, this strategy was explored with the anions of homophthalic esters, i.e. **86** → **88** (equation 31)[57b,c]. Subsequently, the anion of the cyanophthalides[15,57b,74] **89** and sulfone[57a,b,75] **90** were used to produce the corresponding anthraquinone **91** directly, with **89** generally affording significantly better yields in this annelation (equation 32). The lower yields of anthraquinone product when using **90** in the reaction was attributed to competing 1,4 addition of the phenylsulfinate anion, X = $PhSO_2$, released in the final step of the annelation (i.e. **92** → **93**), with the unreacted



SCHEME 9. Key synthetic steps in the synthesis of racemic deacetamidoisocolchicine



SCHEME 10. Synthetic strategy to daunomycinone using a β,α annelation of a quinone monoketal

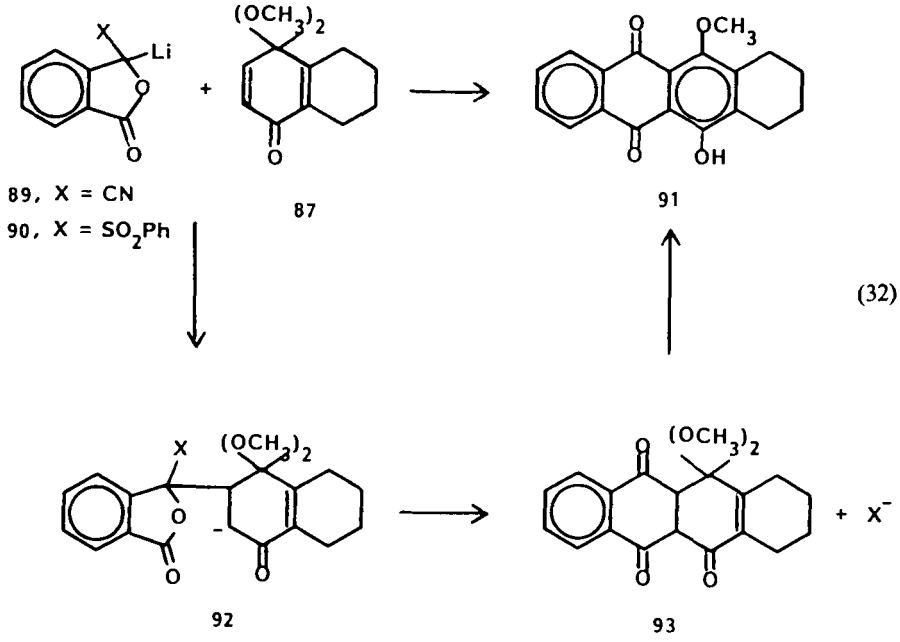


86 87 88 (60%)

(31)

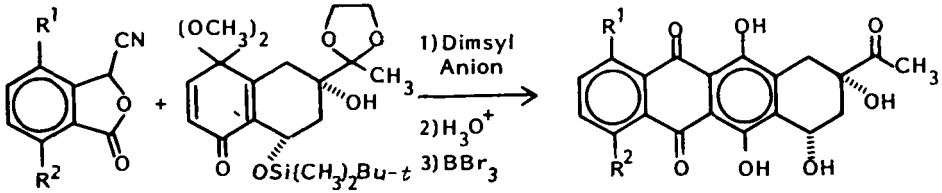
quinone monoketal[57b]. This serves again to emphasize the Michael reactivity of quinone monoketals with soft nucleophiles.

Using the highly functionalized quinone monoketal **94** and the cyanophthalides **89a–e**,



(32)

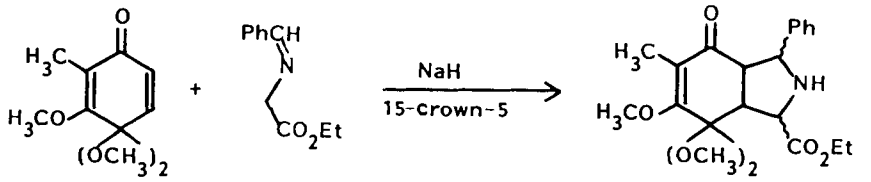
a regiospecific route to fully functionalized anthracyclinones **95** was achieved (equation 33)[15, 57, 76]. Over 30 g of anthracyclinone analog, **95a**[15], as well as a variety of other



R^1, R^2 (overall yield): a, H,H (84%); b, H,OCH_3 (42%); c, H,F (70%); d, F,H (48%); e, F,F (52%)

(33)

analogs, **95b–e**, were prepared, using this chemistry. This particular annelation of quinone monoketals is an excellent regiospecific procedure for the preparation of anthraquinones having acid-sensitive and thermally labile substituents and is now a preferred method for preparation of anthracyclinone analogs[74, 75]. Interestingly, reaction of **89a** with the quinone derived from **94** gave very low yields of annelation product. A number of variants of the β,α annelation such as the reaction of **96** with a monoketal to give **97** (equation 34) are possible[77]. Undoubtedly, many other annelations of this type will be investigated in the coming years.

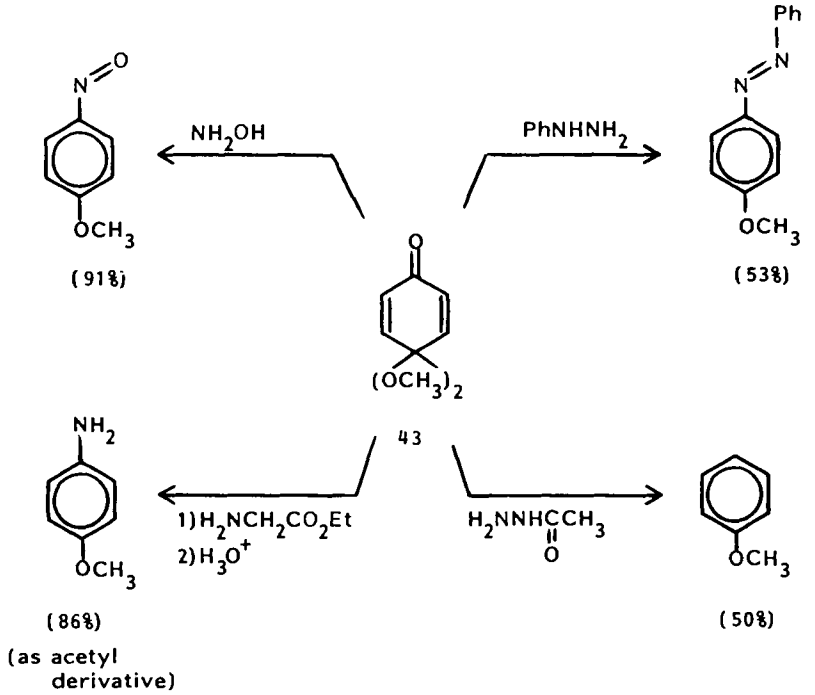


96

97 (45%) (34)

E. Reactions of Quinone Monoketals with Derivatives of Ammonia

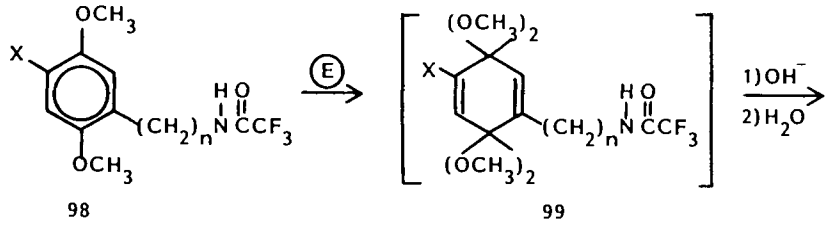
In principle, ammonia derivatives have two major pathways available for reaction with quinone monoketals. The 1,4 addition of secondary amines to the parent quinone monoketal was mentioned in Section V.B. Addition to a carbonyl group followed by loss of water to form an imine is commonplace in carbonyl chemistry, and products derived from this mode of addition would be especially favored if subsequent chemistry rendered the addition irreversible. The reaction of quinone monoketals with several ammonia derivatives was examined as a method for conversion of the carbonyl group of the quinone monoketal to other functionalities. Scheme 11 illustrates the use of this chemistry for the conversion of quinone monoketals to the corresponding nitroso, amino, phenylazo and hydrogen compounds[78,79]. The condensation of the NH_2 group of the reagent with the carbonyl group of the monoketal is undoubtedly the initial step in all of these reactions.



SCHEME 11. Reaction of quinone monoketal **43** with ammonia derivatives

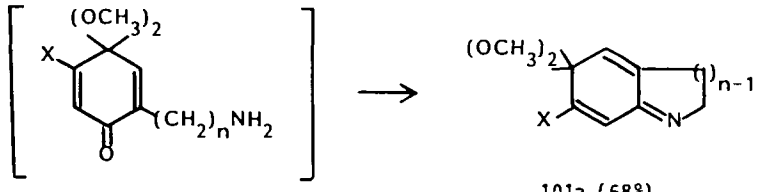
Since the quinone monoketal is often derived from the corresponding *p*-methoxyphenol, this constitutes a method for replacement of the phenolic hydroxyl group by NO, N = N–Ph, NH_2 and H.

The quinone imine unit has been of long-standing interest in chemistry[80,81], but protected forms of these molecules appear not to have been reported. The intramolecular condensation of an amino group with a quinone monoketal carbonyl group serves as a route to the ketals of quinone imines. Two variants of this chemistry are known. Anodic oxidation of **98a–d** followed by direct hydrolysis of the reaction mixture affords in one operation the quinone imine ketals **101a–d** via intermediates **99** and **100** (equation 35)[81,82]. However, the success of this method depends on the selective hydrolysis of the ketal linkage adjacent to the side chain bearing the amino group of **99** to give the intermediate **100**. It was not possible to prepare the unsubstituted quinone imine ketal using this approach.



98 99

(35)



100

101a (68%)
b (45%)
c (40%)
d (57%)

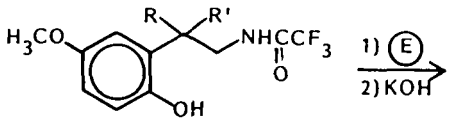
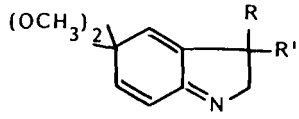
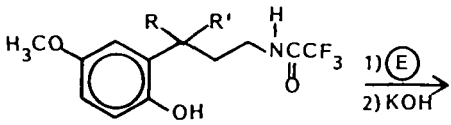
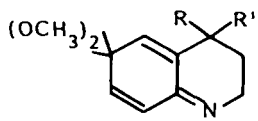
a, X = OCH_3, n = 2; b, X = OCH_3, n = 3;
c, X = Br, n = 2; d, X = Br, n = 3

A more general method for the formation of the quinone imine ketals involves oxidation of the respective *p*-methoxyphenol followed by *in situ* hydrolysis of the trifluoroacetyl group and intramolecular condensation (Table 21)[81]. The protection of the amine from anodic oxidation via its trifluoroacetamide derivative is especially convenient since this amide linkage is cleaved under mild basic conditions to generate the reactive amino moiety which then undergoes intramolecular condensation with the carbonyl group.

F. Acid-catalyzed Cycloaddition Reactions of Quinone Monoketals

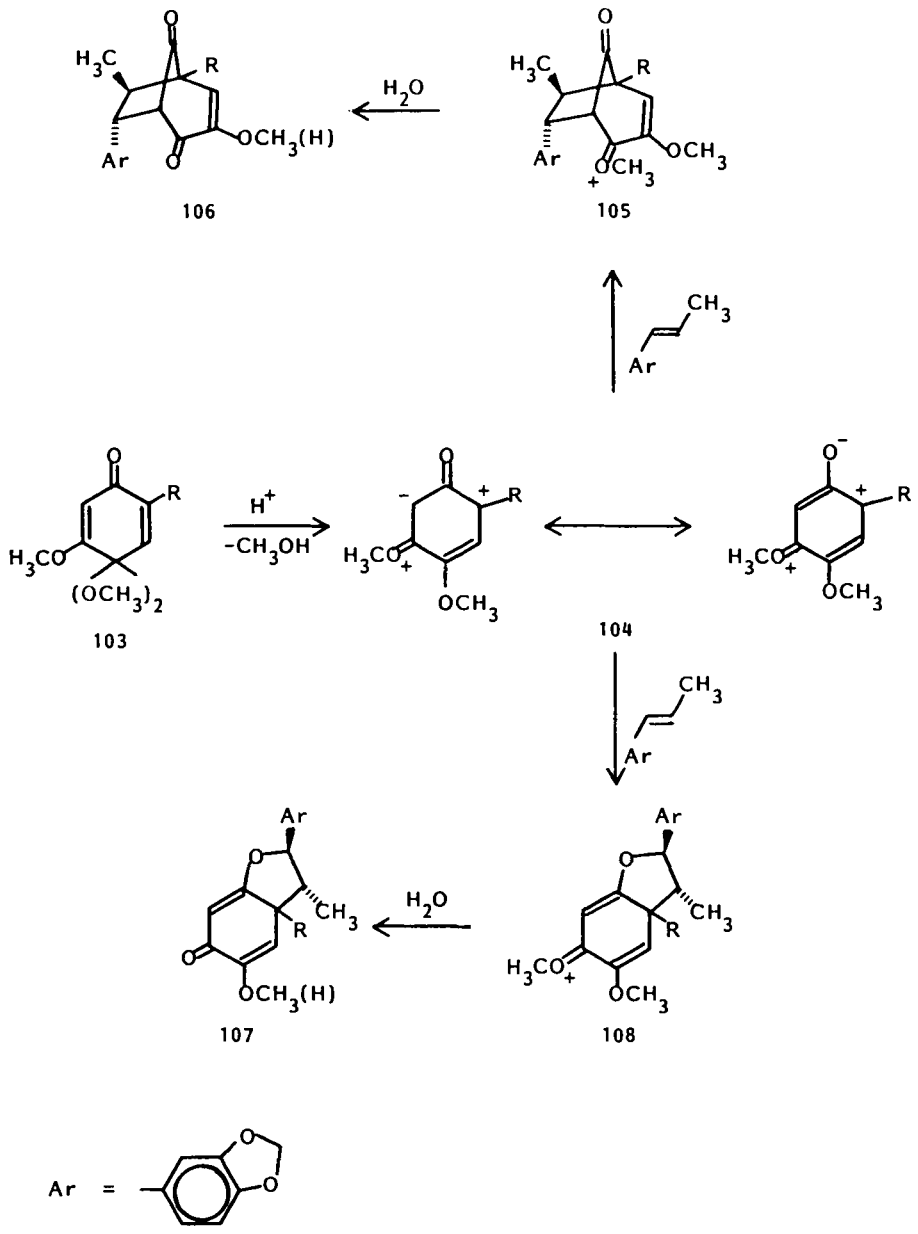
Neolignans[83] are a group of secondary plant metabolites structurally characterized by the presence of two arylpropanoid units. Several members of this class of natural products

TABLE 21. Quinone imine ketals from phenol derivatives

Compound	Imine
	
R = R' = H	(82%)
R = OH, R' = H	(91%)
R = OH, R' = CH_3	(81%)
	
R = OH, R' = H	(91%)
R = OH, R' = CH_3	(89%)

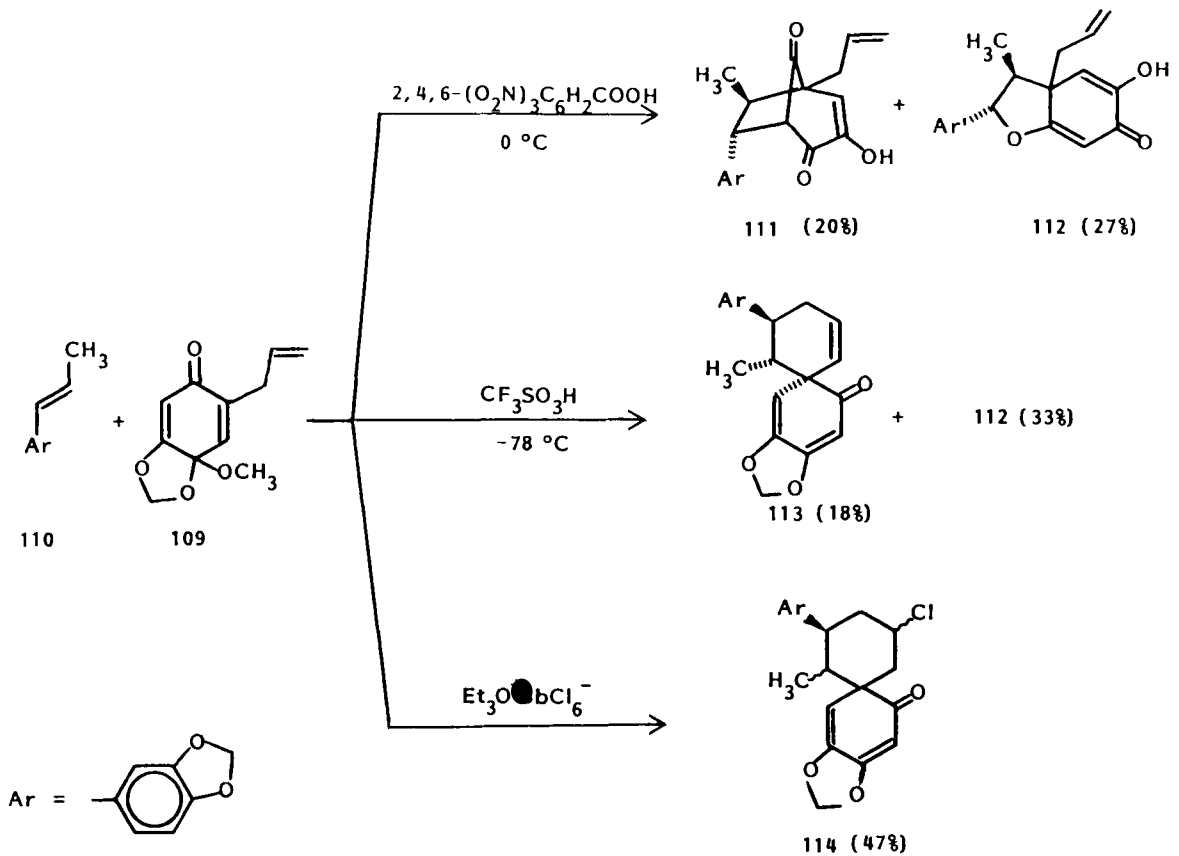
have been synthesized by an interesting cycloaddition reaction of a 3-alkoxy-substituted quinone monoketal and isosafrole[84, 85]. The chemistry involved is conveniently rationalized by a cycloaddition of a positively charged 1,3-dipole intermediate, **104**, formed by acid-catalyzed loss of methanol from the quinone monoketal **103**, and an olefin as outlined in Scheme 12. The cations **105** and **108** produced from this initial cycloaddition can undergo hydrolysis, or rearrangement and hydrolysis, to afford the observed products **106** and **107**. In some cases, the vinyl ether linkage of **107** undergoes hydrolysis under the workup to give the enol.

The products from this type of cycloaddition are markedly dependent upon the acid catalyst and the reaction media as illustrated by the reactions of **109** and **110** below[84]. This reaction in acetonitrile catalyzed by 2,4,6-trinitrobenzenesulfonic acid gives a mixture of **111** and **112**. However, if the same reaction was performed in methylene chloride at $-78°C$ using trifluoromethanesulfonic acid as catalyst, **113** was formed in addition to **112**. Finally, when using triethyloxonium hexachloroantimonate as catalyst in methylene chloride, the spiro dienone **114** was the major product (equation 36). The products from the first set of conditions can be rationalized by assuming an initial cycloaddition to produce intermediates analogous to **105** and **108** which undergo hydrolysis to afford **111** and **112**. When the reactions are conducted in methylene chloride, a non-nucleophilic medium, these initially formed cations undergo rearrangement and cyclization to the allyl linkage, affording **113** and **114**.



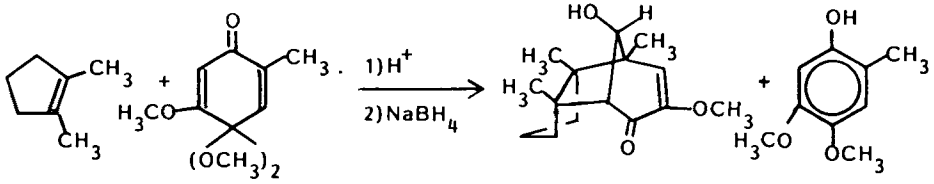
Ar =

SCHEME 12. Generalized reaction scheme for acid-catalyzed cycloaddition of quinone monoketals and olefins


2, 4, 6-(O2N)3C6H2COOH
0 °C
CF3SO3H
-78 °C
Et3OBbCl6−
Ar =
110
109
111 (20%)
112 (27%)
113 (18%)
112 (33%)
114 (47%)

(36)

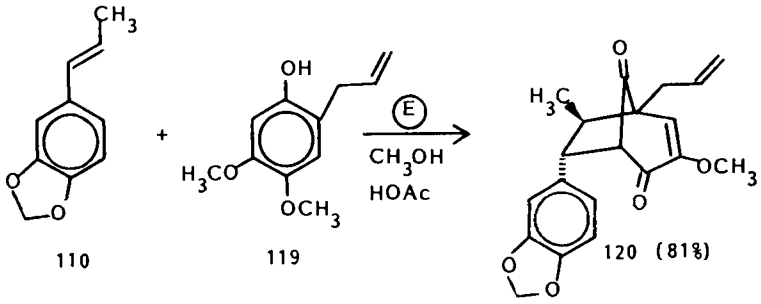
The overall yields of these cycloadditions are not high, and the reactions may be specific for 3-oxygenated quinone monoketals. However, the availability of the starting materials and the one-step formation of a rather complex ring system with good control of the stereochemistry makes this type of reaction an attractive, albeit limited, synthetic method. Variants of this cycloaddition have been used as key steps in the synthesis of Gymnomitrol[86] and Megaphone[87] and in a route to tropolones[88]. The reaction of **115** with **116** to give **117**, a key intermediate in the synthesis of Gymnomitrol, illustrates a common competing reaction when quinone monoketals are reacted with Lewis acid even under mild conditions: reduction of the quinone monoketal to the respective phenol (e.g. **116** → **118**, equation 37). Presumably, the methoxy moiety of the quinone monoketal, **116**, is the reducing agent and is oxidized to formaldehyde in the course of the reaction.



115 116 117 (10%) 118 (30-45%)

(37)

An especially interesting variant of this chemistry is the direct electrochemical oxidation of **119** in the presence of isosafrole (**110**) to produce **120** in 81% yield (equation 38)[89]. It



110 119 120 (81%)

(38)

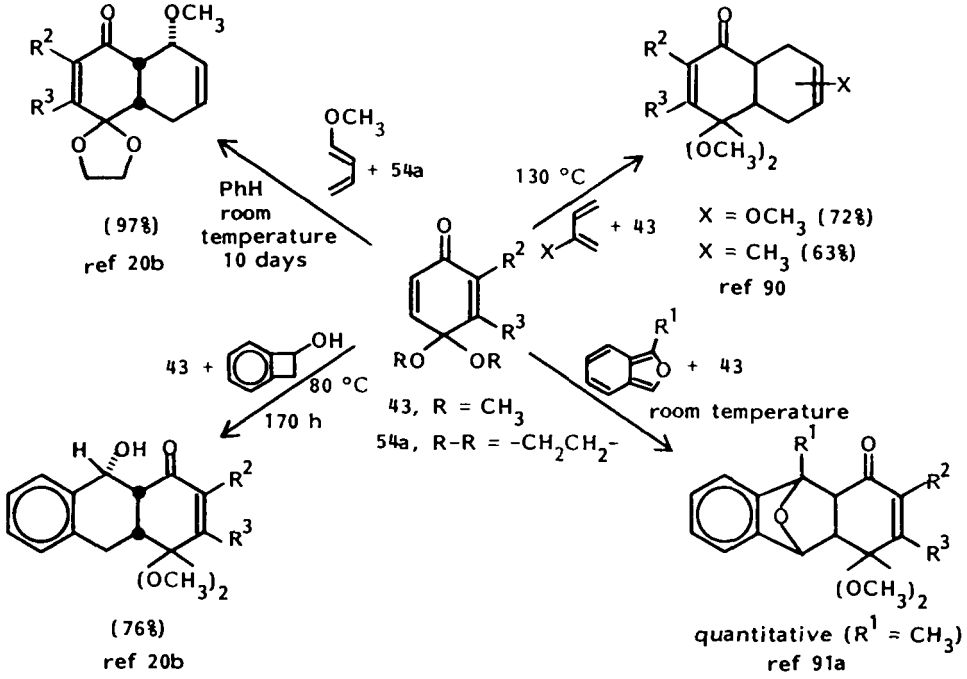
is proposed that the electrochemical oxidation of the phenol forms a cation analogous to **104** which then undergoes the cycloaddition reaction. In general, this electrochemical procedure would offer an attractive alternative to using the quinone monoketal as the positively charged 1,3-dipole precursor in the cycloaddition reaction.

G. Diels–Alder Reactions of Quinone Monoketals

While the thermal stability of quinone monoketals has not been extensively investigated, they appear to be moderately stable when heated in a non-nucleophilic solvent. The parent quinone monoketal ($R^2 = R^3 = H$ in Scheme 13) undergoes thermolysis at 180°C in tetrahydrofuran solution (sealed tube) to produce *p*-methoxyphenol and presumably formaldehyde, or a product derived from formaldehyde[27]. The half-lives of **43** at 165°C and 190°C are about 7 and 1 hours, respectively. Thus, the thermal stability of **43** and presumably of other dimethyl ketals of this type is sufficient to perform many bimolecular

thermal cycloaddition reactions at temperatures below 165°C. In addition, the ethylene glycol quinone monoketal, **54a**, is more thermally stable than **43**, further extending the temperature range for thermal cycloaddition reactions of **54a**[27].

Thus far, Diels–Alder reactions of the parent quinone monoketal **43** have been studied with 1-[20a,b] and 2-substituted[90] dienes, 1-substituted isobenzofurans[91] and cyclobutadiene[92] (Scheme 13). The reaction of **43** with 1-methoxybutadiene is fast and highly regioselective while reactions with 2-substituted dienes proceed more slowly (ca. 130–140°C for 140–200 hours) and produce a mixture of regioisomers. The reactions of **43** with benzocyclobutenol[20a] and isobenzofurans[91] are also highly regioselective and allow a facile entry into linear polycyclic ring systems. This latter reaction was investigated for a number of 1-substituted isobenzofurans [R^1 = H, Me, $Si(Me)_3$, CH_2OH, CO_2Me] with quinone monoketals (R^2, R^3 = H, H; H, Me; H, OMe; OMe, H). The reaction proceeded with high regioselectivity for all of the compounds studied. However, whereas 1-methyl isobenzofurans and **43** reacted at room temperature to afford a quantitative yield of the Diels–Alder product, isobenzofurans having electron-withdrawing groups at position 1 (e.g. CO_2Me) required higher temperatures and gave lower yields for the reaction.



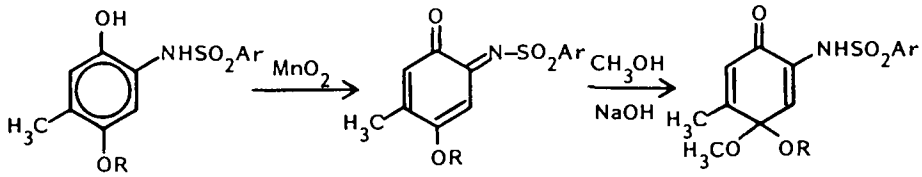
SCHEME 13. Representative Diels–Alder reactions of quinone monoketals

The major advantages of conducting Diels–Alder reactions with the quinone monoketal relative to the quinone is the higher regioselectivity[91] of the addition and the formation of a product in which the two quinone carbonyl groups are differentiated chemically. In some cases, this compensates for the somewhat lower reactivity of the quinone monoketal as compared to the corresponding quinone in the Diels–Alder reaction.

H. Concluding Remarks on Quinone Monoketal Chemistry

The previous sections have dealt with quinone monoketal chemistry that could be reasonably placed into certain categories. This section illustrates those reactions of quinone monoketals which are not included in the prior discussions. The previous sections have been concerned with using quinone monoketals as quinone equivalents. However, the generality of the anodic oxidation of 1,4-dimethoxyaromatic systems to quinone bisketals and the often facile hydrolysis of these compounds to monoketals and thence to quinones, has prompted the use of this anodic oxidation/hydrolysis sequence as a method of oxidation of 1,2,4-trimethoxy-3-methylbenzene to 2-methoxy-3-methylbenzoquinone[93]. Thus, in addition to the use of anodic oxidation/hydrolysis as a route to quinone monoketals, the convenience of the method makes it a practical route to the analogous quinones.

An interesting route to amino-substituted quinone monoketals involves the regiospecific attack of methoxide ion on 4-alkoxy-*o*-quinone imines[94]. Since the imines are available from manganese dioxide oxidation of the corresponding phenol, e.g. **121**, this comprises another method for conversion of phenols to quinone monoketals. However, the yields for the methoxide addition reaction to **122** to form **123** (equation 39) are less than 20%.



121 122 123

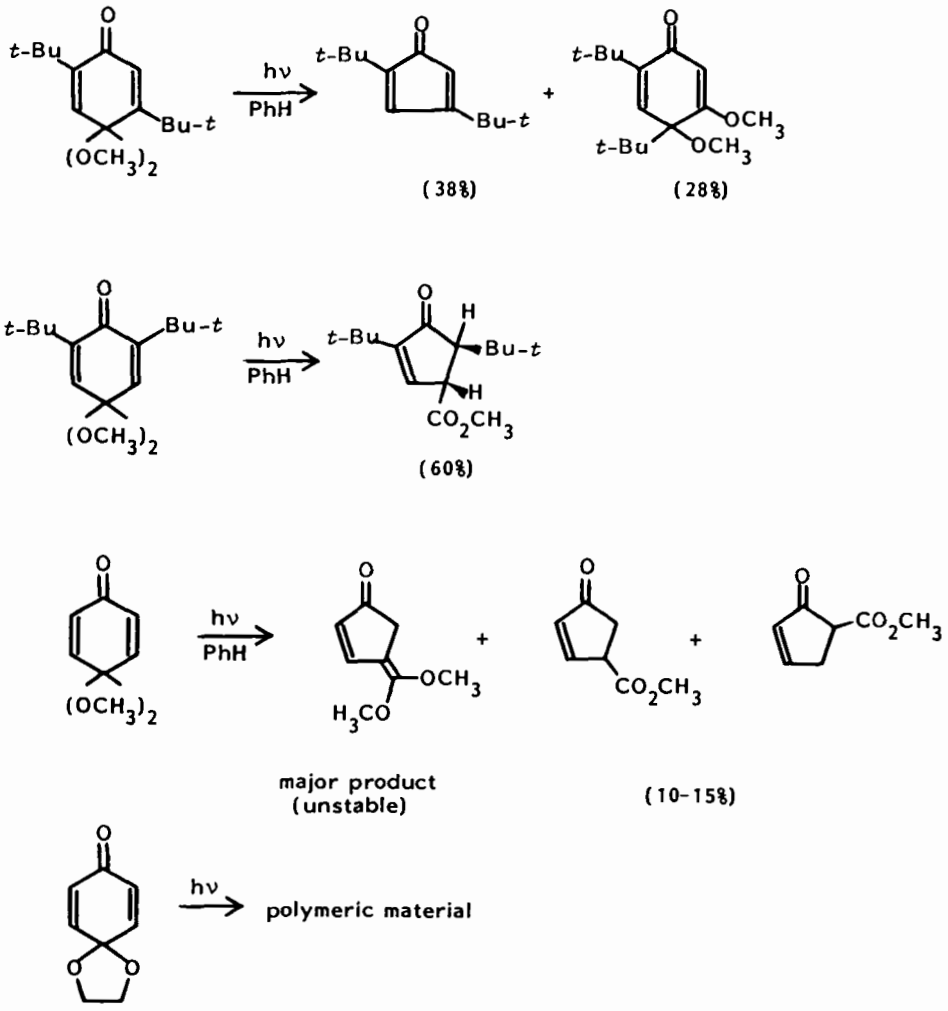
R = CH_3, $(CH_2)_{15}CH_3$ (39)

Finally, the photochemistry of four quinone monoketals has been studied, and the results are given in Scheme 14[95]. All four quinone monoketals afford different products in poor-to-moderate yields. Thus, it is not possible to present any general discussion of the photochemistry of quinone monoketals.

VI. *o*-BENZO- AND NAPHTHOQUINONE BISKETALS AND MONOKETALS

A. *o*-Benzo- and Naphthoquinone Bisketals

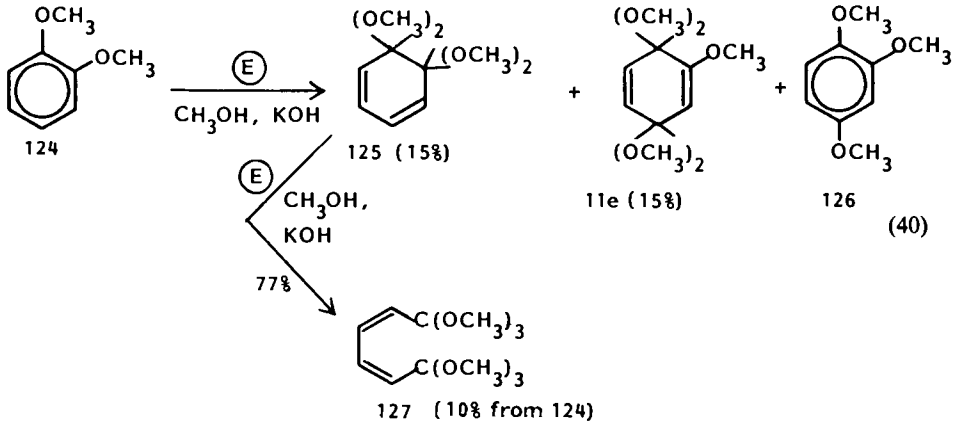
The preceding pages illustrate the diverse range of chemistry of *p*-quinone bisketals and monoketals; however, much less information is available on their *o*-quinone analogs. There are relatively few electrochemical preparations of *o*-quinone bisketals. The parent *o*-quinone bisketal **125** was first reported in 1963 as one of the products [together with **11e** (R^2 = MeO, R^3 = H), **126** and **127**] from anodic oxidation of 1,2-dimethoxybenzene **124** in methanolic potassium hydroxide (equation 40)[6]. The interesting bis-*o*-ester **127** formed in 10% yield from the oxidation of **124** is apparently a secondary product since it is formed in 77% yield from the oxidation of **125**. Presumably, the low yield of the material discouraged the study of its chemistry. The anodic oxidation of the veratrole analog **128**



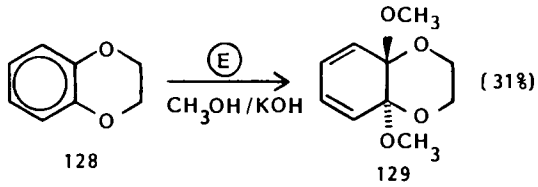
SCHEME 14. Photochemistry of quinone monoketals

afforded the analogous *o*-quinone bisketal **129** (equation 41), and the *trans*-stereochemistry of the addition product was established by detailed ^{1}H-NMR spectroscopic studies[96]. However, it was noted in 1977 that anodic oxidation of **124** on a 38-g scale at $-30°$C afforded **125** in 54% yield after distillation—making the compound now readily available[97].

The simple *o*-naphthoquinone bisketals are formed from anodic oxidation of 2-methoxy- and 1,2-dimethoxynaphthalene derivatives[18]. In most cases, the compounds were not characterized but instead hydrolyzed directly to *o*-naphthoquinone monoketals. Thus, anodic oxidation of 1,2-, 2,6- and 2,7-dimethoxynaphthalene followed by acid



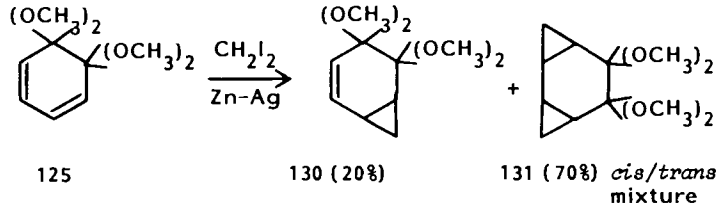
(40)



(41)

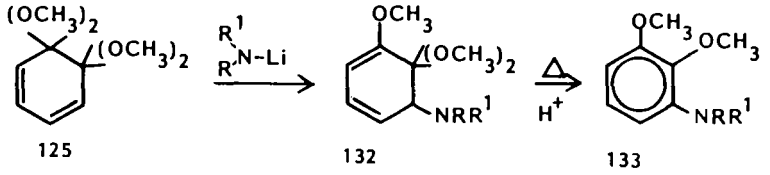
hydrolysis of the crude reaction mixture afforded the *o*-naphthoquinone monoketals shown in Table 22. In contrast to the *o*-quinone monoketals of the benzenoid series, these compounds are quite stable (*vide infra*) since one double bond of the diene unit is part of an aromatic ring.

The chemistry of *o*-benzoquinone bisketals has not been extensively studied. Reaction of **125** under the Simmons–Smith conditions afforded a mixture of **130** and **131** (equation 42)[97]. This contrasts with similar unsuccessful efforts to cyclopropanate quinone bisketals



(42)

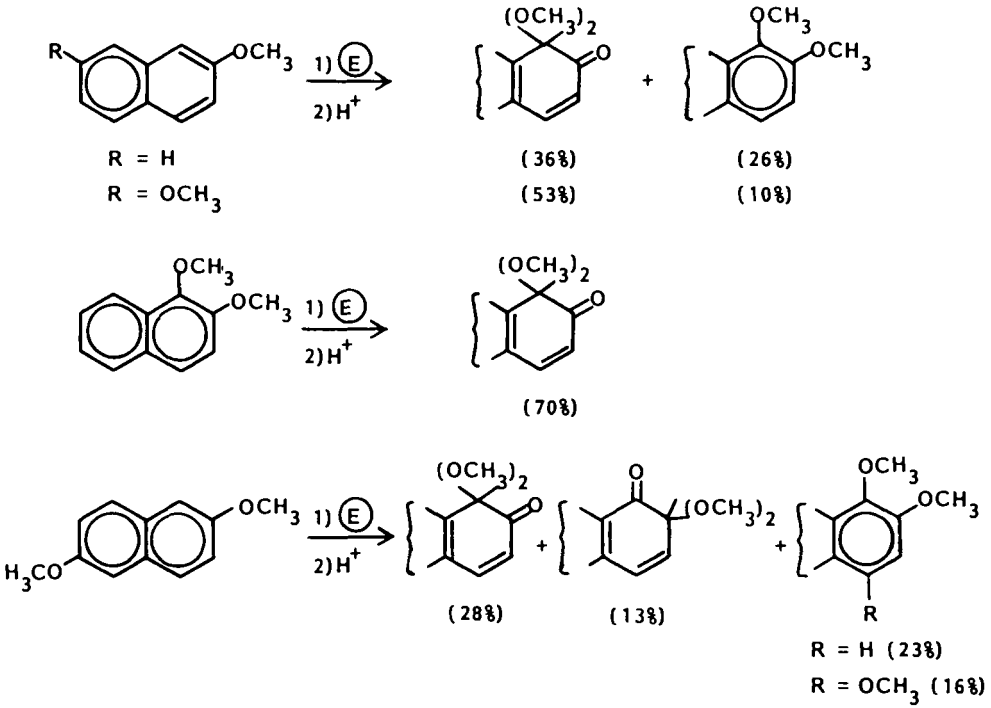
discussed earlier. However, the reaction of organolithium reagents with **125** has been studied in detail, and this serves as a useful route to substituted 1,2-dimethoxybenzenes (veratroles). The lithium amides shown in equation 43 react regiospecifically with **125** to afford initially the adduct **132** which is subsequently aromatized to 3-substituted veratrole derivatives **133**[98a]. This mode of addition contrasts with the 4-substituted products formed from reaction of amines with *o*-quinones. Alkyllithium reagents also react with **125** to give mixtures of 3- and 4-substituted veratrole derivatives[98b], the ratio of which is



125 132 133 (43)

RR^1NLi (% Yield): CH_3NHLi (66); $PhCH_2NHLi$ (69); $CH_2{=}CH{-}CH_2NHLi$ (84); $p\text{-}CH_3C_6H_4NHLi$ (64); NH_2Li (0)

TABLE 22. Preparation *o*-naphthoquinone bis- and monoketals

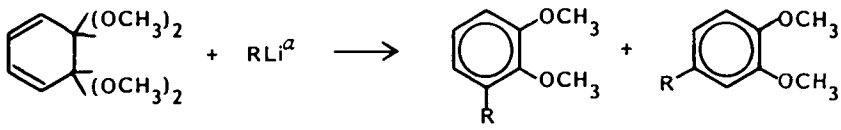


dependent upon the particular alkyllithium reagent (Table 23). A priori, it appears that the functionalization chemistry of quinone bisketals depicted in Table 7 should be applicable to the preparation of functionalized 1,2-dimethoxybenzenes.

B. *o*-Benzo- and Naphthoquinone Monoketals

Monoprotected derivatives of *o*-benzo- and naphthoquinones have been known for many years. Naphthoquinone bromo- and chlorophenoxyhydrins such as **134** were

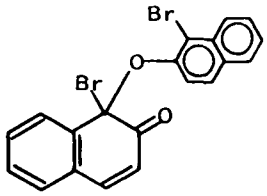
TABLE 23. Reaction of *o*-quinone bisketal (125) with organolithiums



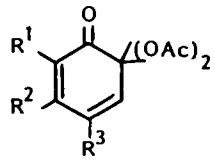
R	Temperature (°C)	Yield (%)	Yield (%)
CH_3	-78	67	9
n-$C_{15}H_{31}$	room temp.	62	13
n-$C_{17}H_{35}$	room temp.	64	11
$CH_3CH{=}CH$	room temp	32	0
C_6H_5	-78	83	0
$CH_2{=}CHCH_2$	-78[b]	13	46
$(CH_3)_2CH$	-78	26	14
$(CH_3)_3C$	-78	33	41

[a] 2.0–2.2 equivalents of RLi were used in ether.
[b] THF was used as solvent.

reported as far back as 1919[99]. Diacetates of *o*-benzoquinones such as **135** were prepared in poor yields from lead tetraacetate oxidation of the corresponding phenol[100]. The *o*-benzo- and naphthoquinone monoketal moieties have been obtained in both the benzene and naphthalene series from oxidation of *o*-alkoxy phenols[39,40] and naphthols[38d].



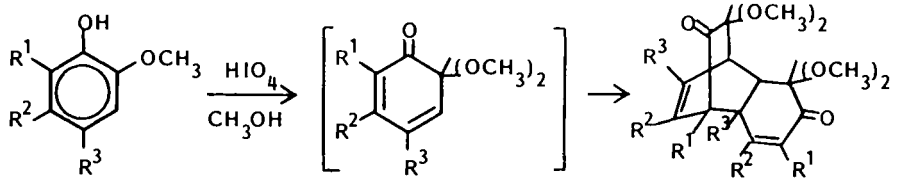
134



135, $R^1 = R^2 = H$, $R^3 = CH_3$
$R^1 = R^3 = CH_3$, $R^2 = H$
$R^1 = H$, $R^2 = R^3 = CH_3$

Relatively little chemistry has been reported for these ketal derivatives although the Diels–Alder reaction of an analog of an *o*-quinone monoketal served as a key step in the synthesis of Ryanodol[101].

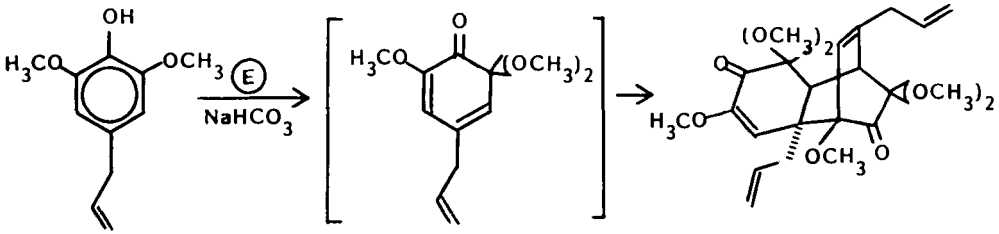
The dearth of chemistry for simple benzenoid systems is undoubtedly related to their facile dimerization **137** → **138** (equation 44). Andersson and coworkers[40] found in their



136 137 138 (44)

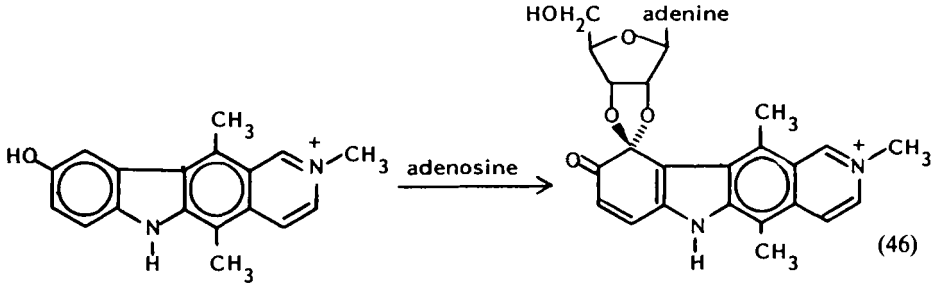
R^1	R^2	R^3	Yield (%)
H	H	H	23
CH_3	H	H	34
H	H	CH_3	12

studies of *o*-quinone monoketals and other 2,4-cyclohexadienone derivatives that only *o*-quinone monoketals having substituents at the 5-position were stable as monomers (e.g. 5,6,6-trimethoxy-2,4-cyclohexadienones). However, in one case the dimerization of an electrochemically generated *o*-quinone monoketal was shown to be advantageous in a novel but low-yielding synthesis of astone, **141**, a neolignan natural product, from **139** via **140** (equation 45)[102]. Interestingly, the related 6,6-diacetoxy-2,4-cyclohexadienones are



139 140 141 (3.3%) (45)

less reactive toward dimerization and can be isolated as monomers[100]. Although anodic oxidation of naphthalene derivatives followed by acid hydrolysis is a useful route to *o*-naphthoquinone monoketals (see Table 22), their chemistry has not been extensively



142 143 (46)

studied[18]. Finally, an *o*-quinone monoketal fused to a furan ring was postulated as an intermediate in a thallium(III) oxidation of an *o*-methoxyphenol[103].

Recently, an especially interesting *o*-quinone monoketal (**143**) has been reported as a major product from the biological oxidation of 9-hydroxyellipticinium acetate (**142**, equation 46)[104]. The product is of obvious importance in developing an understanding of the mode of biological activity of 9-hydroxyellipticinium acetate, and undoubtedly the chemistry of these special types of *o*-quinone monoketals will be the subject of future publications.

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CHAPTER **16**

Quinhydrones and semiquinones

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ABBREVIATIONS

AQ	anthraquinone
AZQ	3,6-diaziridinyl-2,5-bis(carboethoxyamino)-1,4-benzoquinone
BQ	1,4-benzoquinone
BQH_2	1,4-benzohydroquinone
CQ	camphorquinone
CIDMP	chemically induced dynamic magnetic polarization
CIDEP	chemically induced dynamic electron polarization
CIDNP	chemically induced dynamic nuclear polarization
DIOP	2,3-*o*-isopropylidene-2,3-dihydroxy-1,4-bis-(diphenylphosphino)butane
2,6-DTBQ	2,6-di-*t*-butyl-1,4-benzoquinone
3,5-DTBQ	3,5-di-*t*-butyl-1,2-benzoquinone
DQ	1,4-duroquinone (2,3,5,6-tetramethyl-1,4-benzoquinone)
DQH_2	1,4-durohydroquinone
E/A	emissive/absorptive
FQ	2,3,5,6-tetrafluoro-1,4-benzoquinone
FQH_2	2,3,5,6-tetrafluoro-1,4-benzohydroquinone
FT-IR	Fourier transform-infrared spectroscopy
HFS	hyperfine splitting
ISC	intersystem crossing
$MBPh_4$	alkali metal tetraphenylborate
NQ	1,4-naphthoquinone
NQH_2	1,4-naphthohydroquinone
PBN	phenyl-*N*-*t*-butyl-nitrone
P–Q	porphyrin–quinone
RPM	radical pair mechanism
TM	triplet mechanism
T_1	spin lattice relaxation time
TEA	triethylamine
TFA	trifluoroacetic acid
SDS	sodium dodecyl sulphate
SOD	superoxide dismutase

I. INTRODUCTION

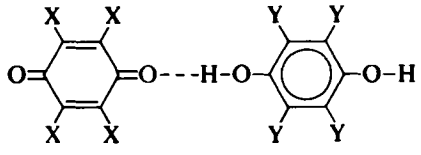
Historically and today semiquinones as a class of organic radicals continue to play a major role in chemistry and biological chemistry. In the early development of ESR applications to free radical chemistry, the apparent ease of preparation and generally interesting structural aspects of many semiquinones have provided important models for the spectroscopists to advance a better understanding of the nature and correlation of ESR parameters with the structure of free radicals. The parents of these semiquinones usually contain two reactive carbonyl groups structurally integrated into an aromatic ring system which are attractively amenable to photochemical and photobiological investigations. Indeed the basic understanding of the primary photochemical processes of simple *para*-quinones has greatly enhanced the development of the photoexcited triplet mechanism in the CIDEP (chemically induced dynamic electron polarization) and CIDNP (chemically induced dynamic nuclear polarization) phenomena, as the earlier, critical studies employed exclusively the semiquinone radicals in photochemical systems. Today a systematic study, combining both ESR and time-resolved CIDMP techniques, on quinone reactions can yield rather detailed information not normally obtained from conventional magnetic resonance experiments.

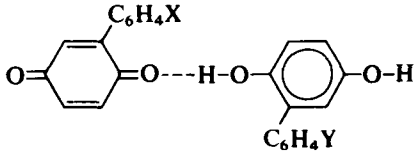
It is not our intention to present here a review of the techniques and theories of ESR and CIDMP phenomena since many past and current reviews are readily available in literature. Rather, we shall attempt to focus our attention on a number of aspects directly concerned with semiquinones and to emphasize the contributions to semiquinone chemistry advanced by the modern experimental techniques, especially in ESR and time-resolved CIDEP methods. As well, we shall touch upon some other important areas such as photosynthesis in which semiquinones play significant roles. Some of these related fields are clearly outside our expertise and no effort will be claimed to give a complete list of references to the enormous amount of work published in these fields. Although the original edition of this book contained excellent discussions concerning the quinhydrones, we shall begin in this chapter by considering some further work concerning this interesting class of complexes.

II. QUINHYDRONES

Quinhydrones are 1 : 1 complexes formed between quinones (Q) and hydroquinones (QH_2); their existence has been known for many years. Although quinhydrones are largely dissociated in solution, in the solid state X-ray structures have shown alternating Q and QH_2 molecules held together in chains by H-bonding in one dimension and π-bonding in a second. The parent or prototype is of course the complex of 1,4-benzoquinone (BQ) and its corresponding hydroquinone (BQH_2) and is usually referred to as quinhydrone; it exists as a conventional donor–acceptor complex in solution and crystallizes in both a monoclinic[1] and a triclinic form[2]. The crystal structures and properties of quinhydrones have been discussed in some detail in the first edition of this series[3,4]. This information will therefore be referred to only very briefly and most of the focus will be on the literature published in this field since 1974.

Unsymmetrically substituted quinhydrones readily undergo redox reactions in solution; this also occurs in the solid state but at a much lower rate. For example, the quinhydrones formed from deuterium-labelled 1,4-benzoquinone and hydroquinone (**1**), and ^{14}C-duroquinone (DQ) and durohydroquinone (DQH_2) (**2**) were found not to exchange at room temperature and although **1** and **2** did exchange slowly[5] at 107–120 °C, the phenyl-substituted quinhydrones **3** and **4** did not[6]. Indeed these compounds could not be made to





(**1**) X = D, Y = H
(**2**) X = $^{14}CH_3$, Y = CH_3

(**3**) X = H, Y = Cl
(**4**) X = Cl, Y = H

isomerize under any known conditions in the solid state. A number of unsymmetrically substituted quinhydrones have been formed both by crystallizing from solution and by grinding together in a mortar and pestle the desired Q/QH_2 pair[7]. While grinding the initially yellow solids together the authors noted a rapid darkening in colour as the π complex formed. The product quinhydrones whether synthesized by either method have been shown to have the identical spectral and X-ray powder patterns.

This solid state method has enabled the synthesis of several quinhydrones which would be inaccessible by crystallization from solution due to rapid redox hydrogen exchange. For example, BQ and 2-methylhydroquinone as well as 2-phenylquinone and naphthohydro-

quinone form quinhydrone products which have distinctly different X-ray powder patterns from those of the isomeric complex[7]. The reactions forming these 'unstable' quinhydrones were readily followed by differential scanning calorimetry and by FT-IR. The formation of a quinhydrone complex has previously been shown by Slifkin and Walmsley[8] to result in a shift of the carbonyl resonance of the starting quinone to a lower frequency. Formation of both the 'unstable' quinhydrone and its stable isomer resulted in this expected carbonyl shift; however, the spectra of the two redox isomers were quite different. Thus no hydrogen transfer resulted from the initial synthesis (grinding together) or from preparation of the paraffin mull; however, standing for longer periods of time in the paraffin suspension did result in some conversion of the unstable to the more stable redox isomer.

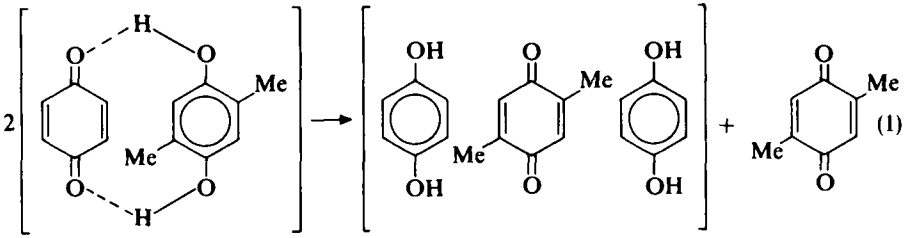
The formation of quinhydrone complexes is influenced by the donor properties of the hydroquinone, the acceptor strength of the quinone, and also steric factors. For example, chloranil and tetrachlorohydroquinone do not form a quinhydrone presumably because of the weak donor capabilities of the hydroquinone[6]. These factors also affect the redox behaviour of unsymmetrically substituted quinhydrones in solution. Slow exchange rates are favoured by a close balance of the redox potentials of the two component pairs. Substitution of the starting materials also reduces the exchange rate and can in fact stop formation of the desired complex. For example, quinhydrone complexes were not formed from the following Q/QH_2 pairs in DMSO: 1,4-naphthoquinone/durohydroquinone, chloranil/hydroquinone, 2,5-diphenyl-1,4-benzoquinone/2,5-di-*t*-butylhydroquinone. In addition the strong H-bonding solvent DMSO retards exchange compared with benzene.

Although reaction of BQ with 2,5-dimethylhydroquinone gave the expected quinhydrone, reaction of 2,5-dimethylquinone with BQH_2 produced a 1 : 2 complex[7, 9]. Similar behaviour was noted for 2-methylquinone and BQH_2 which formed a complex in a ratio ranging from 1 : 1.5 to 1 : 2, while the corresponding redox partners BQ and 2-methylhydroquinone gave the quinhydrone as previously mentioned. These non-equimolar products were formed whether the reaction was solid state or by crystallization of the product from solution and manipulation of the molar ratios of the starting compounds did not affect the outcome. Apparently the products of these reactions are controlled by the energetics of crystal packing rather than the stoichiometry of the starting materials. In addition 2,5-dimethylquinone and 2,5-dimethylhydroquinone formed a 2 : 1 complex on crystallization and not the quinhydrone[10]. The crystal structure of this 2 : 1 complex has been determined to consist of basic triplet structural units of one hydroquinone molecule forming hydrogen bonded bridges to two quinone molecules. The quinone therefore has one carbonyl group hydrogen bonded to a neighbouring hydroquinone and the other carbonyl group directed towards an aromatic C–H of an adjacent triplet. The FT-IR spectrum of this complex shows two carbonyl stretching frequencies at 1628 cm^{-1} and 1663 cm^{-1} consistent with this structure. This unusual behaviour has so far only been noted for quinones having one or two methyl substituents; in contrast DQ and DQH_2 form a 1 : 1 quinhydrone complex[10].

Although quinhydrones are largely dissociated in solution their ^{13}C-NMR spectra have been studied in the solid state to search for evidence of the effects of complexation and charge transfer stacking in the crystal[11]. The quinone carbonyl and the hydroquinone hydroxylic carbons are the atoms most likely to be perturbed by these effects. Both the monoclinic and triclinic polymorphs of quinhydrone have relatively simple spectra with single resonances for the carbonyl carbon of the quinone and also for the phenolic carbon of the hydroquinone component of the complex. The resonances occurred at the same chemical shift position in both the mono- and triclinic complexes. The authors found upfield shifts (relative to the uncomplexed quinone) of 3–4 ppm for the quinone carbonyl resonances of BQ complexed with BQH_2 and also in the 1 : 2 complex of 2,5-dimethyl-1,4-benzoquinone with BQH_2. This effect is similar in magnitude but opposite in direction to

that noted due to hydrogen bonding between the phenolic hydroquinone H and the quinone carbonyl O in, for example, the quinhydrone formed from DQ and DQH_2. This latter quinhydrone is of interest because the hydroxyl stretch is at a higher frequency (3495 cm^{-1}) than expected suggesting substantial differences in hydrogen bonding than that found in less substituted quinhydrones[10]. Apparently the crystal structure geometry is distorted by the steric requirements of the *ortho* methyl groups. The authors have noted that the differences in chemical shifts between the complexed quinhydrones and the uncomplexed starting materials are substantial enough to make solid state ^{13}C-NMR a useful technique for their differentiation although it is difficult to establish the source of the hydrogen bonding or crystallographic effects.

This technique has also been used to follow the solid state redox reaction of the 1 : 1 complex of BQ and 2,5-dimethyl-1,4-hydroquinone complex to form the 1 : 2 complex of 2,5-dimethyl-1,4-benzoquinone and BQH_2 shown in equation 1. Monitoring this reaction



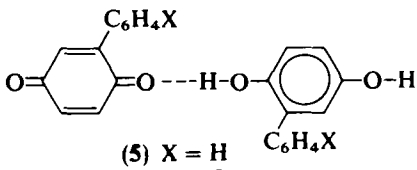
(1)

in nujol mulls by FT-IR was complicated by redox exchange in this medium; it was hoped that solid state NMR would circumvent this problem. By mixing all the possible combinations of the starting quinones, hydroquinones and quinhydrones involved it was found that exchange of one hydroquinone for another was rapid relative to the redox hydrogen transfer between quinone and hydroquinone. In the solid state the redox reaction was complete after 8 h at 85 °C or 30 min at 115 °C.

The charge transfer energies of several simple substituted BQ/BQH_2 complexes in solution and in the solid phase[12, 13] have been studied. Correlations were made between the E_{CT} and the activation energy for the redox transformations (equation 2).

$$Q' + QH_2 \rightleftharpoons Q'H_2 + Q \tag{2}$$

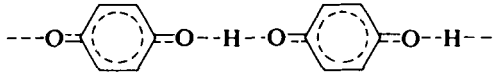
Curtin and Paul[14] have discussed an interesting centre of symmetry noted in the X-ray crystal structure of the phenyl and *p*-chlorophenyl quinhydrones **5** and **6**. The centre of symmetry lies midway between an oxygen atom of a hydroquinone and the oxygen atom of



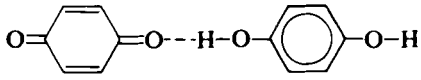
(5) X = H
(6) X = Cl

the adjacent hydrogen bonded quinone; this suggests a structure (**7**) having the hydrogen equidistant from the two oxygens in the quinhydrone. However, the chemical non-equivalence of the quinhydrones prepared from the isomeric phenylquinone and hydroquinone pairs **3** and **4** has been demonstrated as well as their lack of interconversion

in the solid phase. Also since it is known that in quinhydrones the hydrogen is generally unsymmetrically bonded as shown[15] (**8**), they explained the anomalous X-ray result as due to the formation of large ordered polar regions in the crystal which when averaged over a large volume give the appearance of being centrosymmetric to the X-ray diffractometer.



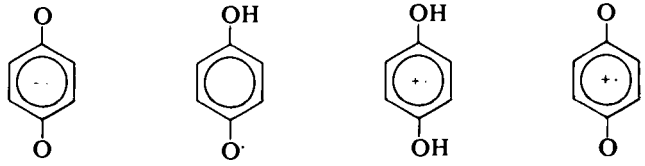
(**7**)



(**8**)

III. SEMIQUINONES

One-electron oxidation of hydroquinones or reduction of quinones results in the formation of semiquinones; they can exist as radical anions ($Q^{-\cdot}$) or neutral radicals ($\dot{Q}H$). In addition, in this chapter we will discuss the formation of the hydroquinone cation radical ($QH_2^{+\cdot}$), and the quinone cation radical ($Q^{+\cdot}$). The structures of these radicals are represented below. These radicals are often the intermediates in redox reactions and they will be our primary focus in this chapter.



($Q^{-\cdot}$) ($\dot{Q}H$) ($QH_2^{+\cdot}$) ($Q^{+\cdot}$)

Semiquinones can be generated by reduction of quinones in a variety of ways, several of the more common of these being:

(1) radiolysis of aqueous solutions of quinones

$$e_{aq}^- + Q \rightarrow Q^{-\cdot}$$

(2) electron abstraction from oxygen species or other inorganic ions

$$Q + OH^- \rightarrow Q^{-\cdot} + \dot{O}H$$

(3) quenching of photoexcited molecules such as triplet chlorophyll

$$Chl^* + Q \rightarrow Chl^{+\cdot} + Q^{-\cdot}$$

(4) electron transfer

$$Q + RH \rightarrow Q^{-\cdot} + RH^{+\cdot}$$

(5) hydrogen abstraction

$$Q + RH \rightarrow \dot{Q}H + R^{\cdot}$$

Corresponding oxidation of hydroquinones can occur by reactions such as:

(1) photoionization

$$QH_2 \rightarrow QH^{\cdot} + e_{aq}^- + H^+$$

(2) oxidation by excited state molecules such as dyes (D)

$$D^* + QH_2 \rightarrow DH^{\cdot} + QH^{\cdot}$$

(3) oxidation by radicals such as hydroxyl radical

$$OH^{\cdot} + QH_2 \rightarrow QH_2OH \rightarrow QH^{\cdot} + H_2O$$

Clearly the interconversion of the neutral and anionic semiquinone radicals shown in equation 3 may occur in any of these systems with the equilibrium being strongly influenced by the medium.

$$QH^{\cdot} \rightleftharpoons Q^{-\cdot} + H^+ \tag{3}$$

Recently a comprehensive tabulation of ESR data up to the end of 1984 concerning the radicals derived from the quinones has been published[16]. Obviously this chapter cannot hope to discuss all the radical species documented and will not attempt to do so. Some general trends in the ESR parameters for certain families of quinones will be described, applications of LCAO-MO and INDO calculations for the interpretation of the spectra, and ESR and related techniques such as CIDEP and CIDNP amenable to the study of radical reaction intermediates, rates of formation and decay, and mechanisms will also be briefly described. In addition, although other chapters in this volume are concerned with the spectral, redox and acid–base properties of the quinones we will briefly document some of the corresponding information for the radical intermediates.

Subsequent sections deal with radical intermediates in some model systems of substitution and addition reactions of quinones, and with quinone metal and organometal radical complexes. A brief summary of the literature describing the importance of semiquinones in antibiotics, and in biologically important systems such as micelles, vitamins, photosynthesis and respiration will be given in Section VI.

A. ESR Spectral Parameters of Semiquinones

It has been shown that a principle of additivity reasonably describes the changes in the hyperfine coupling parameters that result from substitution of the aromatic ring protons of the simplest quinone, 1,4-benzoquinone. The principle holds for alkyl and halogen substituents and also for several bulkier chemical functions[16]. This principle can be expressed as shown in equation 4

$$a_i^{j,k} = a_i^j + a_i^k + a_i^o \tag{4}$$

where a_i^o is the coupling constant of the proton at position i in the unsubstituted radical, a_i^j is the coupling constant at position i observed when R^1 is introduced at position j and $a_i^{j,k}$ is the value of the coupling constant observed at position i when R^1 and R^2 are introduced at positions j and k respectively.

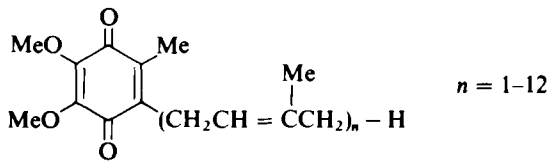
Pedersen presents a table of additivity parameters for several substituents to 1,4-benzoquinone[16]. Limitations of this method for calculation of hyperfine coupling constants appear to be that the additivity principle applies only to sets of spectra obtained under identical experimental conditions; also any conformational changes will obviously perturb the values of the coupling constants. Although used for the qualitative prediction of coupling constants for a number of simple substituted quinones[16–19] both *o*- and *p*-, a deviation from expected values was noted for the methoxyl-substituted quinones. The breakdown occurs when two methoxyl groups are adjacent to one another; in this instance

the usually observed methoxyl hydrogen splitting of ~ 0.8–1.0 G is reduced to zero[20]. This indicates a breakdown of hyperconjugation between the two adjacent methoxyls due to steric effects. This phenomenon is not observed for the corresponding methyl-substituted quinones (Table 1). One of the biologically important methoxyl-containing quinones, ubiquinone (**9**), has an ESR spectrum showing no observable methoxyl hydrogen hyperfine couplings[21].

TABLE 1. Hyperfine coupling constants for some methyl[b]- and methoxyl[b,c]-substituted semiquinone radicals

Semiquinone	Hyperfine coupling (a_HG)				
	a_2	a_3	a_4	a_5	a_6
1,4-BQ	2.33	2.33		2.33	2.33
2-OMe-BQ	0.86[a]	3.69		1.99	0.52
2,3-$(OMe)_2$-BQ	0.00[a]	0.00[a]		2.65	2.65
2,5-$(OMe)_2$-BQ	1.01[a]	1.01		1.01[a]	1.01
2,6-$(OMe)_2$-BQ	0.78[a]	1.45		1.45	0.78[a]
2,3,5-$(OMe)_3$-BQ	0.00[a]	0.00[a]		0.84[a]	0.67
2,3,5,6-$(OMe)_4$-BQ	0.00[a]	0.00[a]		0.00[a]	0.00[a]
Ubiquinone	1.02[a]	2.04[a]		0.00[a]	0.00[a]
2-MeBQ	2.10[a]	1.70		2.55	2.37
2,3-Me_2BQ	1.67[a]	1.67[a]		2.54	2.54
2,5-Me_2BQ	2.36[a]	1.70		2.36[a]	1.70
2,6-Me_2BQ	2.12[a]	1.87		1.87	2.12[a]
2,3,5-Me_3BQ	2.33[a]	1.91[a]		1.76[a]	1.94
Duroquinone	1.90[a]	1.90[a]		1.90[a]	1.90[a]
1,2-BQ					
3,4-$(OMe)_2$-BQ		0.00[a]	0.44[a]	3.92	1.70
3,4-$(OMe)_2$,-6-Me-BQ		0.00[a]	0.53[a]	2.95	1.85[a]
3,6-$(OMe)_2$,-4-Me-BQ		0.00[a]	5.61	1.70	0.61[a]
4,5-$(OMe)_2$-BQ		0.32	1.10[a]	1.10[a]	0.32
3,4,5-$(OMe)_3$-BQ		0.00[a]	0.10[a]	1.20[a]	0.60
3,4,6-$(OMe)_3$-BQ		0.00[a]	0.90[a]	1.10	0.68[a]

[a] Splittings at substituted positions are for 3 equivalent Hs of the Me or OMe group.
[b] Ref. 20.
[c] Ref. 22.

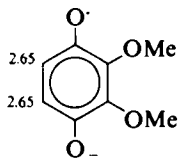


(**9**)

The methoxyl-substituted quinones shown in Table 1 also do not exhibit a linear shift in electrochemical midpoint potential with increasing substitution (Hammett substituent relationship). Gascoyne and Szent-Gyorgyi[20] suggest $\Delta E = -101$ mV for a freely mobile methoxyl group and $\Delta E = -41$ mV for a methoxyl group with a methoxyl neighbour as appropriate values for estimation of the midpoint potentials for this family of quinones. Several *o*-quinones having methoxyl substituents show similar effects in their ESR

spectra[22,23] with sterically crowded OMe groups having no observable hydrogen couplings although adjacent unhindered OMe groups show measurable splittings (Table 1). This is quite noticeable for the *o*-quinones 4,5-dimethoxy-1,2-benzoquinone and 3,4,5-trimethoxy-1,2-benzoquinone in which the coupling constant decreases almost to zero from 1.0 G with the addition of the adjacent substituent.

The ESR spectra of several quinones having fused heterocyclic ring systems have been assigned recently by Clay and Murphy[17]. Simplified McLachlan SCF calculations were inadequate to verify the assignments but by comparisons with related species and by noting smooth variations in the splittings with substitution they were able to explain the spectra. Very little alteration of spin density results from heterocyclic substitution as can be seen by examination of the splittings of the hydrogens at positions 5 and 6 in compounds **10**–**16**.



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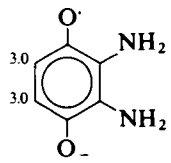

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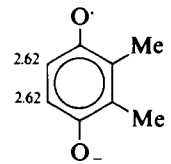

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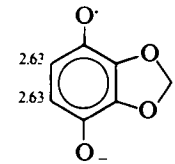

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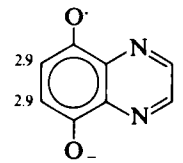

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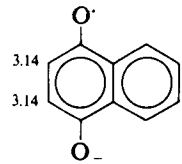

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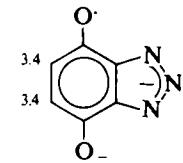
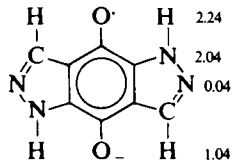


(16)

These authors also assigned the ESR spectra of adrenochrome as well as benzo[1,2-c:4,5-c']dipyrazole-4,8-(1*H*,5*H*)-quinone (**17**) and 3-ethoxycarbonylnaphthindiazole-4,9-semiquinone (**18**) by comparisons with simpler model systems.



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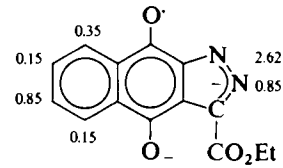
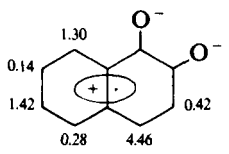


(18)

The ESR spectral parameters of the 2-amino- and 2,5-diamino-1,4-naphthosemiquinone anions have also recently been described[24].

A similarity noted for ratios of the splittings for the *o*-semiquinones and their radical cations (comparable to that observed for phenoxyl radicals and phenol radical cations) shows the correspondence of the spin densities in these compounds[22,25,26]. In each pair the magnitude for the cations exceeds that of the anions by about 20%. Using this observation the radical cation from 1,2-methylene-dioxynaphthalene (**20**), a potent synergist for carbamate insecticides, has been assigned by comparison with 1,2-



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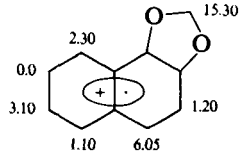

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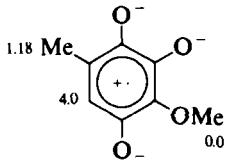
naphthosemiquinone (**19**). The ESR spectrum of the radical anion from fumigatin (**21**) has also been assigned using this procedure.



(21)

Many of the hyperfine coupling constants observed in semiquinone ESR spectra have been discussed using molecular orbital theory with the McLachlan SCF refinement[27] in order to explain or predict the magnitudes, signs and trends [26, 28, 29]. For example, Das and coworkers[21] used such a treatment to show that the long alkyl side chains in the semiquinone anions of vitamins E, K_1 or ubiquinone perturbed the spin density in the aromatic ring to about the same extent as did a methyl substituent. For these same radicals an alternating linewidth effect was attributed to hindered rotation about the bond connecting the carbon atom of the alkyl side chain to the aromatic ring.

The observed hyperfine coupling from the hydrogen bonded to an aromatic ring carbon a^H can be related to the spin density on the atom to which the hydrogen is bonded (ρ_C^π) using McConnell's equation (5),

$$a^H = Q_{CH}^H \rho_C^\pi \tag{5}$$

where Q_{CH}^H is considered to be constant for similar systems. The ^{13}C hyperfine coupling a^C from a carbon atom bonded to three other atoms X_1, X_2, X_3 can be related to the spin densities also[30] as shown in equation 6.

$$a^C = \left(S^C + \sum_{j=1}^{3} Q_{CX_j}^C\right)\rho_C^\pi + \sum_{j=1}^{3} Q_{X_jC}^C \rho_{X_j}^\pi \tag{6}$$

Karplus and Fraenkel calculated the values $S^C = -12.7$ G, $Q_{CC'}^C = 14.4$ G, $Q_{C'C}^C = -13.9$ G and $Q_{CH}^C = 19.5$ G so that for the $C_2'CH$ fragment

$$a^C = 35.6\,\rho_C^\pi - 13.9 \sum_{C'} \rho_{C'}^\pi \tag{7}$$

and for $C_3'C$

$$a^C = 30.5\,\rho_C^\pi - 13.9 \sum_{C'} \rho_{C'}^\pi \tag{8}$$

and these equations have been tested and found reliable in several systems[31]. (A more complete discussion of the derivation of these parameters can be found in Refs 31 and 159,

pp. 511–524.) There is, however, some disagreement in the literature concerning the appropriate parameters to relate the ^{13}C and ^{17}O hyperfine splittings to the spin densities in the carbonyl-containing fragment C'_2CO of the semiquinone radicals. Several authors[32–34] use the value $Q^H_{CH} = -27$ G although Luz and coworkers suggested quite different Q parameters[35]. Prabhananda has reconsidered the systems of Das and Fraenkel[32]: (1) 2,5-dioxo-1,4-benzosemiquinone in KOH/H_2O, (2) $BQ^{-\cdot}$ in $DMSO/H_2O$, (3) $BQ^{-\cdot}$ in $EtOH/H_2O$ and also (4) $BQ^{-\cdot}$ in H_2O and obtained the values $Q^H_{CH} = -26.2$ G, $Q^C_{CO} = 18.66$ G and $Q^C_{OC} = -30.64$ G. This author also introduced the parameter $Q^H_{OH} = 6.0$ G to acknowledge the effects of hydrogen bonding in aqueous and alcohol solutions, ($Q^H_{OH} = 0$ in aprotic solvents). Using these parameters he also predicted spin densities in some phenoxyl radicals and the benzophenone ketyl radical[36].

Strauss and Fraenkel[37] have estimated $Q^C_{CC''} = 30$ G for the C'_2CC'' fragment when C'' is sp^3 hybridized and has zero spin density. Fessenden[38] predicted that $Q^C_{CC''}$ is unlikely to be much greater than 19.5 G (the value of Q^C_{CH}). However, Prabhananda's calculations of $Q^C_{CC''}$ of 16.9 G for 2,6-di-*t*-butylphenol and 22.2 G for durosemiquinone are more consistent with Fessenden's prediction[36].

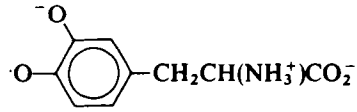
Pedersen in a study of naphthoquinones (NQ) and anthraquinones (AQ) has noted that α-OH groups give rise to an observable proton hyperfine splitting even in relatively basic solutions[39]. This is a consequence of hydrogen bonding to the adjacent carbonyl group which disfavours dissociation. The assignments of splittings in anthrasemiquinones having β-OH groups are complicated by the small size of these splittings. However, β-OH groups in a number of substituted anthrasemiquinone radicals were found to dissociate at pH $\simeq$ 12; following dissociation the resulting O^- substituents cause a greater perturbation in the spin density distribution than does OH. Thus comparisons of splittings in spectra obtained below and above the pH of dissociation can frequently aid in the assignments of splittings in these relatively complex spectra. In addition it has been noted that replacing OH by OMe in these positions causes very little alteration of the splitting pattern[16, 39].

Considerable controversy has surrounded the calculations of spin density distribution and the signs of the hyperfine coupling constants for the 1,2-benzosemiquinone radicals and their derivatives. Experimental values measured under a variety of conditions are given[16]; for example Felix and Sealy[40] have observed $a_{H_{3,6}} = 0.75$ G and $a_{H_{4,5}} = 3.67$ G in aqueous solutions. Theoretical calculations, however, have generally been in poor agreement with these results. For example, Huckel calculations in which the coulomb integral was varied to give $|\rho_4| > |\rho_3|$ suggest that the values are both positive[41]. McLachlan calculations suggest that ρ_3 is negative[42]. The INDO method has predicted the opposite order of spin densities[43], i.e. $|\rho_3| > |\rho_4|$; although by using the molecular geometry optimization refinement described by Shinagawa[44, 45] the correct relative magnitudes of spin density are predicted. However, this method has been criticized for requiring an extremely distorted radical structure[46]. Spanget-Larsen has suggested addition of effective solvent field parameters to correct the ordering predicted by INDO calculations[46, 47]. Finally Kuwata and Shimizu[48] have described an open shell calculation which reproduces the experimental splittings and predicts both ρ_3 and ρ_4 are positive. This is in agreement with the observations and calculations described by Felix and Sealy using both proton and ^{13}C-ESR measurements and Karplus–Fraenkel theory relating the ^{13}C splittings to the aromatic spin densities[40].

The INDO method of Shinagawa has also been applied to 1,3-semiquinone radicals[49]. The relative magnitudes of the spin densities at positions two and five were found to change when the radicals were generated by alkaline or acidic oxidation.

The regioselective coupling of acyl and alkyl radicals with 1,2-naphthosemiquinone anion has been explained in terms of the estimated spin densities in the radical. Radicals such as benzyl and diphenylmethyl preferentially couple at C(4) while phenacetyl attacks at C(3) of the semiquinone[50].

The ESR spectra of substituted 1,2-benzosemiquinones from molecules such as L-dopa (**22**) and tyrosine exhibit the effects of magnetic inequivalence of the diastereotopic methylene protons in the side chain. Although slightly different hyperfine coupling constants are measured for these hydrogens some selective broadening of the lines can occur due to restricted rotation about the $ArCH_2$–$CHNH_3^+CO_2^-$ bond[51, 52].



(22)

Another characteristic parameter obtainable from ESR spectra is the g factor. For semiquinones the g factor is usually considerably higher than values for aromatic hydrocarbons; the appreciable spin density on oxygen is the main reason for the deviation from near free spin value. For several semiquinones g factors were found to be linearly dependent on $\Sigma\rho_0^\pi$ in agreement with equation 9 and[53] where ρ_0^π is the spin density on the oxygen. Γ_0 depends on the spin-orbit coupling on oxygen as well as energy differences involving the unpaired electron π orbital, non-bonding orbitals on the oxygen and the C–O bonding orbitals. It was determined that $\Gamma_0 = 0.008$ and $g_0 = 2.0025$; thus, as expected when the spin density on the oxygens is zero the g factor

$$g = g_0 + \Sigma\Gamma_0\rho_0^\pi \tag{9}$$

approaches that of the aromatic hydrocarbons[36]. This linear relationship also applies to the hydroquinone cation radicals of BQ, NQ, or 9,10-AQ in acid solvents[54]. The authors again found it was necessary to use an additional parameter $Q_{OH} \simeq 50$ G to account for the observed ^{17}O hyperfine splitting which is affected by hydrogen bonding between the hydroxyl group and the solvent. This study estimates spin density on oxygen lower than that of Sullivan and coworkers[55].

Q-band ESR spectra of the tetrahalogenated semiquinones have been studied to determine the origin of the effects of the halogens on the g tensor. It was noted[56] that g_x and g_y (the components in the plane of the aromatic ring) were increased with respect to the unsubstituted parent $BQ^{-\cdot}$ following the series Cl, Br, I while the perpendicular component g_z was decreased. The authors suggest that the halogen d orbitals are not predominantly responsible for the noted g anisotropy but that the effects are due to σ–π interactions changing the spin density on halogens. This is consistent with the observed order of magnitude of the effect on g_z, i.e. tetrachloro < tetrabromo < tetraiodosemiquinone. The contributions to g_x and g_y are positive and are attributed to spin density delocalized in the π^* orbital. Further perturbation of the g_z component for tetraiodosemiquinone on changing the solvent from DMSO to ethanol was attributed to changes in the energy separation between the orbital of the unpaired electron and the lone-pair orbitals on the halogens.

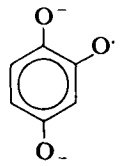
B. Solvent Effects in ESR Spectra of Semiquinones

Changes in solvation of radicals in solution are frequently observed by changes in the magnitude and even sign of hyperfine splitting constants. The radicals derived from quinones are solvated in protic solvents in such a way as to perturb these values substantially due to the formation of hydrogen bonds. As well, aprotic solvents may interact with the quinone radical anions via ion–dipole and ion–induced-dipole effects.

Although it was originally thought that hydrogen bonding to a C=O function resulted in lowering of the ground state energy with little effect on the excited state[57, 58] it has been suggested that the excited state is also involved and that geometry changes for both the ground and excited states are affected differently as a result of hydrogen bonding. This is reflected in a blue shift of 0.13–0.25 eV in the carbonyl n-π^* transition in H-bonding solvents. This shift has been interpreted by Beecham and coworkers[57] to arise from a differential lengthening of the CO bond in the excited state with respect to the ground state. This lengthening (of $\sim$ 0.002 Å) resulted in a redistribution of intensity in the vibrational subbands which are resolved in CD spectra. The use of additional parameters in MO calculations to account for changes in the spin density at oxygen for semiquinone radicals in hydrogen bonding solvents was mentioned previously (Section II.A).

Simple semiquinones have been found to have $a_{^{13}C}$ and $a_{^{17}O}$ correlated in a linear fashion to the Kosower Z value (or less well to the solvent dielectric constant ε) for solvents such as water, ethanol and DMSO; however, the correlation is not good for sterically hindered semiquinone radicals[59] such as 2,6-dimethyl-1,4-$BQ^{-\cdot}$. Steric effects were also noted by Gough[60] for the neutral semiquinone radicals of BQ and DQ. He concluded that the hydroxylic proton lies in the plane of the ring and that its splitting varies linearly with solvent polarity. For $DQH^{\cdot}$ the steric hindrance of the Me groups caused a solvent dependence of a_H reflecting the effective molecular size of the surrounding solvent molecules which would be expected to distort the hydroxylic bond out of the plane of the ring on hydrogen bonding.

In several mixed protic–aprotic solvent systems such as H_2O/DMSO and H_2O/HMPA there appeared to be competition between the solute and the aprotic solvent for hydrogen bonds. This complicates the measurements of equilibrium constants for solvation in the mixed solvent systems and it is suggested that the equilibrium being measured by these ESR studies is between H-bonded and non-H-bonded radicals[59]. Previously it had been determined that the dianion radicals from the trihydroxybenzenes **23** and **24** could not



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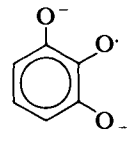


(24)

persist in solution unless the H_2O/HMPA ratio was > 2. This suggested that water must be sufficiently free from being H-bonded to aprotic solvent in order to solvate the dianion radical[61].

A number of semiquinone and semidione type radicals have been investigated by Loth and Graf[62, 63] in order to obtain both structural and kinetic information from the temperature and solvent dependence of their ESR spectra. For example, the tautomeric radicals (2-hydroxy-4-methylphenoxyl and 2-hydroxy-5-methylphenoxyl) derived from 4-methylcatechol were observed and their splittings compared with INDO calculations. In general the formation of intramolecular hydrogen bonds in these and related radicals is disturbed and sometimes prevented by steric hindrance, internal rotation or intramolecular proton exchange.

An unusual solvent effect was observed in the study of $BQ^{-\cdot}$ in frozen DMSO and DMSO–EtOH solvents[64]. Even at 50 K below the freezing points of the solutions the ESR spectrum of $BQ^{-\cdot}$ remained isotropic; the authors suggest that liquid-like pockets exist in the solvent in which the quinone can tumble rapidly. The dominant contributions to spin

lattice relaxation in this medium are apparently spin rotation in origin while the dominant linewidth effect comes from anisotropic g and hyperfine tensor modulation.

Dynamic processes such as H^+ or e^- exchange can also have dramatic effects on the ESR spectra of quinone radicals. The effects usually involve line-broadening of the resonances due to the species undergoing the exchange processes. The study of the neutral radicals of the *o*-, *m*-, and *p*-quinones in acid solution has been complicated by this problem; poorly resolved and unanalysable spectra are frequently obtained (Ref 65 and references therein). Dixon and Murphy[65] analysed the spectra of the neutral radicals from hydroquinone, catechol, resorcinol and phloroglucinol and estimated rate constants for protonation of the neutral radicals to be 1.1, 1.0, 4.1 and 4.4 ($\times 10^9$ dm^3 mol^{-1} s^{-1}) respectively. Degenerate electron exchange has been cited by Hore and McLauchlan[66] to have significant effects on the time-resolved ESR spectrum of radical anions such as duroquinone (equation 10).

$$DQ^{-\cdot} + DQ \rightleftharpoons DQ + DQ^{-\cdot} \tag{10}$$

Since time-resolved spectra of systems exhibiting CIDEP provide early (0.5 μs to $\sim$ 200 μs) information about the behaviour of the radicals generated, fast processes such as electron transfer would be expected to be a factor in their appearance and analysis. The authors suggest that degenerate electron exchange is an important factor affecting both longitudinal and transverse relaxation in such systems. They discuss methods of dealing with exchange processes in the calculations of T_1 and T_2 and the factors affecting recording and analysis of the radical time profiles[66, 67].

Meisel and coworkers[68, 69] measured degenerate electron exchange rates for several *p*-quinone radical anions in acetone/isopropanol from the effects of concentration on the linewidth of their ESR spectra. The values they obtained are given in Table 2. Equation 11 was used to describe the linewidth effect of electron transfer between pairs of non-equivalent quinones in the slow exchange region.

$$\Delta H = \Delta H_o + \frac{k_{ex}[Q][1 - g_i/\sum_i g_i]}{\sqrt{3}\pi(2.83 \times 10^6)} \tag{11}$$

TABLE 2. Rates of degenerate electron exchange and electron transfer in benzosemiquinones

Quinone	Electron exchange k_{ex} (M^{-1} s^{-1})	E_7 (V vs. NHE)
Benzoquinone	6.2×10^7	0.99
2,5-Dimethylbenzoquinone	5.5×10^7	−0.65
2,6-Dimethylbenzoquinone	1.7×10^8	−0.80
Duroquinone	2.0×10^8	−0.247

Reaction	Electron transfer k_f (M^{-1} s^{-1})[a]	k_b (M^{-1} s^{-1})[a]	K_{eq}[b]
2,5-DMBQ$^-$ + BQ	$6.5 \pm 0.3 \times 10^8$	9.7×10^5	6.7×10^2
2,6-DMBQ$^-$ + BQ	$1.0 \pm 0.1 \times 10^9$	8.3×10^5	1.2×10^3
DQ$^-$ + BQ	$1.1 \pm 0.05 \times 10^9$	1.9×10^3	5.7×10^5
DQ$^-$ + 2,5-DMBQ	$1.0 \pm 0.1 \times 10^9$	1.2×10^6	8.5×10^2
DQ$^-$ + 2,6-DMBQ	$9.6 \pm 1.0 \times 10^8$	2.0×10^6	4.7×10^2

[a] k_f and k_b are the rate constants for the forward and back reactions as shown in equation 12.
[b] K_{eq} = the equilibrium constant for equation 12.

In equation 11 g_i is the statistical line intensity of the i^{th} line[70]. Since one-electron redox potentials for the quinone/semiquinone couples they studied were available from pulse radiolysis the electron transfer rates for equation 12 could be predicted using Marcus theory from the self-exchange reaction rates. The experimentally measured and calculated rates were in good agreement, some experimental values are shown in Table 2.

$$Q_1^{-\cdot} + Q_2 \underset{k_b}{\overset{k_f}{\rightleftharpoons}} Q_1 + Q_2^{-\cdot} \tag{12}$$

C. Photoreduction and CIDMP of the Quinones

The photochemistry of simple quinones has been quite well understood for several decades; thus these compounds have been extensively used as model compounds for the investigation of phenomena such as chemically induced dynamic electron (CIDEP) and nuclear polarization (CIDNP). Early experiments were largely directed towards understanding the mechanisms by which these processes occurred and the development and testing of the theory describing them. Indeed the study of quinone photoreductions was largely responsible for the development of the Triplet Mechanism (TM) of CIDEP. Now, however, CIDEP and CIDNP experiments can be applied to probe the nature of more complex quinone reactions especially those initiated by photolysis or radiolysis. With time-resolved CIDEP studies much information may be obtained including determination of reaction mechanisms, identification of transient radical intermediates often undetectable by other experiments, measurement of radical spin lattice relaxation times, precursor triplet dynamic properties, radical ion-pair interactions in the solid state, and often relative reaction rates by the employment of appropriate experimental conditions. On the other hand, CIDNP provides complimentary information on the products formed from the radical reactions whether these are in or escaped from the primary radical cage.

Absorption of a photon of light by a quinone results in excitation to the first excited singlet state S_1 followed by rapid intersystem crossing to the triplet state T_1 from which the subsequent reactions occur. In the presence of a magnetic field semiquinone radicals produced by irradiation of quinones in the presence of reducing agents show CIDEP arising from both triplet (TM) and radical pair (RPM) mechanisms. Briefly the TM results from anisotropic intersystem crossing (ISC) into the triplet sublevels resulting in a non-Boltzmann population (i.e. polarization) which can be transferred to subsequently produced radicals if the reactions forming them are faster than the triplet state spin lattice relaxation. Since triplet T_1s are of the order of nanoseconds in liquids this requires near diffusion-controlled reaction rates. Secondarily polarized radicals can also arise if the initially formed polarized radicals react faster than their spin lattice relaxation (not an unlikely occurrence since radical T_1s are of the order of microseconds). In the radical-pair mechanism the polarization arises from the magnetic interactions of encountering pairs of radicals which may involve either the initial pair (correlated pair) formed in the primary photochemical reactions, or pairs of radicals encountered at random (random pair).

The coexistence of the two mechanisms of CIDEP in quinone photolyses is now well established[71–78]. In general, the intersystem crossing process led to a strongly spin-polarized quinone triplet state and its polarization was transferred during the chemical reactions to the primary radicals such as the semiquinone radicals and to some secondary radicals derived from the intermediate semiquinones. In viscous solvents and/or using high intensity light sources such as an excimer laser, the semiquinone radical concentrations would be increased while their separation rates (diffusion) would be reduced. These factors combined to enhance the magnitude of the RPM polarization. Thus, Pedersen and coworkers[76] have estimated that less than 20% of the polarization in the photolysis of BQ in ethylene glycol is due to RPM. The contributions due to the RPM can

also be enhanced for semiquinone radicals such as durosemiquinone which have larger hyperfine couplings[77,79]. Several authors have discussed the separation of initial polarization and secondary polarization in quinone systems and assessed the agreement with theoretical predictions[71,72,76]. The effects of solvent viscosity and heavy atom perturbations on the TM enhancement factor and the rates of ISC have been described[73].

In time-resolved experiments CIDEP studies provide a simple method to estimate the transient radical spin lattice relaxation times. The radical spin lattice relaxation offers a sensitive probe of local radical environments. The large initial polarizations of radicals created by the TM permit calculation of effective T_1s from extrapolation or fitting of their exponential decay curves. Advancements in experimental techniques have involved gating the microwave power after the laser flash[80] and the use of rapidly modulated light sources coupled with phase-sensitive ESR detection[81]. These techniques are hampered somewhat by the requirement of multiple parameter fitting (to account for among other things microwave power levels and inhomogeneous contributions to linewidths)[66,82].

Earlier experiments using the direct detection ESR methods after laser flash photolysis estimated that T_1s for semiquinone radicals from a series of benzoquinones, naphthoquinones and anthraquinones depended both on the extent of the aromatic system and on the effective molecular size of the semiquinone radical[83,84]. In addition a simplified 'rotating rod' primitive model has been developed to describe the effect on T_1 of restricting rotation in one direction by addition of a long polymer chain to the radical[85]. The polymer radicals were treated as freely rotating about the rod axis but motion was frozen about the transverse axis. The model neglects complex vibrational and crankshaft motions of the polymeric chain; it predicts that T_1 values will be relatively insensitive to chain length but will be sensitive to values of individual second rank g tensor components in such hindered rotation situations. Ullman[86] and Monnerie and coworkers[87] have also proposed models for the study of the dynamics of polymers in solution; in the latter case the ESR line shape analysis can also probe effects on the transverse relaxation time T_2. The T_1 values for some quinone–organometallic radical adducts have recently been studied; the formation of these species will be described later (Section IV). For the uranyl-phenanthrenequinone radical ion $(UO_2PQ)^{+\cdot}$ the value of T_1 was found to be considerably shorter than for the parent $PQ^{-\cdot}$ semiquinone (i.e. $< 0.8\ \mu s$ and $4\ \mu s$ respectively). This significant reduction in relaxation time is due to the extremely large spin-orbit coupling of the uranyl atom which provides an additional relaxation mechanism[88,89]. This large spin-orbit coupling is also evidenced by the low g factor of the radical ion complex (1.9940 ± 0.0001). T_1 values of benzoquinone–uranyl radical complexes having bulky t-butyl substituents on the quinone showed little or no effect of radical size on the magnitude of T_1. Organotin–quinone radical adducts also show little variation in T_1 compared with the values of the parent semiquinones[90]; apparently the organotin moiety does not appreciably contribute to the quinone system.

As predicted by the TM theory no hyperfine dependence for T_1 or T_2 has been noted[71,72,83]. Fessenden and coworkers[91] have obtained values of T_1 and T_2 for benzoquinone radicals using a saturation recovery method applied to steady state radical concentrations. Although somewhat hampered by transient mutations due to the high microwave powers used in the experiments the values obtained were in good agreement with those described previously. The spin lattice relaxation times are extremely sensitive to changes in viscosity, H-bonding and temperature and correlations can only be made reliably for a series of compounds of similar structure measured under identical experimental conditions.

Bartels and coworkers have recently described a dynamic polarization recovery method for T_1 measurements that is particularly successful for small, very reactive transient radicals which can be generated in high concentrations by laser photolysis or pulse radiolysis[92]. The method is valid even in the presence of CIDEP or fast chemical decay. They conclude

that spin rotation is the dominant relaxation mechanism in the series of small radicals studied.

CIDEP effects have also been utilized in order to obtain information about the precursor triplet properties of the quinones. The time-resolved ESR spectra for the triplet quinone molecules can frequently be obtained in glassy matrices at 77 K[93-96]. Values for the zero field splitting parameters D and E for several quinones in various matrices were obtained as shown in Table 3. The values obtained in these glassy media are believed to be more representative of the triplet states in liquids than are those obtained in crystalline matrices[96]. It was found necessary to postulate a distribution of D and E values in glassy matrices for the quinones since the zero field splitting parameters are sensitive to environment and the guest molecules are probably trapped in sites which are not homogenous. Therefore, the time-resolved spectra can be more accurately simulated if Gaussian distributions of D and E values are used[95, 96]. For these 1,4-quinones the authors find the centre of the distribution of D values to be larger than 0.30 cm^{-1}. The value of D for the 9,10-anthraquinone triplet state was slightly lower in non-polar than in polar solvents. In non-polar solvents the triplet states of 1,4-BQ and 1,4-NQ reacted too quickly for adequate triplet state time-resolved spectra to be obtained. The values of $|D'|$ estimated by Murai and coworkers[96] are larger than those estimated earlier for 1,4-BQ (700 G[76] as a lower limit, and 3000 G[71]) but these earlier values were indirectly measured and have wide uncertainties.

TABLE 3. Zero field splitting parameters for some 1,4-quinones obtained in glassy matrices at 77 K

Quinone	Solvent	$D(cm^{-1})$	$E(cm^{-1})$	Reference
1,4-BQ	1,4-dibromobenzene	−0.1767	0.0026	291, 292
1,4-BQ	EPA[b]	−0.330	0.019	96
1,4-BQ	1,4-BQ-d_4	−0.0684	0.0038	292
1,4-NQ	EPA[b]	−0.330	0.019	96
9,10-AQ	EPA[b]	−0.351	0.005	95
9,10-AQ	PM[a]	−0.318	0.005	96
9,10-AQ	*n*-Octane site 1	−0.2894	0.041	293
	n-Octane site 2	−0.309	0.007	293

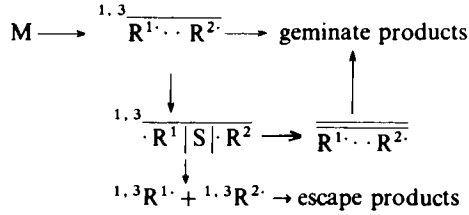
[a] PM = isopentane : methylcyclohexane (1 : 4 v/v).
[b] EPA = diethyl ether : isopentane : ethanol (5 : 5 : 2 v/v).

The negative sign of D indicates that the Z-spin sublevel is exclusively populated by intersystem crossing in these quinones. Conservation of triplet spin polarization in energy transfers between a triplet molecule and ground state acceptor has been recently demonstrated in glassy matrices[97, 98] and the direction of polarization, absorptive or emissive, correlated to the signs of the zero field splitting parameters for triplet states of biacetyl[99] and benzophenone[100]. Triplet T_1s in solution for duroquinone have been estimated from CIDEP experiments to range from 2.7 ns in methanol to 17 ns in cyclohexanol[73] at 260 K.

A technique called CIDEP-enhanced-ENDOR in which the pumped NMR transitions in a transient radical are observed by changes in the CIDEP intensities in the ESR spectrum has been used to study 1,4-BQ. The ENDOR enhancement of the ESR signal was $\sim 10\%$, somewhat larger than obtained in continuous wave (CW) ENDOR[101, 102].

The coexistence of the TM and RPM in CIDEP is now well accepted; however, for CIDNP the origin of the polarization is generally attributed to the RPM which can briefly

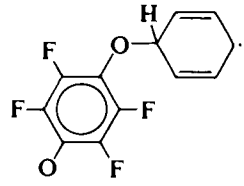
be illustrated as in Scheme 1. Several excellent reviews of this technique and its theory and applications exist[103–106].



SCHEME 1

A singlet or triplet state excited molecule can dissociate to form a corresponding singlet or triplet radical pair $\overline{R^1 \cdots R^2}$ which can then give geminate recombination or disproportionation products. Alternatively it can diffuse apart, subsequently to re-encounter, or the radicals can form escape products. The spin sorting that occurs during the diffusion of the radicals and the nuclear spin dependence of the reactions is responsible for the nuclear polarizations in the geminate products and the equally large polarization of opposite sign in the escape products. There has also been described a relatively little known CIDNP mechanism called the triplet Overhauser mechanism which has been invoked in certain quinone photolyses. This mechanism involves large initial electron polarization of the radicals by the TM followed by a key electron-nuclear cross-relaxation step (Overhauser effect) prior to formation of the diamagnetic products exhibiting the abnormal nuclear polarizations. The theory has been described in the literature[107]. This mechanism was initially proposed by Vyas and Wan[108] to account for observed polarization in tetrafluoro-1,4-benzoquinone (FQ) in chloroform or with FQH_2 in benzene.

Roth and coworkers[109] recently re-examined the same systems and studied the magnetic field dependence and quencher concentration dependence of the reactions. For photolysis of FQ and the corresponding tetrafluorohydroquinone in benzene at magnetic fields below 100 G the experimental observations are consistent with RPM involving S–T_1 mixing[107, 109]. At higher fields two independent contributions to the polarization are operating. One is assigned to be due to a biradical adduct (**25**) between triplet quinone and solvent benzene. Minor cross-combination products between semiquinone radical and solvent have also been observed in CIDNP studies of fluoranil with dioxane and chloranil



(25)

with 3,5-di-*t*-butylphenol[108, 110]. The second contribution to the polarization which increases monotonically with magnetic field is attributed to the triplet Overhauser mechanism.

CIDNP studies of benzoquinone photolysis with BQH_2 in $CDCl_3$ noted that the sign of the polarization changed from enhanced absorptive to emissive as the hydroquinone concentration was increased[107]. A similar effect was observed in the electron transfer

quenching of trifluoroacetophenone. Competing RPM and triplet Overhauser polarizations with the triplet mechanism 'exposed' at the higher hydroquinone concentration can account for these results. Similarly simultaneous operation of TM and RPM CIDNP has been observed by Kuznets and coworkers[111] for the photolysis of BQ and diphenylamine in hexafluorobenzene.

The study of BQ photolysis in isopropanol by combined CIDNP and CIDEP concluded that the formation of hydroquinone and the enol $CH_2 = C(Me)OH$ were the main in-cage products while acetone was formed largely from scavenged reactions[106].

A study of the effects of pumping the ESR transitions of radical pairs formed in the photolysis of quinones and observing the changes in the CIDNP spectra has been reported[112].

Magnetic field effects on reaction rates and products are of considerable interest in micelles; quinone photolyses in micelles will be discussed briefly in Section VI. In solution, application of a magnetic field of 3360 G was found to increase the yield of escaping alkoxy radicals from photolysis of BQ in isopropanol[113].

Most triplet state quinones are strong electron and hydrogen acceptors and it is frequently difficult to determine whether the primary photochemical event in their photoreduction involves direct electron transfer or hydrogen abstraction or both. The question was first raised by Bridge and Porter[114] and attempts to provide an unequivocal answer have employed primarily ns and ps laser flash photolysis and ESR/CIDEP experiments. Although H-abstraction is generally accepted as the primary event in solvents such as alcohols there have been dissenting opinions.

The reactions following photolysis of a quinone in hydrogen donating solvents can be written as shown below:

$$Q \xrightarrow{h\nu} {}^1Q \xrightarrow{ISC} {}^3Q^* \tag{13}$$

$${}^3Q^* + RCH_2OH \rightarrow QH^{\cdot}{}^* + R\dot{C}HOH^{\cdot}{}^* \tag{14}$$

$$Q + R\dot{C}HOH \rightarrow QH^{\cdot} + RCHO \tag{15}$$

$$2QH^{\cdot} \rightarrow QH_2 + Q \tag{16}$$

$$QH^{\cdot} \rightleftharpoons Q^- + H^+ \tag{17}$$

$${}^3Q + QH_2 \rightarrow 2QH^{\cdot} \tag{18}$$

If oxygen is present several other steps are possible; however, ESR studies frequently are carried out in deoxygenated solutions.

Kambara and Yoshida[115, 116] have proposed an anionic mechanism to account for their ESR observations for the photoreduction of 1,4-benzoquinone in alcohols. The mechanism describing the one-electron transfer from ethanol to excited state quinone is shown in reactions 19–22 below.

$${}^3BQ + EtOH \longrightarrow BQ^{-\cdot} + EtOH^{+\cdot} \tag{19}$$

$$EtOH^{+\cdot} + EtOH \longrightarrow EtO^{\cdot} + EtOH_2^+ \tag{20}$$

$$2BQ^{-\cdot} \longrightarrow BQ + BQ^{2-} \tag{21}$$

$$BQ^{2-} + 2H^+ \longrightarrow BQH_2 \tag{22}$$

The authors observed a radical having hyperfine coupling constants of 14.6 G (N) and 2.6 G (H) when the quinone was photolysed in the presence of phenyl-*N*-*t*-butyl-nitrone in ethanol. This major component was attributed to the trapped ethoxyl radical which can be produced as shown in equation 20. They also note the presence of a minor component due to the trapping of the hydroxyethyl radical (a_N = 15.3 G and a_H = 3.7 G) and although this may arise by hydrogen transfer from the triplet quinone it is suggested that it is

produced from the ethoxyl radical as shown in equation 23.

$$CH_3CH_2O^{\cdot} + C_2H_5OH \rightarrow C_2H_5OH + CH_3\dot{C}HOH \quad (23)$$

Although they could observe both $BQ^{-\cdot}$ and $BQH^{\cdot}$ in the experiments the neutral radical was noted only when high concentrations of the starting quinone were employed. In addition the authors saw no increase in the concentration of $BQH^{\cdot}$ when acetic acid was added to the medium suggesting that equilibrium 24 was not operating. Instead they propose that the neutral radical was generated by reaction between the quinone and the product hydroquinone as shown in equation 18; a large increase in the signal due to BQH was noted when additional hydroquinone was added. A trapped alkoxyl radical was also detected by McLauchlan and Sealy[117] in the spin-trap ESR study of several quinones and solvent alcohols.

$$BQ^{-\cdot} + H^+ \rightleftharpoons BQH^{\cdot} \quad (24)$$

A similar one-electron transfer mechanism was invoked by Scheerer and Gratzel[118] in a study to correlate the net rate constants for electron transfer and free energy changes involved in the reactions. They measured the yields of $DQ^{-\cdot}$ produced when ^3DQ was photolysed with a variety of electron-donating quenchers. Using their reaction conditions (detection by fast conductance measurements and aqueous ethanol 2:1 v/v as solvent) it is quite possible that electron transfer was favoured or that if any neutral radical were produced it would be undetected.

Wong[119] investigated the photolysis of 1,4-naphthoquinone in isopropanol and 2-butanol and concluded on the basis of the CIDEP behaviour of the system that the experimental results are due to a hydrogen abstraction mechanism even in the presence of pyridine which stabilized the anion radical ($NQ^{-\cdot}$) after deprotonation of the initially formed $NQH^{\cdot}$. In isopropanol the neutral $NQH^{\cdot}$ was strongly emissively polarized consistent with TM CIDEP; the $NQ^{-\cdot}$ observed was not polarized indicating that deprotonation was slower than the T_1 for $NQH^{\cdot}$. In the presence of triethylamine no $NQH^{\cdot}$ was observed and $NQ^{-\cdot}$ was strongly emissively polarized indicating either photoreduction by a different mechanism or that in the presence of this strong base the rates of H-abstraction and deprotonation are dramatically increased.

Kobashi and coworkers[120, 121] have studied the photoreduction of chloranil by dioxane and tetrachlorohydroquinone and determined the relative efficiencies for H-atom abstraction to be 0.13 and 0.58 respectively. The mechanism of H-abstraction in the reaction of triplet chloranil with durene[122] was proposed by these authors to be a simultaneous competition of two mechanisms. One is a two-step process of electron transfer followed by proton transfer via a triplet ion pair, and the other is rapid H-atom transfer in the non-relaxed encounter complex.

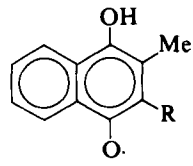
Kanemoto and coworkers detected only the neutral durosemiquinone radical in a CIDEP study of the photoreduction of duroquinone and phenol in alcohols; no $DQ^{-\cdot}$ was observed suggesting direct H-abstraction[73]. In a later publication[123] both the neutral and anionic semiquinones, $NQH^{\cdot}$ and $NQ^{-\cdot}$ were observed when naphthoquinone was photolysed with phenol in ethanol or isopropanol. TM CIDEP indicated the initial formation of the neutral radical in these solvents (by H-abstraction) followed by deprotonation to the anion. No polarization was detected for the anion indicating that spin lattice relaxation had returned the system to equilibrium before deprotonation. In isopropanol the authors did not observe any deprotonation to the anion.

The CIDEP behaviour of triplet quinones has been employed by Wan and Elliot[79] to estimate the relative triplet quenching (H-abstraction) rate constants when these quinones are phororeduced in the presence of a variety of hydrogen donors such as alcohols and phenols. They noted a much lower quenching rate for DQ than for BQ or its methyl-substituted derivatives, or AQ when alcohols were the donors. In addition 2-methylphenol,

phenol and pentachlorophenol were found to have quenching reaction rates approximately the same as triethylamine towards ^{3}DQ; durohydroquinone, however, reacts approximately one order of magnitude faster than the phenols. Of the phenols, pentachlorophenol is the most effective H-donor. The phenols are of course much more reactive as H-donors than isopropanol.

Recent improvements in the traditional[93] experimental set-ups for conducting CIDEP studies include the use of commercial boxcar integrators[100, 124] and similar devices[125]. With these modifications it is possible to obtain polarization spectra by sweeping the ESR spectrum at various time intervals (0.5–200 μs) after an initiating laser pulse. Thus it is possible to observe the evolution of the time profile of the CIDEP signal.

In addition, Wan and coworkers have described a method for the simultaneous recording and display of both the CW ESR spectrum and the CIDEP spectrum for a given experiment. This involves the installation of an external narrow bandwidth microwave amplifier between the ESR cavity and the crystal detector and division of the signal prior to detection[126]. This experimental set-up has proven extremely useful for the study of CIDEP in a number of quinone photoreductions including benzoquinone, 2,5-dimethylbenzoquinone, menadione, naphthoquinone and vitamin K_1. As an example the CW ESR and CIDEP spectra simultaneously observed for benzoquinone at time intervals 0.5 and 1.5 μs after the laser flash are shown (Figure 1). It is immediately apparent that the polarization spectrum of the neutral radical ($BQH^{\cdot}$) is much more intensely emissively polarized at 0.5 μs than at the longer delay time. In addition signals due to the anion radical $BQ^{-\cdot}$ are seen to appear in the second spectrum consistent with its formation by deprotonation from the neutral radical. When BQ was photolysed in acetic acid/isopropanol 1:1 the polarized neutral radical was the only species observed, the equilibrium being shifted away from deprotonation to the anion. Frequently the neutral semiquinone radical is observable only in the time-resolved CIDEP spectra and not in the CW ESR spectra. In such cases, its intermediacy in reaction mechanisms can only be surmised unless appropriate CIDEP experiments are performed. For example, menadione and vitamin K_1 exhibit well documented CW ESR spectra and strongly emissively polarized time-resolved spectra due to their respective semiquinone anions when photolysed in basic alcoholic solvents. Photolysis in a variety of polar and non-polar solvents even with added phenol resulted in no neutral radical detectable by CW ESR. However, strong emissively polarized spectra were observed under these conditions and attributed to the neutral radicals of these quinones (**26**). Although not completely resolved the quartet structure observable in the



(26)

menadione: R = H

vitamin K_1: R = $CH_2CH{=}C{-}[(CH_2)_3{-}CH(Me){-}]_3{-}Me$

vitamin K_1 neutral radical spectrum had a_H^{Me} = 8.0 G consistent with the value reported in the literature for this species[127]. The CW and polarization spectra for the vitamin K_1 and menadione radical anions and the polarization spectra of their corresponding neutral

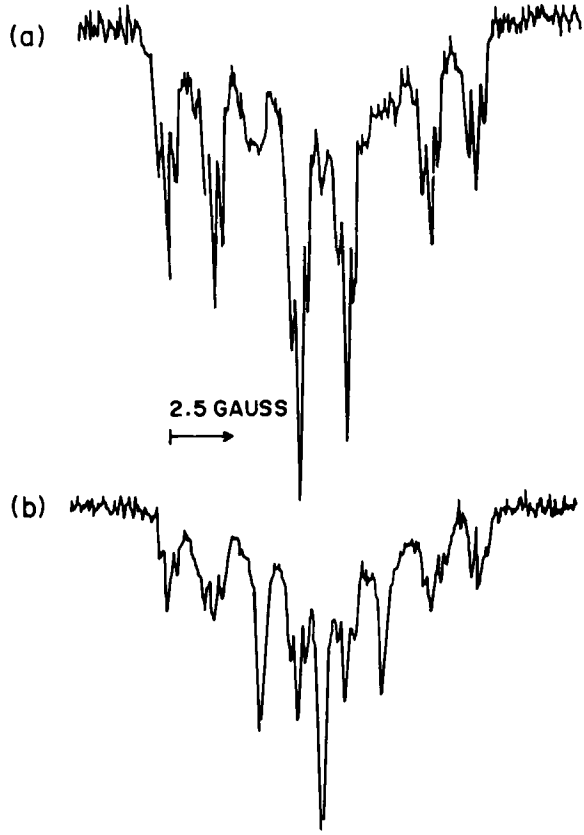


FIGURE 1. Time-resolved CIDEP ESR spectra of benzosemiquinone radicals (a) 0.5 μs and (b) 1.5 μs after the laser flash

radicals are shown (Figure 2). The lack of resolution in the anion radical polarization spectra can be attributed to line broadening as a result of the dynamic equilibrium of deprotonation to the anion after the initial formation of the neutral radical. The fast time resolution (500 ns) of the CIDEP experiment can detect this effect while the CW ESR spectrum is unaffected.

Another attempt to shed some light on the initial event problem in quinone photoreductions was made by Lazarev and coworkers[128]. They photolysed a single crystal of 3,6-di-*t*-butylpyrocatechol (**27**) doped with 10^{-2} M 3,6-di-*t*-butyl-*o*-benzoquinone (**28**) at 77 K. They observed both ion-radical ($Q^{-\cdot} + AH^{+\cdot}$) and neutral ($QH + A^{\cdot}$) radical pairs and although the former were short-lived they appeared not to be converted to the neutral pairs but rather to recombine to form initial reactants. Thus the authors suggest that the processes of H-abstraction and electron transfer compete in this system.

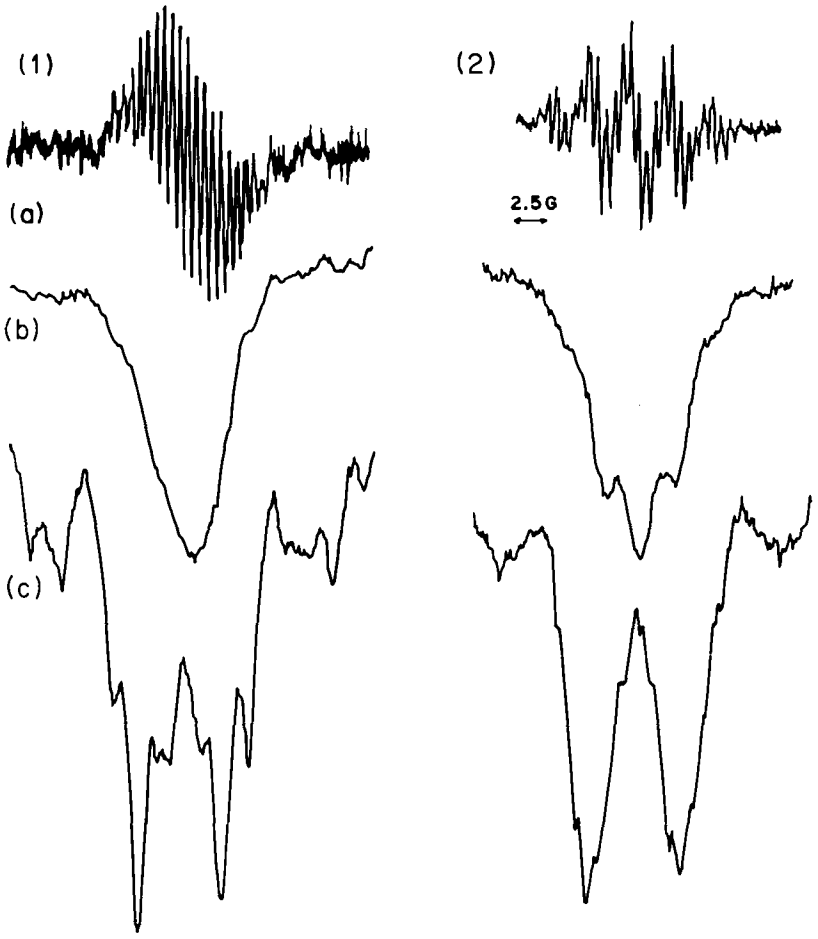
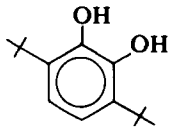


FIGURE 2. ESR spectra of menadione (1) and vitamin K_1 (2) semiquinone radicals at 25°C: (a) CW ESR spectra of the semiquinone anions in basic ethanol solution; (b) time-resolved CIDEP spectra for the semiquinone anions in basic ethanol solution taken 1.0 μs after the laser flash; (c) time-resolved CIDEP spectra in isopropanol/toluene 3:7 v/v containing 10^{-2} M phenol taken 0.5 μs after the initiating laser flash



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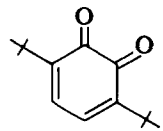


(28)

In the study of the photochemical behaviour of ketones and quinones it has been suggested that the mechanism of photoreduction is dependent on the $n\pi^*$ or $\pi\pi^*$ character of the lowest triplet state (T_1). For example, Porter and Suppan[129], and Formosinho[130]

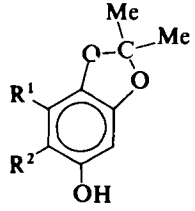
have noted that the $\pi\pi^*$ states of substituted ketones have approximately 10^{-2} to 10^{-4} times lower predilection for H-abstraction than do the $n\pi^*$ states. Kemp and Porter[131] have suggested that changing solvent from ethanol to water switches the lowest triplet state from $n\pi^*$ to $\pi\pi^*$; this accounts for their lack of observation of $BQH^{\cdot}$ when BQ was photolysed in water. Increasing methyl substitution in the quinone is suggested to stabilize the $\pi\pi^*$ state with respect to the $n\pi^*$ (for example, the lowest triplet states of duroquinone and benzoquinone have $\pi\pi^*$ and $n\pi^*$ character respectively).

Effects of substitution on the relative excited state energies are also noted for the halogenoanthraquinones. For the α-halogenoanthraquinones the lowest triplet states are mixed $n\pi^*$–$\pi\pi^*$ or $\pi\pi^*$ in character while the β-substituted isomers have $n\pi^*$ character. $n\pi^*$ triplet anthraquinones react by abstraction of a hydrogen atom from solvent to give the ketyl radical[132]. Inoue and coworkers[133] have proposed that as a result of their $\pi\pi^*$ triplet character the photoreduction of the α-halogenoanthraquinones occurs by direct electron transfer from ethanol; Hamanoue and colleagues[134, 135] do not agree. Their pico- and nanosecond laser photolyses of the chloroanthraquinones showed no indication of electron transfer; however, the greater $\pi\pi^*$ triplet state character of, for example, 1,8-dichloroanthraquinone with respect to 1-chloroanthraquinone is reflected in their H-abstraction rates in ethanol which are $1.6 \times 10^4\ s^{-1}$ and $2.3 \times 10^6\ s^{-1}$ respectively. Several other haloanthraquinones including 1,5-dichloro, 1-bromo, 1,5-dibromo and 1,8-dibromo, all of which have triplet states of mixed $n\pi^*$–$\pi\pi^*$ or $\pi\pi^*$ character, apparently react by H-abstraction from ethanol. Thus it appears that lowest triplet $n\pi^*$ character favours H-abstraction in the photoreduction of quinones in alcohol solvents; the switching of the lowest triplet state to $\pi\pi^*$ in nature, although it will decrease the rate of H-abstraction, may not always cause a switch to another mechanism such as electron transfer.

Photolysis of ketones and quinones is enhanced dramatically by the addition of amines; in general, the mechanism is believed to result from transfer of an electron from the amine to the triplet carbonyl compound forming an exciplex or ion pair followed by proton transfer[136, 137]. Roth deduced the presence of both neutral and anionic radical intermediates in the CIDNP study of quinone photoreductions in the presence of triethylamine (TEA)[138]. For BQ in acetonitrile the CIDNP observations on the product diethylvinylamine which must be formed via the neutral aminoalkyl radical could be explained only by considering the contribution from the radical ion pair. It was therefore concluded that net H-abstraction is a two-step process in such a system.

Hamanoue and coworkers[139] noted a dramatic increase in the quantum yields of photoreduction of AQ, 1-chloro-AQ, and 1-bromo-AQ in the presence of Et_3N. They proposed that the initially formed exciplex between lowest triplet AQ and Et_3N changes into a contact ion pair ($AQ^{-\cdot} + TEA^{+\cdot}$) and then following proton transfer into $AQH^{\cdot}$ and the triethylamine radical. The contact ion pair was much more stable in ethanol than in toluene as would be expected. The authors also suggest[140] that the electron transfer mechanism from Et_3N to triplet quinones and dissociation of the exciplex depend on the nature of the solvent. For example Chen and Wan have remarked that a flash photolysis study of 2,6-di-*t*-butylbenzoquinone by triethylamine in benzene appears to give only the neutral radical; no anion radical was detected[141].

CIDEP experiments have also been an asset in the study of photoreductions of quinones having substituents such as *t*-butyl or isopropyl which can undergo intramolecular H-abstraction and rearrangements. The *t*-butyl quinones have been shown to form substituted 1,3-benzodioxole derivatives (**29**) when photolysed in benzene or acetic acid and hydroquinones such as **30** with rearranged side chains when photolysed in isopropanol[142]. Farid has suggested a biradical intermediate resulting from internal H-abstraction from the *t*-butyl side chain which can then react in a number of ways depending on experimental conditions including formation of a spirocyclopropyl ketone[143, 144].



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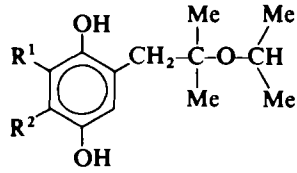
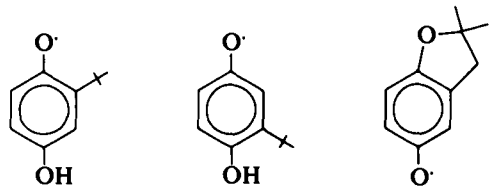


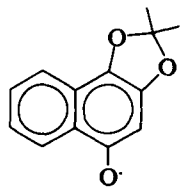
(30)

Wan and coworkers[142] have detected two primary polarized radicals **31** and **32** which arise from the same excited triplet quinone when 2-*t*-butyl-1,4-benzoquinone and a phenol were photolysed in isopropanol. CIDEP studies monitoring the dependence of the initial polarization on phenol concentration indicated that although the radicals were formed in the ratio 2:1 the rate of formation of **32** was five to seven times faster than that of the major component **31**. An additional secondary benzohydrofuran radical **33** was formed when toluene was used as solvent. It is interesting to note that although two radicals corresponding to structures **31** and **32** are noted for the photolysis of certain quinones such as 2-methylbenzoquinone[145] this is not usually the case. Indeed 2,6-di-*t*-butyl and 2,5-di-*t*-butyl-benzoquinone form only the radical corresponding to **31**.



(31) (32) (33)

A biradical intermediate was proposed in the photolysis of 2-isopropoxy-1,4-naphthoquinone to account for the observed formation of the rearranged radical (**34**)

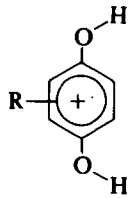


(34)

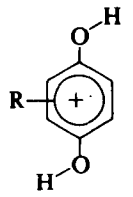
observed[146]. This compound and other substituted quinones are of commercial interest as photoredox agents in non-silver imaging processes and have been used for the development of novel high gain photothermographic imaging processes[147]. The ethereal oxygen at the 2-position in such compounds has been shown to participate efficiently in formation and stabilization of organometallic radical adducts, thus the 2-isopropoxy-substituted *p*-quinones can behave as 1,2-*ortho*-substituted quinones (see Section IV).

D. Quinone Cation Radicals

ESR spectra for a considerable number of *o*-, *m*- and *p*-hydroquinone cation radicals have been recorded as well as those from a few substituted 1,4-naphthohydroquinones, and 9,10-anthrahydroquinones (Ref. 16 and references therein). In general the radicals are formed in strong acid solutions by oxidation of the corresponding hydroquinone. For several of the cations such as those from 1,4-hydroquinone and durohydroquinone both *cis* and *trans* rotamers can be observed at reduced temperatures and their splittings measured.



cis



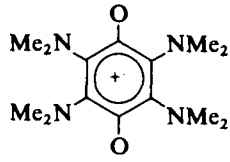
trans

		a_1^{OH}	a_4^{OH}	a_2	a_3	a_5	a_6
R = H	*cis*	3.294	3.294	2.147	2.147	2.356	2.356
	trans	3.294	3.294	2.456	2.055	2.456	2.055
R = Me	*cis*	2.887	2.887	2.171	2.171	1.931	1.931
	trans	2.887	2.887	2.785	1.389	2.785	1.389

The ESR spectra of these hydroquinone cation radicals show a relatively large temperature dependence for the hydroxyl proton splitting; this observation can therefore be used to estimate potential barriers to rotation about the carbon–oxygen bond. For the hydroquinone cation radicals from benzoquinone, duroquinone, naphthoquinone, 2,3-dimethyl-1,4-naphthoquinone, and 9,10-anthraquinone these were 10 ± 2, 6.6 ± 1.5, 5.9 ± 1.5, 4.6 ± 1.3 and 3.2 ± 4.0 kcal mol^{-1} respectively[148].

Although the hydroquinone cation radicals are reasonably well documented, the one-electron oxidized quinone radical, i.e. the quinone cation radical $Q^{+\cdot}$, has rarely been reported.

A novel stable radical cation (**35**) has been generated from tetrakis(dimethylamino)-*p*-benzoquinone[149]. The radical exhibits a dark purple colour and is stabilized by the strong donor effect of the dimethylamino function which can delocalize the positive charge. The cation was generated at a platinum anode in DMF/0.1 M TBAP (tetrabutylammonium perchlorate) solution at room temperature and gives a 19 line ESR spectrum having g factor 2.0032 and $a_H \simeq a_N = 3.32$ G for 24 protons and four nitrogens. The corresponding



(35)

radical anion was generated in tetrahydrofuran with Na likely as the triple ion complex $[Na^+Q^{-\cdot}Na^+]^{+\cdot}$. This radical exhibited an ESR spectrum having $g = 2.0046$, $a_H = 0.112$ G, and $a_{Na} = 1.43$ G (from ENDOR spectra).

Few other quinone radical cation species have appeared in the literature. A radical cation of benzoquinone was claimed to have been generated at 77 K but the spectrum was reassigned to unidentified impurity[150].

Wan and coworkers have studied the formation of several quinone radical cations in trifluoroacetic acid (TFA)[151–153] including those from benzoquinone, menadione, vitamin K_1, 2,5-dimethyl- and 2,5-diphenylbenzoquinone. Duroquinone and chloranil do not form cations in this solvent. TFA has been suggested to stabilize the cations primarily by interactions with the trifluoromethyl group[154–156]. In TFA benzoquinone gives a five line ESR spectrum ($g = 2.0040$, $a_H = 2.22$ G) thermally which increases in intensity when irradiated[151]. The stability of this cation radical in TFA has permitted its use in charge transfer studies forming known S- and N-containing cation radicals such as *N,N,N',N'*-tetramethyl-*p*-phenylenediamine, diphenylamine, thianthrene, phenothiazene and thianaphthene as shown in equation 25.

$$BQ^{+\cdot *} + S \rightarrow BQ + S^{+\cdot *} \tag{25}$$

Time-resolved CIDEP spectra show that the emissive TM polarization of the quinone cation is transferred to the newly formed S-containing cation[157].

A possible mechanism for formation of $BQ^{+\cdot}$ which is consistent with the CW and time-resolved CIDEP ESR observations is shown in equations 26–30. Initial protonation of benzoquinone in the acidic solvent may occur at either the carbonyl oxygen or at the quinonoid ring. In the photolysis of cyclopentadiene in TFA Davies and coworkers[158] have proposed an intermediate carbenium ion which subsequently loses a hydrogen atom to form the cyclopentadienyl radical cation. Both in the thermal and photochemical production of $BQ^{+\cdot}$ the oxidation of the quinone (reactions 27 and 29 respectively) may involve either H-atom transfer or charge transfer between BQH^+ and BQ. The product cation radical is stabilized by solvation with TFA but the neutral radical BQH rapidly decays in this medium. Although no hydroquinone cation is observed with benzoquinone a small amount of the deuterated hydroquinone cation is observed when BQ-d_4 is irradiated in TFA. This species may arise as shown in reaction 30. Observations supporting this mechanism involving initial protonation of the quinone are:

$$BQ + CF_3COOH \rightarrow BQH^+ + CF_3COO^- \tag{26}$$

$$BQ + BQH^+ \rightarrow BQ^{+\cdot} + BQH^{\cdot} \tag{27}$$

$$BQ \overset{h\nu}{\rightsquigarrow} {}^3BQ^* \tag{28}$$

$${}^3BQ^* + BQH^+ \rightarrow BQ^{+\cdot *} + BQH^{\cdot *} \tag{29}$$

$$BQH^{\cdot *} + H^+ \rightarrow BQH_2^{+\cdot} \tag{30}$$

(1) No reaction was detectable when trifluoroacetic anhydride was used as solvent; addition of one drop of water, however, resulted in immediate formation of $BQ^{+\cdot}$.

(2) When formic acid is used as the solvent, the $BQ^{+\cdot}$ formed decays at least three times faster than in TFA. Thus formic acid is acidic enough for protonation of the quinone but lacks the stabilizing trifluoromethyl moiety.

(3) No $BQ^{+\cdot}$ is formed when acetic acid is employed as solvent. Only $B\dot{Q}H$ is observed in this less acidic medium, likely as a result of H-abstraction from the solvent by the photoexcited quinone.

Although the ESR parameters of $BQ^{+\cdot}$ and $BQ^{-\cdot}$ show an initially surprising similarity the much greater linewidth in the CIDEP spectra of the $BQ^{+\cdot}$ species demonstrates the differing relaxation times for the two radicals. INDO calculations on the possible different radical species derived from benzoquinone show very little difference in the expected ring proton hyperfine couplings[151]. This observation is consistent with the reported small difference in hydrogen coupling constants for $C_6H_6^{+\cdot}$ compared with $C_6H_6^{-\cdot}$. The values of a_H are 4.44 and 3.82 respectively, i.e. a difference of only 15%[159]. Since the quinone radicals have proportionally less spin density in the aromatic ring the hyperfine coupling constants may well vary only slightly between the possible paramagnetic species. The total behaviour of quinones in acidic solvents such as TFA and formic acid is not yet completely understood. Hopefully investigations of the formation, reactions and properties of such cation radical species will be stimulated by these few reports.

IV. METAL AND ORGANOMETAL SEMIQUINONE COMPLEXES

A. Introduction

In the last decade the use of *o*- and *p*-quinones to trap reactive transient organometallic radicals has attracted increasing attention. The use of a variety of nitroxides as spin traps is well known, but the formation of quinone spin adducts with organometals is of interest for a variety of reasons. Primarily of course, the increased stability which results from the quinone–metal association increases the radical lifetime and thus facilitates identification of either semiquinone or metal radical structure. Often additional information is provided by the observation of metal hyperfine splittings or HFS constants associated with other ligands attached to the metal centre or changes in g factors in the radical adducts. In extreme examples, such as the spin adducts resulting from quinone trapping of rhenium carbonyl radicals, the resultant radical complex is so persistent that it can be isolated and its properties, spectral and physical, extensively investigated. This has included a rare example of an emission–fluorescence characterization of a radical, the 3,5-di-*t*-butyl-1,4-benzoquinone–$Re(CO)_4$ adduct. The persistence of the group VIIB metal carbonyl–quinone radical adducts and the lability of the CO ligand makes these radicals ideal substrates for ligand-exchange studies[160–162]. Ligand exchange using optically active ligands has resulted in the formation of stable optically active quinone–organometal radical adducts whose spectral and optical properties have been characterized. The stereoselective nature of subsequent reactions of such optically active adducts has been demonstrated[163, 164].

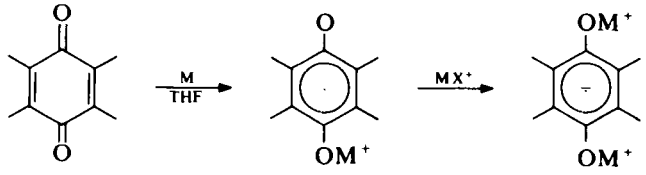
Quinones and semiquinones are often associated with metal ions or organometals in biological systems and for the most part their interactions are not well understood. In a quinone–organometal radical complex both the metal and the quinone have redox potentials in easily accessible and biologically useful ranges. Metal–quinone electron transfer reactions have been found to occur in mitochondria and in bacterial photosynthesis[165–167]. The catecholate ligands are well known for their affinity for ferric ion; it has been estimated[168] that enterochelin, an iron sequestering agent found in enteric

bacteria which uses three catecholate groups to encapsulate the ferric ion, has a complex formation constant of 10^{52}.

The literature on quinone–metal radical adducts is not comprehensively covered in this section. Our focus is on the intermediate quinone–metal ion pairs and quinone–organometal complexes and not on product complexes which frequently form complex solvates. The use of CIDEP and ESR techniques to elucidate some of the reaction mechanisms involved in the radical adduct formation will be briefly discussed. Free radical intermediates in photochemical reactions of carbonyl compounds (including quinones) with organometals[169] and transition metal *o*-quinone complexes[170] have been reviewed recently.

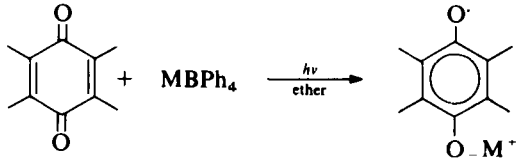
B. Radical Ion Pairs

Radical ion pairs can be generated electrochemically but are usually formed by alkali metal reduction in ethereal solvents. Depending on the stability of the ion pair, this process can also lead to the formation of triple ions[171].



Crown ethers have been used to facilitate the observation of ion pairs in non-polar solvents when the quinones were reduced thermally by alkali metals[172,173]. In addition the use of the appropriate crown ether and alkali metal alkoxide in the photolysis of 2,6-di-*t*-butylbenzoquinone in benzene resulted in the observation of the $Na^+Q^{-\cdot}$ contact ion pair[141] for which the Na HFS could be seen.

A photochemical method for the generation of radical ion pairs involving irradiation of a quinone with alkali tetraphenylborates in ethereal solvents has been described[174,175]. This technique is applicable also to other carbonyl containing compounds. In general, it was discovered that for *o*-quinones and sterically hindered *p*-quinones the photolysis results in the formation of radical ion pairs; however, triple ions result with unhindered *p*-quinones.



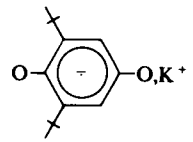
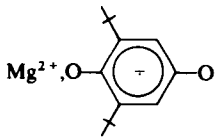
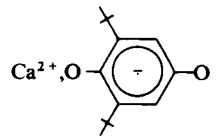
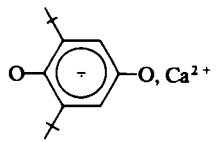
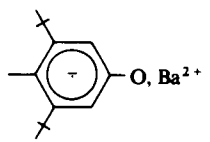
(31)

M = Li; K, Na

In solvents such as HMPA alkali metal reductions of quinones yield the free radical anions; however, addition of metal salts such as perchlorates or iodides to the anion radical solutions can result in the formation of the ion pairs which exist in rapid (on the ESR time-scale) equilibrium with the free ions. For 2,6-di-*t*-butylbenzoquinone (2,6-DTBQ) in HMPA the ion pair with K^+ was formed only at the unhindered quinone oxygen while Na^+ and Li^+ could interact at either oxygen[176,177]. The rapid equilibrium between the ion-paired and free semiquinone results in the observation of time-averaged spectra from

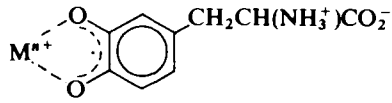
the species involved. When the alkali metal counterion has two alternative sites for ion pairing it is sometimes possible to observe cation migration between the two sites. For example, when the perchlorate salts of Mg^{2+}, Ca^{2+} and Ba^{2+} were added to HMPA solutions of 2,6-DTBQ the equilibria between the ion pairs and free ions were sufficiently slowed down that both species could be observed simultaneously in the ESR spectra. For Ca^{2+} different ESR spectra for the hindered and unhindered radical-ion pairs could be detected. The hydrogen HFS constants for a series of metal ion pairs with DTBQ are shown in Table 4[178].

TABLE 4. Coupling constants for 2,6-di-*t*-butylbenzoquinone (2,6-DTBQ) radical ion pairs

Ion pair	a_H (G)
2,6-DTBQ$^{-\cdot}$ (free)	2.39
	2.10
	0.86
	1.12
	1.46
	1.42

A novel method for the formation of *o*-quinone metal ion chelates was described by Felix and Sealy[40]. These complexes were formed by photolysis of catechols in the presence of diamagnetic metal ions from groups IIA, IIB, IIIA and IIIB in aqueous solution at neutral pH. The quinone–metal ion pairs were characterized by lower g factors and reduced spin densities at the carbonyl oxygens. The changes in quinone hyperfine couplings were correlated to the ratio of charge to ionic radius for the metal ion. The group IIA metals

were associated more weakly with the quinone anions as evidenced by the lack of observed HFS constants for the major metal magnetic isotopes. These couplings were observed with the IIB, IIIA and IIIB metals. The metal ion pairs of the substituted *o*-quinone L-dopa (**36**) were also studied by this method[52]. The zwitterionic form of this *o*-quinone is observed at



$n = 1, 2$

(36)

neutral pH; this species deprotonates at pH 9. The complexity of the ESR spectrum of this radical is partially due to the non-equivalent chiral methylene hydrogens in the amino acid side chain. Formation of the metal ion pairs especially those involving Cd^{2+} or Zn^{2+} considerably increases the stability of the dopa semiquinone radical as well as the radicals of dopamine and adrenaline[179].

A number of *o*-quinones and ene-diols such as vitamin C form organothallium complexes which have been suggested to be radical-ion pairs[180–182].

Ion-exchange reactions are frequently used to convert less stable radical ion pairs to more stable ones (equation 32). Calcium ions in blood can be replaced by potassium ions by an exchange reaction with potassium phenanthrasemiquinone (equation 33)[169].

$$K^+PQ^{-\cdot} \xrightarrow{Na^+} Na^+PQ^{-\cdot} + K^+ \tag{32}$$

$$K^+PQ^{-\cdot} \xrightarrow[H_2O/THF]{Ca^{2+}\text{ in blood}} Ca^{2+}PQ^{-\cdot} + K^+ \tag{33}$$

Uranyl–quinone ion pairs have been generated by photolysis in THF of the quinone and uranyl salts (equation 34). Using CIDEP techniques as well as CW ESR observations a mechanism for the reaction has been suggested[88,89]. This involves transfer of energy from the polarized excited phenanthroquinone triplet to the uranyl ion followed by water splitting and then formation of the quinone–organometal ion pair (reactions 35–38). The $[UO_2HPQ]^{2+\cdot}$ which is also formed in the system is believed to result from a secondary process and may form as shown in equations 39–41.

$$PQ + UO_2(NO_3)_2 \cdot \tilde{n}H_2O \xrightarrow[THF]{h\nu} UO_2^{2+}PQ^{-\cdot} + UO_2H^{3+}PQ^{-\cdot} \tag{34}$$

$$PQ \xrightarrow[ISC]{h\nu} {}^3PQ^* \tag{35}$$

$${}^3PQ^* + UO_2^{2+} \cdot nH_2O \rightarrow {}^3(UO_2^{2+} \cdot nH_2O)^* + PQ \tag{36}$$

$${}^3(UO_2^{2+} \cdot nH_2O)^* \rightarrow UO_2^{+\cdot *} + H^+ + \dot{O}H \tag{37}$$

$$UO_2^{+\cdot *} + PQ \rightarrow [UO_2PQ]^{+\cdot *} \tag{38}$$

$$[UO_2PQ]^{+\cdot} \xrightarrow{h\nu} UO_2^{2+} + PQ^{-\cdot} \tag{39}$$

$$PQ^{-\cdot} + H^+ \rightarrow HP\dot{Q} \tag{40}$$

$$HP\dot{Q} + UO_2^{2+} \rightarrow [UO_2HP\dot{Q}]^{2+} \tag{41}$$

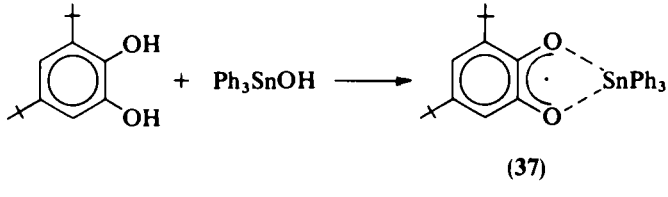
C. Organometal–Quinone Radical Adducts

There are several methods by which quinone–organometal radical adducts can be formed. For example, ion-exchange reactions were mentioned in the previous section. Metal–quinone ion pairs which are generated by methods such as alkali metal reduction can be exchanged for organometals to form stable heavy metal–quinone radical adducts[183] (equation 42).

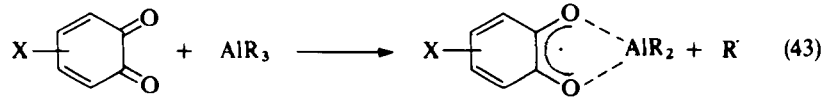
$$K^+PQ^{-\cdot} + MeHgCl \xrightarrow{THF} MeHgP\dot{Q} + KCl \tag{42}$$

Oxidation of catechols by organometallic hydroxides can also result in the organometal–quinone complex (**37**). This method was extensively used by Stegmann and coworkers in the formation of organothallium complexes of quinones[180, 181, 184].

S_N2 reactions by excited quinones have been described[185, 186] (equation 43).



(37)



(43)

Most commonly, however, quinone–organometal radical adducts are formed as a result of radical addition reactions. Often the initial organometal radicals can be generated by thermal or photochemical homolysis of species containing a M–M′ bond (equations 44 and 45), followed by addition of the radicals to quinones. For example photolysis of $Me_3SnMn(CO)_5$ resulted in addition of $M\dot{n}(CO)_4$ where two adjacent oxygens were available for chelation while $Me_3S\dot{n}$ added to one carbonyl oxygen only[187].

$$R_xMM'R_y \longrightarrow R_xM^{\cdot} + M'R_y^{\cdot} \tag{44}$$

$$Q + R_xM^{\cdot} \longrightarrow Q^{-\cdot}MR_x \tag{45}$$

Organometals can react with a variety of compounds to produce paramagnetic intermediates by a charge transfer mechanism which may be initiated thermally, or photochemically by irradiation of the charge transfer band or via a triplet exciplex. CIDEP experiments were consistent with the charge transfer mechanism involving quenching of excited quinone triplet by organometals such as R_3SnX to form a primary radical ion pair of the quinone and organometal[90, 188]. Organotin compounds are effective electron donors and reactions with phenanthrenequinone[189], substituted *o*-quinones[190, 191] and *p*-quinones[192, 193] supported this mechanism. In addition direct spectroscopic evidence was obtained when the quinones in host organotin crystals were photolysed at 77 K. The ESR spectrum of the triplet state of the primary radical ion pair was observed consistent with the following mechanism (equations 46–48)[194].

$$Q + Ph_3SnX \xrightarrow{h\nu} {}^3[Q^{-\cdot} \ldots Ph_3SnX^{+\cdot}] \rightarrow {}^{77K}[Q^{-\cdot} + Ph_3SnX^{+\cdot}]pair \tag{46}$$

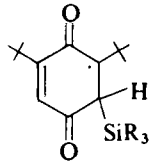
$$[Q^{-\cdot} + Ph_3SnX^{+\cdot}] \rightarrow Q^{-\cdot} + Ph_3Sn^+ + \dot{X} \tag{47}$$

$$Q^{-\cdot} + Ph_3Sn^+ \rightarrow Ph_3Sn \cdot Q \tag{48}$$

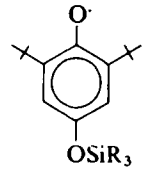
1. p-Quinones

Spin adducts of organosilyl, -germyl and -stannyl radicals with several *p*-quinones have been described[192, 195–197]. Relatively stable adducts have been obtained with the hindered 2,6-DTBQ and trialkyl C, Si, Ge, Sn and Pb radicals as well as with the diphenylphosphinyl radical ($\dot{P}Ph_2$) and the phenylthiyl radical (PhS)[192]. Some controversy concerning radical addition to such quinones still persists due to the presence of two distinct reactive sites, the carbon–carbon double bond and the carbonyl group. Isomeric radical adducts in the addition of silyl and germyl radicals to unsaturated carbonyl containing compounds such as maleic anhydride have been observed[198] with addition to C=C predominating at low temperatures and addition only to C=O oxygen being observed at room temperature. (Certain organometals such as the organotin and lead adducts prefer to add only to the carbonyl oxygen.)

The addition of trialkylsilyl radicals to 3,6-dimethylthieno[3,2-b]thiophen-2,5-dione was felt to occur faster at the carbon–carbon double bond although addition of this radical to the carbonyl function was also observed. This prompted a thorough CIDEP investigation of the addition of trialkylsilyl radicals to substituted *p*-benzoquinones[124]. Addition to both the ring and the carbonyl group of 2,6-DTBQ was observed giving adducts **38** and **39**. The oxygen adduct was confirmed to be the more thermally stable species.



(**38**)



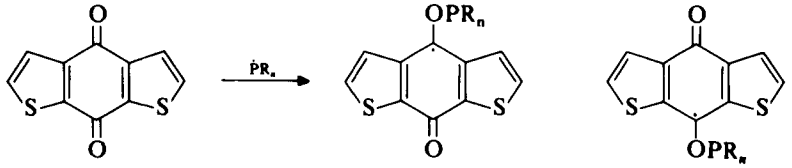
(**39**)

The effect of differences in the organometal character on the site of addition to such *p*-quinones was evident when 2,6-DTBQ was photolysed with $Me_3Sn–Mn(CO)_5$. As mentioned earlier in this section the two primary radicals $Me_3\dot{S}n$ and $\dot{M}n(CO)_5$ showed very different behaviours; the trialkyltin radical adding to the carbonyl group and the manganese radical at the ring carbon.

The dual reactivity of the quinones is also exhibited in reaction with the methyl radical which has been shown to form a ring adduct[199] and the *t*-butyl radical which formed a stable phenoxyl radical by addition to the C=O group[192]. A recent study of the reaction of several phosphorus containing radicals with quinones demonstrated that for 2,6-DTBQ, $\dot{P}(O)Ph_2$ and $\dot{P}(O)(OEt)_2$ added to both C=C and C=O functions giving ESR spectra for both ring and oxygen adducts. However $\dot{P}Ph_2$ and $\dot{P}(S)Et_2$ gave only observable oxygen adducts. With duroquinone the only adducts which were definitely identified were the ring adducts of DQ with $O\dot{P}Ph_2$ and $O\dot{P}(OEt)_2$. The heterocyclic sulphur containing quinone benzo[1,2-b;5,4-b′]dithiophen-4,8-dione (**40**) was observed to form oxygen adducts with all the above mentioned phosphorus containing radicals; both isomeric forms (**41a** and **b**) were observed except in the case of $S\dot{P}Et_2$ which appeared to form only the isomer corresponding to **41b**[200].

Some adducts of 2,6-DTBQ and several phosphine oxides have been described[201]. These authors noted only oxygen adducts and suggested that rotation about the phosphorus–oxygen bond is strongly hindered.

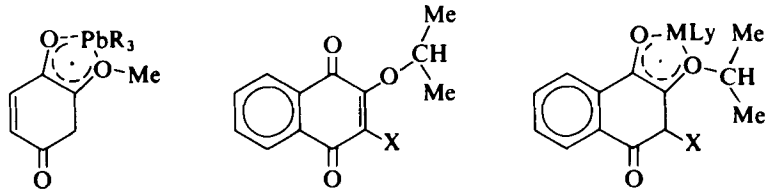
The reaction of quinones with nitrosoarenes gives the 2,3-disubstituted dinitrone product[202] rather than the expected 2,5-disubstituted product. The mechanism of the



(40) (41a) (41b)

reaction is not known but was suggested to be a radical process involving electron transfer and to involve either trapping of the PhN–O radical by the quinone or addition of the nitrosobenzene to the semiquinone anion.

Spin adducts of metals and *p*-quinones can in certain instances be stabilized by the presence of a heteroatom in a position available for participation in chelation of the metal centred radical. The trialkyllead adduct **42** was described when 2-methoxy-*p*-benzoquinone was photolysed with Pb_2R_6[169]. The 2-isopropoxy-1,4-naphthoquinones **43a** and **b** efficiently formed organometal adducts **44** with Re, Mn, V and Mo radicals. Comparison of the ESR parameters of these organometallic radical adducts with those of

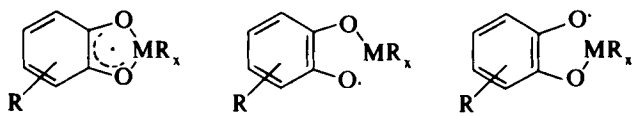


(42) (43a) X = H (43b) X = Cl (44)

the corresponding 1,2-naphthoquinone metal adducts supported the participation of the ethereal oxygen in the chelation[146]. The 2-isopropoxyl–naphthoquinone complexes with $\dot{R}e(CO)_5$ were unusual in that both 1:1 and 1:2 rhenium–quinone adducts could be observed simultaneously, relative concentrations of the two complexes could be varied by changing the ratio of metal to quinone.

2. *o*-Quinones

o-Quinones are able to interact with a great variety of organometallic radicals by chelation with the adjacent carbonyl oxygens. Examples of adducts from metals of all the main groups, transition metals[170] and the actinides have been recorded in the literature (Ref. 169 and references therein). The *o*-quinones can act as bidentate ligands towards organometals (**45**) or as monodentate ligands forming unsymmetric adducts **46** and **47** which may or may not be in rapid dynamic equilibrium. Determination of the structure of

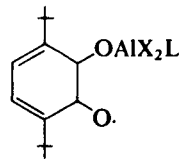


(45) (46) (47)

the radical adducts is usually based on ESR parameters, especially linewidth alternation studies and analysis of quinone and metal ligand splitting patterns. Factors affecting the relative stability of the mono- or bidentate adducts and the rate of cation migration between the two oxygens in the monodentate structures include the nature of the metal and its other ligands as well as the steric and electronic properties of the quinone.

For a series of tin radicals α-dicarbonyl compounds such as biacetyl have been shown to chelate $SnCl_3$ and $SnBuCl_2$ through both oxygens; however, $SnBu_2Cl$ and $SnBu_3$ coordinate through one oxygen only, the adducts being non-fluxional and fluxional respectively in the latter two cases[195]. Similarly the activation parameters for intramolecular cation migration were found to increase with increasing chlorine substitution in alkyltin–quinone radical adducts[191]. Activation energy for intramolecular migration was found to decrease in the order $SiR_3 > GeR_3 > SnR_3$ for such radical adducts.

The structure of adducts of aluminium salts with 3,6-di-*t*-butyl-*o*-quinone were influenced by solvent; non-coordinating solvents such as toluene favoured symmetrical coordination of the metal between the quinone oxygens but more strongly coordinating solvents such as ether, or THF converted the structure to a monodentate radical as shown



(48)

below (**48**) where L is the coordinating solvent molecule. Depending on the nature of the coordinating solvent the aluminium moiety may be fluxional or non-fluxional on the ESR time-scale with strongly coordinating solvents increasing the rate of intramolecular migration[186]. These observations are consistent with the postulation of two rapidly equilibrating tautomers for $PQ^{\cdot}AlCl_2$ in THF[203].

Complex tautomeric behaviour of tris-quinone metal radical complexes has also been observed[204–206].

Complexes of *o*-quinones with organomercury complexes have been studied quite extensively. Since heavy metal cations such as HgR^+ readily displace alkali metal cations in $M^+Q^{-\cdot}$ complexes this method was regarded as an important procedure for the detection and removal of trace amounts of toxic organomercurials[183,207]. Interactions of organomercury and mercuric salts with several *o*-quinones and also with vitamin C which has three oxygen functions available for complexation with metal centres have been reported[208]; ^{199}Hg splittings were observed for the *o*-quinone and vitamin C adducts. Many of the quinone–organomercury radicals exhibit very low *g* factors; similar dramatic *g*-shifts were noted in the uranyl–quinone radical complexes. Therefore, a simple theoretical model describing the relative contributions to the *g*-shift from spin-orbit coupling of the metal and from d-p_π-bonding has been discussed[208]. The mercury salts were also found to interact with vitamin C; however, the observed *g*-shifts were small and no metal hyperfine splittings were detected. These observations were consistent with the formation of mercury–vitamin C ion pairs similar to that proposed for $VTC\text{-}Ph_2TlOH$[182].

A charge transfer mechanism has been suggested for the reactions of organomercury with *o*-quinones (equations 49–51); however, thermal or photochemical decomposition of the organomercury is another possible route for initiation of the adduct formation which cannot be eliminated (equations 52, 53)[208].

$$Q + HgR_2 \rightarrow Q^{-\cdot} + R_2Hg^{+\cdot} \quad (49)$$

$$R_2Hg^{+\cdot} \rightarrow RHg^+ + R^\cdot \quad (50)$$

$$Q^{-\cdot} + HgR^+ \rightarrow Q\text{-}HgR \quad (51)$$

$$R_2Hg \rightarrow RHg^\cdot + R^\cdot \quad (52)$$

$$RHg^\cdot + Q \rightarrow RHg\text{-}Q \quad (53)$$

No evidence for intramolecular migration of mercury between the quinone carbonyl groups has been found[208, 209] consistent with a structure having Hg coordinated equally to the two functional groups. For the quinone–mercury radical adducts of compound **40** the spin density at the metal atom was approximately one order of magnitude lower than that for the paramagnetic complexes of this compound with manganese or rhenium carbonyls or with As, Sb or Bi biphenyls[209].

In *o*-quinones charge delocalization onto the quinone–metal chelate ring is not as extensive as in their sulphur-containing analogues such as the 1,2-benzodithiolates (Ref. 170 and references therein). Dithiocarbonyl compounds are well known as superior spin traps compared to the dicarbonyls[210].

Considerable work in our laboratory has been concerned with the reactions of group VIIB organometals (especially the carbonyls) with *o*-quinones. The extreme persistence of the $Re(CO)_4$-Q radical adducts and the lability of the carbonyl ligands makes them ideal subjects for ligand-exchange studies. In addition development of ESR–HPLC techniques for isolation of the radicals enabled their complete spectral characterization even including emission–fluorescence studies. Formation of the adducts results from trapping of the primary $Re(CO)_5$ radicals formed by photolysis of the Re–Re bond (equations 54, 55). The metal atom chelates symmetrically to all the *o*-quinones studied to form persistent 1:1 Q:M adducts. The sole exception to this noted so far is the previously mentioned 2-isopropoxyl-1,4-naphthoquinone. However, different ratios of quinone to metal have been observed for other group members. $Cr_2(CO)_6$ forms $Cr(CO)_2PQ_2^\cdot$ as the major component whether the reaction with phenanthrenequinone is carried out in the dark or under irradiation. $Cr(CO)_4PQ^\cdot$ is produced as a minor component but only by photolysis[161].

$$Re_2(CO)_{10} \xrightarrow{h\nu} 2Re(CO)_5 \quad (54)$$

$$Re(CO)_5 + Q \longrightarrow Q\text{-}Re(CO)_4 + CO \quad (55)$$

For the Q-$Re(CO)_4$ radical adducts the order of stability is 3,5-di-*t*-butyl-1,2-benzoquinone (3,5-DTBQ), tetrabromo-1,2-quinone, 1,2-naphthoquinone ~ acenaphthoquinone ~ phenanthrenequinone > camphorquinone ≫ tetrachloro-1,2-quinone. Once the initial quinone–rhenium complex is formed substitution of one or more of the CO ligands by a variety of P, N, As, Sb containing species is possible. For the most part only one CO is substituted even when bidentate substituents are employed; however, for the phosphites disubstituted adducts were also formed. This can be observed in Figure 3 in which the initial $Re(CO)_4$-3,5-DTBQ second derivative ESR spectrum (3a) changes on addition of one $P(OMe)_3$ substituent (3b) and then further splitting results on substitution of the second $P(OMe)_3$ group (3c). The *g* factors and hydrogen HFS constants can be seen to decrease on substitution while the values of a_{Re} increase consistent with withdrawal of the electron density from the quinone ring towards the phosphorus ligands.

During reaction of these adducts with a series of N-containing substituent ligands it was discovered that effective substitution required that the ligand not be sterically hindered at the donor atom and that a possibility for delocalization of electron density into, for example, an aromatic π system or empty d orbitals must exist. The substitution mechanism is not proven but appears to be dissociative rather than associative[161].

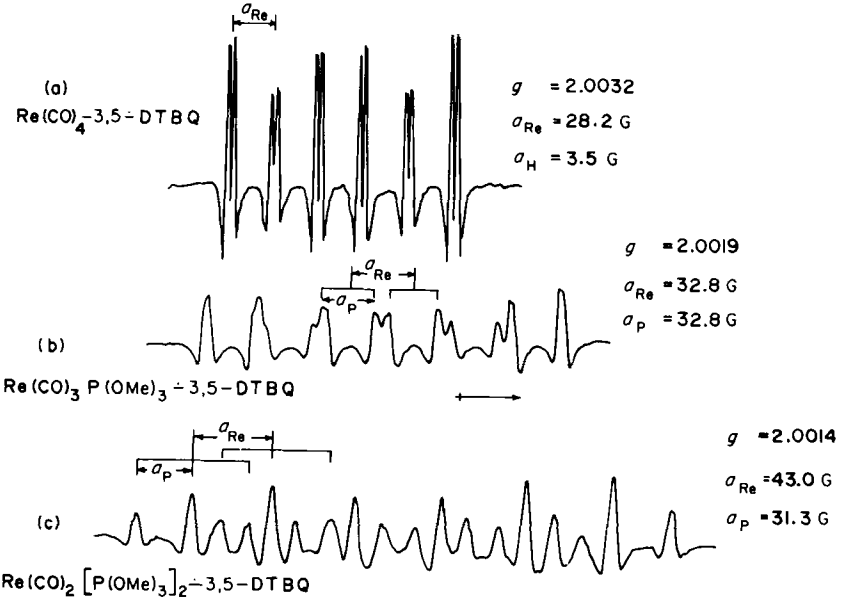
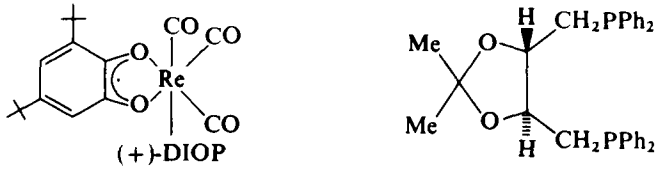


FIGURE 3. Second derivative ESR spectra in toluene at 25°C for: (a) $Re(CO)_4$–3,5-DTBQ; (b) $Re(CO)_3P(OMe)_3$–3,5-DTBQ; (c) $Re(CO)_2[P(OMe)_3]_2$–3,5-DTBQ

Similar ligand substitution reactions occur for the other group VIIB metal carbonyl–phenanthrenequinone radical adducts. However, differences in reactivity are apparent; PPh_3 substitutes two equatorial CO groups in $Mo(CO)_4$–PQ while in $Cr(CO)_2$–PQ_2 only one axial carbon monoxide is replaced.

Substitution of $Re(CO)_4$–3,5-DTBQ with the optically active phosphorus-containing ligands (+) or (−)-DIOP results in the formation of an optically active metal–quinone radical (**49**). The isolation by HPLC and full spectral characterization of these optically active intermediates is unique[161]. The word unique was used in this description since to our knowledge no other *optically active radical* has been isolated, purified and characterized. Usually the reactivity of such radicals precludes their determination other than in reaction mixtures containing other starting materials and products. The optical rotation values were obtained for both the (+) and (−) DIOP complexes.



(**49**)

In addition a rare example of the emission–fluorescence characterization with quantitative fluorescence quantum yield and lifetime measurement for a radical in solution at room temperature was obtained in the study of the $Re(CO)_4$–3,5-DTBQ radical adduct[211]. The radical was discovered to have λ_{max}^{abs} 230 and 500 nm in cyclohexane and λ_{max}^{em} = 320 nm.

The fluorescence yield and lifetimes were found to be 0.06 ± 0.01 (compared with standard anthracene) and 10.3 ± 0.1 ns respectively[211]. Another quinone radical whose fluorescence behaviour has been recently examined is that of camphorquinone[212] (see Section V.B).

V. PHYSICAL CHEMISTRY OF THE SEMIQUINONES

Much of the data concerned with the physical properties of the semiquinones has relied on the formation of these radicals by pulse radiolysis or flash photolysis. Generation and stabilization of the radical anions in basic aqueous media is fairly simple but accurate spectral data for the less stable neutral radicals is more difficult. The spectral, acid–base and redox properties of the hydroquinone and quinone cation radicals have not yet been systematically studied.

Swallow[213, 214] has recently reviewed the physical data relevant to the semiquinones.

A. Acid–Base Properties

The equilibrium reaction 56 between the neutral and anionic semiquinone radicals has been studied for a variety of quinones in aqueous solution and pK_a values obtained. Frequently the data were obtained from pH dependence of optical density measurements at a wavelength where the extinction coefficients of the anion and neutral radicals are quite different (usually at λ_{max} for $Q^{-\cdot}$) after the radicals have been generated by pulse radiolysis, or from conductivity measurements. The pK_a values for several *o*- and *p*-semiquinones are collected in Table 5. In general, the pK_a values for the semiquinones are approximately 5 pH units lower than those for the corresponding quinones.

$$QH^{\cdot} \rightleftharpoons Q^{-\cdot} + H^{+} \tag{56}$$

Often the measurements are made in solvents of differing composition which makes the absolute numbers difficult to compare. However, for the series of simple substituted BQs the electron-donating capacity of the methyl group increases the pK_a value by 0.25 units per substituent. This trend is not followed as well in the 1,4-naphthoquinone series. The pK_a value for 2,3-dimethyl-1,4-naphthoquinone is lower than that for the 2-methyl derivative, menadione.

The pK_a values for the semiquinones from vitamin K_1 and ubiquinone appear to be considerably higher than the analogous 2,3-dimethylnaphthoquinones; however, the higher percentage of alcohol in the solvent required to dissolve these compounds is likely the causative factor[213]. This effect is also noted for durosemiquinone which exhibits a pK_a value of 6.0 ± 0.1 in aqueous isopropanol/acetone 7:1 v/v and 5.0 ± 0.1 in aqueous isopropanol/acetone 1:1 v/v. Indeed determination of ubisemiquinone pK_a in methanol gives a value of 6.45 ± 0.15, even higher than in isopropanol/acetone 7:1 (5.90). Swallow suggests that if ubisemiquinone and vitamin K_1 semiquinone could be prepared in aqueous solutions the pK_a values expected would be 4.9 and 4.5 respectively. The small differences in pK_a values for the semiquinones of DQ, vitamin K_1, and ubiquinone indicate that this property is relatively insensitive to the nature of the long alkyl side chain. This is not unexpected since these alkyl substituents have been shown to perturb the aromatic spin density in the semiquinones by an amount similar to the methyl group[21].

The anthraquinone-sulphonates studied show a dramatic decrease in pK_a value when the substituent is in the 2-position but little or no effect for substitution at positions 1 or 6.

The *o*-semiquinones have pK_a values very similar to the *p*-semiquinones; the only value observed for a *m*-semiquinone generated from resorcinol was somewhat higher (7.0). The semiquinone radicals generated from epinephrine, adrenalone and camphorquinone are somewhat more acidic than those of the other quinones; the reasons for this are not readily apparent. Complications in the acid–base properties due to participation of the amino acid

TABLE 5. Acid–base properties of semiquinones

Compound	pK_a	Reference
1,4-Benzoquinone	3.90	23
	4.10	222, 225, 294
2-Methylbenzoquinone	4.45	225
2,3-Dimethylbenzoquinone	4.65	225
2,5-Dimethylbenzoquinone	4.60	225, 294, 295
2,6-Dimethylbenzoquinone	4.75	225
2,3,5-Trimethylbenzoquinone	4.95	225
Duroquinone	5.10	295
	5.00	294
	6.00	225
Diphenoquinone	3.20	295
1,4-Naphthoquinone	4.10	294, 295
2-Methylnaphthoquinone	4.40	225
	4.50	295
2,3-Dimethylnaphthoquinone	4.25	225
2-Hydroxynaphthoquinone	4.70	295
Vitamin K_1	5.50	225
Ubiquinone	5.90	225
	6.45	296
Anthraquinone	5.30	295
Anthraquinone-1-sulphonate	5.40	214
Anthraquinone-2-sulphonate	3.25	214
Anthraquinone-2,6-disulphonate	3.20	214
1,2-Benzoquinone	5.00	23, 222
3-Methoxy-1,2-benzoquinone	5.00	23
4-Methyl-1,2-benzoquinone	4.50	213
4-*t*-Butyl-1,2-benzoquinone	5.20	213, 297
Resorcinol	7.10	23
	7.00	222
1,2-Naphthoquinone	4.80	295
Epinephrine	3.70	295
Adrenalone	3.60	295
Camphorquinone	4.10	214

side chains in the first two may have an effect, and in camphorquinone of course, the usual planar aromatic geometry of the quinones is absent.

Further protonation of the neutral semiquinone is possible in strong acid solutions (equation 57) but has not been extensively studied. Land and Porter measured a pK_a value of -1.1 for the ionization of the durohydroquinone cation radical in 50% aqueous ethanol[215].

$$QH^{\cdot} + H^{+} \rightleftharpoons QH_2^{+\cdot} \tag{57}$$

B. Optical Spectra

Absorption maxima and extinction coefficients have been tabulated quite extensively in the literature from pulse radiolysis and flash photolysis experiments. Although the spectra for both neutral and anionic radicals can be obtained from either technique, accurate determination of extinction coefficients is more readily obtained using pulse radiolysis where standard radiation dosimetry can estimate the radical yields to within about 5% accuracy. The radical anion is the more stable species in alkaline aqueous solutions, alcohol or in organic solutes like DMF. As demonstrated in Table 6 the values of λ_{max} for the

TABLE 6. Optical absorption data for semiquinones

Compound	QH		$Q^{-\cdot}$		Reference
	λ_{max}(nm)	$\varepsilon(M^{-1}cm^{-1})$	λ_{max}(nm)	$\varepsilon(M^{-1}s^{-1})$	
Benzoquinone	415	4700	425	6900	213
	410	5500	435	7100	298
2-Methylbenzoquinone	405	4500	430	6200	225
2,3-Dimethylbenzoquinone	415	5100	430	6700	225
2,5-Dimethylbenzoquinone	415	5000	435	7000	225
	415	3600	440	6800	295
2,6-Dimethylbenzoquinone	405	4900	430	6100	225
2,3,5-Trimethylbenzoquinone	410	4300	435	6700	225
Duroquinone	420	4700	440	7600	225
	425	4000	445	7100	295
1,4-Naphthoquinone	370	7300	390	13 000	225, 295
2-Methylnaphthoquinone	370	9500	390	12 500	225, 295
2,3-Dimethylnaphthoquinone	380	7300	400	11 000	225
2-Hydroxynaphthoquinone	370	5900	390	6300	295
Vitamin K_1	380	9900	400	10 200	225
Ubiquinone	425	5300	445	8600	225
	420	3000	445	8000	296
9,10-Anthraquinone	375	11 000	395	7800	213, 295
			480	7300	
Anthraquinone-1-sulphonate	385	12 000	400	8000	213, 295
			500	8000	
Anthraquinone-2-sulphonate	390	12 500	400	8000	213
			500	8000	
1,2-Naphthoquinone	< 260	16 000	265	40 000	295
4-*t*-Butyl-1,2-benzoquinone	290	7700	313	12 200	297
	390	1850			
Epinephrine	< 260	13 000	265	3300	295
Adrenalone	280	10 000	290	17 000	295

different solvents and methods are in good agreement although as would be expected there is greater variation in the estimates for ε.

The semiquinone radical anions all have λ_{max} at approximately 10–30 nm longer wavelength (red shifted) than the neutral species; the similarity between the two values is not unexpected since protonation causes little perturbation in the orbitals involved[213]. In general it has been observed that basic forms of free radicals absorb at lower energies than the neutral forms. The extinction coefficients are considerably higher in most cases for the anions than for the neutral radicals.

As is readily observed from Table 6 neither λ_{max} nor ε show much variation with substitution for the series of methyl-substituted benzosemiquinones or naphthosemiquinones. The anthrasemiquinone anions exhibit two bands in their absorption spectra in contrast to the single band for the anions of the benzo- or naphthosemiquinones.

Although the values obtained show fairly good agreement there are some differing observations made by flash photolysis experiments for durosemiquinone and ubiquinone. The neutral durosemiquinone radical has been estimated to have ε_{420nm} of 5500 ± 500 in ethanol and $\varepsilon_{407.5} = 8850\ M^{-1}cm^{-1}$ in cyclohexane[216]. The radicals of ubisemiquinones-0* and 10*, vitamin K_1 and plastoquinone-9 all exhibit very similar absorption

* The semiquinones of structure **9**, having $n = 0$, 10, respectively.

spectra[217]. Although these radicals can be prepared in alcoholic media, estimates of their values of ε and λ_{max} in aqueous solution were obtained by extrapolation of the behaviour of durosemiquinone from alcohol to aqueous solvent. For example, although ubiquinone has $\varepsilon_{275-280} = 7400\,M^{-1}cm^{-1}$ for UQH and $\varepsilon_{320} = 10\,700\,M^{-1}cm^{-1}$ for $UQ^{-\cdot}$ in methanol, the predicted values for these neutral and anionic radicals in aqueous solution were $\varepsilon_{425} = 5300\,M^{-1}cm^{-1}$ and $\varepsilon_{445} = 8600\,M^{-1}cm^{-1}$ respectively. Similarly it was estimated that the neutral semiquinone of vitamin K_1 would have $\varepsilon_{380} = 9900\,M^{-1}cm^{-1}$ while the anion would have $\varepsilon_{400} = 10\,200\,M^{-1}cm^{-1}$ if they could be prepared in aqueous solution[213]. Values of λ_{max} for the neutral and anionic semiquinones of a related quinone, α-tocopherylquinone (**60**) are reported as 415 and 435 nm in ethanol respectively[127]. Although no extinction coefficients were reported the similarity of these spectra to those of the durosemiquinone radicals again is consistent with the small perturbation of the aromatic ring orbitals due to the long alkyl substituent.

Land and coworkers[218,219] have suggested that in alkaline methanol solutions of 2-NH_2-9,10-AQ substituted at the 4-position with NHMe, NH_2 or OH, pulse radiolysis results in more than one quinone being lost for each reducing radical introduced into the system. The radical ions from these anthraquinones had extinction coefficients approximately double the values for the monosubstituted anthrasemiquinone anions. They interpret these observations to indicate that the quinone molecules may be aggregated in solution.

The absorption and emission–fluorescence characteristics of camphoroquinone and the corresponding camphorsemiquinone radical anion ($CQ^{-\cdot}$) generated thermally with Na in ethanol have been determined. The parent quinone has $\lambda_{max} = 468$ nm while the $CQ^{-\cdot}$ species has $\lambda_{max} = 324$ nm. At high concentrations the radical appears to dimerize likely as the species $(Na^+Q^{-\cdot})_2$ and exhibits a strong absorption band at $\lambda_{max} = 266$ nm. The fluorescence wavelength bands for the three species CQ, $Q^{-\cdot}$ and $(Na^+Q^{-\cdot})_2$ are 459 nm, 390 nm and 290 nm respectively[212].

C. Redox Properties

Quinones are reduced to hydroquinones in two one-electron steps which can be described by the redox potentials; $E(Q/Q^{-\cdot})$ for reduction to the semiquinone and $E(Q^{-\cdot}/Q^{2-})$ for reduction to the hydroquinone. These quantities can be related by

$$E(Q^{-\cdot}/Q^{2-}) = 2E(Q/Q^{2-}) - E(Q/Q^{-\cdot}) \tag{58}$$

where $E(Q/Q^{2-})$ is the two-electron reduction potential of the quinone.

Values of $E(Q/Q^{-\cdot})$ in aprotic solvents such as DMF have been extensively studied and are well described in the first edition of this series[220] and also in Ref. 221, and since a chapter on electrochemistry of quinones (Chapter 12) is included in this edition we will not discuss these data here. However, the redox chemistry of semiquinones in aqueous systems is of substantial biological significance and we will therefore collate some of the information applicable to aqueous systems in this section. Measurements of redox potentials in aqueous solutions are complicated by dependence on the pH and by the relative instability of the semiquinone radicals except in basic media. When only a single ionization of the semiquinone is involved the value of $E(Q/Q^{-\cdot})$ depends on pH according to

$$E(Q/Q^{-\cdot}) = E(Q/Q^{-\cdot})_7 + 59\log\left(\frac{k_i + [H^+]}{k_i + 10^{-7}}\right) \tag{59}$$

where k_i is the ionization constant. This has been used to calculate redox potentials at pH 7 for a variety of quinones measured at higher pHs. Swallow[213] has collected and discussed values from several authors[68,69,222–224]. Polarographic half-wave potentials have been

found to be good approximations for equilibrium redox midpoint potentials since the electrochemical reduction of the quinones is usually reversible. The half-wave potentials have been qualitatively correlated with substituent and positional constants in Hammett equations[220].

From Table 7 it can be observed that methyl substitution in the *p*-benzoquinones decreases $E(Q/Q^{-\cdot})$ by about 85 mV. For the methoxy-substituted quinones a similar additive effect is not followed as was discussed (Section III.A). The values suggested to account for the observed redox changes in the methoxy-substituted compounds were $\Delta E = -101$ mV for a freely mobile methoxy group and $\Delta E = -41$ mV for a sterically hindered methoxy group[20]. A substituent effect of this magnitude is consistent with the standard midpoint potential for ubiquinone reported by Patel and Willson[225]. Swallow has estimated values of $E(Q/Q^{-\cdot})$ at pH 7 to be -230 ± 20 mV for ubiquinone and -130 ± 20 mV for plastoquinone[213]. These quinones can only be studied in aqueous media containing substantial concentrations of organic solutes.

TABLE 7. Reduction potentials of quinones in aqueous solutions

Compound	mV vs. NHE $E(Q/Q^{-\cdot})_7$	$E(Q/Q^{2-})_7$	$E(Q^{-\cdot}/Q^{2-})_7$
1,2-Benzoquinone	+210	+370	+530
1,4-Benzoquinone	+99	+286	+473
2-Methylbenzoquinone	+23	+230	+437
2,3-Dimethylbenzoquinone	−74	+175	+424
2,5-Dimethylbenzoquinone	−66	+180	+426
2,6-Dimethylbenzoquinone	−80	—	—
2,3,5-Trimethylbenzoquinone	−165	+114	+393
Duroquinone	−240	+57	+354
1,4-Naphthoquinone	—	+70	—
2-Methylnaphthoquinone	−203	−5	+193
2,3-Dimethylnaphthoquinone	−240	−70	—
Vitamin K_1^a	−170	−60	+220
Ubiquinone[a]	—	+90	—
1,4-Naphthoquinone-2-sulphonate	−60	+120	+300
9,10-Anthraquinone-2-sulphonate	−380	−228	−76
Anthraquinone-1,5-disulphonate	—	−170	—

[a] Values were measured in a solution containing isopropanol (5 M) and acetone (2 M). Otherwise solutions contained less than 1 M added solutes.

Steenken and Neta[222,226] have measured redox potentials for a number of biologically important phenols, catechols and hydroquinone derivatives. From measured values of $E(Q^{-\cdot}/Q^{2-})$ at pH 13.5 for these systems they have calculated the values at pH 7 (see Table 8). They noted that hydroquinone and catechol have similar potentials while resorcinol is much less readily oxidized, having a potential 350 mV more positive. Conversion of O^- to OMe, giving 4-methoxyphenol, for example, also raises the redox potential. Several biologically important catechols such as norepinephrine, L-dopa, 5-hydroxydopamine and L-epicatechin have redox potentials similar to catechol; adrenalone is, however, deactivated by a carbonyl group.

Relative electron affinities (EA) for a variety of quinones have been obtained by measuring gas-phase equilibrium constants for the electron transfer reactions using pulsed ion cyclotron resonance[227]. Similar additive substituent effects (i.e. of -1.7 kcal mol^{-1} for each methyl group) are noted for the methyl-1,4-benzoquinones. However, chloro

TABLE 8. One-electron redox potentials

Compound	$E(Q^{\cdot -}/Q^{2-})$ pH 7	mV vs. NHE pH 13.5
Resorcinol	810	385
4-Methoxyphenol	600	400
Catechol	530	43
HTCC[a]	480	192
Hydroquinone	459	23
Ascorbate	300	15
Durohydroquinone	—	−54
2-Methoxyhydroquinone	—	−85

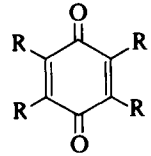
[a] HTCC = 2,2,5,7,8-pentamethylchroman-6-ol.

substituents do not affect EA linearly; an increase of 6.2 kcal mol^{-1} is noted for the introduction of the first chloro group while only 5.25 kcal mol^{-1} is observed when a second *o*- or *p*-substituent is introduced.

$$Q^- + R \rightarrow R^- + Q \tag{60}$$

Comparisons of gas-phase electron affinities with those solution values calculated from polarographic half-wave potentials ($E_{1/2}$) and charge transfer spectroscopic measurements (E_{CT}) for quinones, nitrobenzenes and benzophenones showed reasonably good agreement[228]. The solution values were higher for low electron affinity compounds and lower for those of high EA. This likely reflects the changing solvation energy of the anion with changing substituent charge delocalization.

The half-wave oxidation and reduction potentials of tetrakis(dimethylamino)-*p*-benzoquinone were measured in DMF[149]. The strongly electron-donating substituents shifted the redox potentials substantially as shown below. This reflects the much lower ionization energy of the amino-containing quinone which allowed facile formation of its stable radical cation.



	$E^{ox}_{1/2}$	$E^{red}_{1/2}$
R = H	+2.85 V	−0.40 V
R = NMe_2	+0.25 V	−1.07 V

VI. OTHER SIGNIFICANT CHEMICAL AND BIOLOGICAL ASPECTS OF SEMIQUINONES

A. Semiquinones in Micelles

Micelles are dynamic associations of large numbers of surfactant molecules. They have been extensively studied both because their properties mimic many of those of natural biological membranes and also as effective cages for chemical reactions. The effects of external magnetic fields on primary photochemical processes have been studied using laser flash spectroscopy and time-resolved ESR spectroscopy. A recent review on magnetic field effects in micelles is available[229]. In homogeneous fluids these magnetic field effects are rather small due to the rapidity with which initially generated radicals escape from the primary solvent cage, however, the increased lifetime of the radical pair in the micelle greatly enhances the magnitude of the effects.

Generally micelles such as those consisting of sodium dodecyl sulphate (SDS) act as good H-donors in reactions with photoexcited carbonyl compounds such as benzophenone and the quinones. The reactions of a quinone in a micelle can be written as follows (equations 61–65).

$$Q \xrightarrow{h\nu} {}^1Q^* \xrightarrow{ISC} {}^3Q^* \tag{61}$$

$${}^3Q + RH \rightarrow {}^3(QH^{\cdot}\,R) \tag{62}$$

$${}^3(QH^{\cdot}\,R) \rightarrow {}^1(QH^{\cdot}\,R) \tag{63}$$

$${}^{1,3}(QH^{\cdot}\,R) \rightarrow \dot{Q}H + R^{\cdot} \tag{64}$$

$${}^1(QH^{\cdot}\,R) \rightarrow \text{products} \tag{65}$$

$$\dot{Q}H \rightleftharpoons Q^{-\cdot} + H^+ \tag{66}$$

Laser irradiation of the quinone promotes it to its first excited singlet state from whence it rapidly intersystem crosses to the excited triplet state. Abstraction of a hydrogen from a detergent molecule by the triplet quinone forms the triplet radical pair (reaction 62). The mixing of the singlet and triplet spin states of the radical pair is influenced by the external magnetic field; the intersystem crossing rate may also be perturbed. The radicals escaping from the initial pair are assumed not to react unless they are in the singlet state. Some dissociation of the neutral semiquinone to the anion is to be expected since the pK_a values for the semiquinones are fairly acidic (~ 4–5). Disproportionation of two semiquinone radicals to form quinone and hydroquinone is disfavoured relative to the possibility of this reaction in solution, since the semiquinone radicals are isolated in the micellar matrix.

In general for the quinones the radical pair mechanism provides a reasonable explanation for the magnetic field effects in the micelles at low magnetic fields. Thus it has been found that for the photolysis of quinones in micelles the effect of increasing the magnetic field is to decrease the recombination rate and thus to increase the yield of escaping radicals[230–233]. These effects can be quite dramatic; Sakaguchi and Hayashi have noted[230] that for NQ (or 2-methyl-NQ) the increase in yield of escaping radicals at 1.34 $\times 10^4$ G compared to no external magnetic field is enhanced by a factor of 2.4 (3.1). The magnetic field effects for these quinones at fields below 0.1×10^4 G have been found to be much greater in magnitude than for benzophenone derivatives[230].

It was necessary, however, to invoke an alternative mechanism involving the relaxation of the odd electrons in the radical pairs to explain the magnetic field effects at higher fields[234, 235]. This mechanism has also been applied in other systems[236].

For NQ and menadione the magnetic field effects were observed to behave as follows:

(1) At zero applied magnetic field the radical pairs decayed exponentially at a rate of $4 \times 10^6\ s^{-1}$.

(2) At intermediate fields a biexponential decay was noted with one rate constant decreasing with increasing magnetic field. This decrease saturated at an applied field of 1.34×10^4 G at which point the radical pair decay rate was $6 \times 10^5\ s^{-1}$.

(3) The yields of escaping radicals increased with increasing magnetic field strengths[230].

The effects of the external magnetic field on ISC rates were described for the anthraquinones[231] and benzoquinones[232]; the triplet–singlet ISC rates decreased with increasing magnetic field.

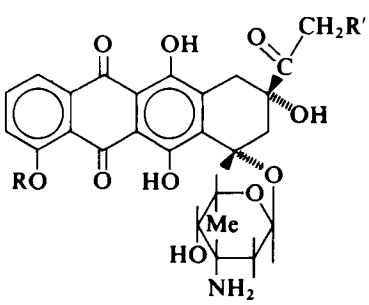
It is difficult to determine the nature of the alkyl radical R generated by hydrogen abstraction from the detergent. In a CIDEP study it was noted that the time-resolved ESR spectrum of $\dot{R}$ could be analysed in terms of four hydrogens, indicating that abstraction had occurred somewhere other than the terminal regions of the SDS chain. In this study

the fast hydrogen abstraction by ^{3}NQ (much faster than that of ^{3}BP) resulted in both the NQH and Ṙ being observed initially in the emissive mode consistent with the TM of CIDEP polarization. Subsequent E/A RPM polarization was superimposed as the radical pairs evolved[237–239]. An attempt to identify the nature of the alkyl radical Ṙ was made by using the spin trap phenyl-*t*-butylnitrone (PBN). The resulting T-N(R)O adduct showed a magnetic field dependence; also the concentration of the adduct which is due to escaped Ṙ increased with increasing magnetic field[240].

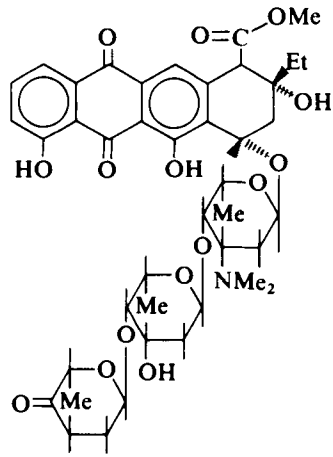
The influence of paramagnetic ions, the lanthanides, on the course of photoreactions of quinones in micelles has also been investigated. Addition of these paramagnetic species is, in essence, the application of an internal magnetic field. Sakaguchi and Hayashi[241] have shown that the decay of the NQH·R pairs depends on the number of unpaired electron spins associated with the micelle. This effect is observed only in the presence of an external magnetic field. The magnitude of the effect decreased in the order $Gd^{3+} > Sm^{3+} > Dy^{3+} > Nd^{3+} > Ho^{3+} > Er^{3+} > La^{3+} > Lu^{3+}$. The increased decay rate is presumed to be effected by increased relaxation of the radical pair electron spins due to tumbling of the paramagnetic ions around the micelle. A similar phenomenon was noted for benzyl radical pairs in the photolysis of dibenzyl ketone when lanthanide ions were added[242].

B. Antitumour Antibiotics

Several of the anthraquinone antibiotics are effective antitumour agents. Some of the best known are adriamycin (**50**), daunomycin (**51**), carminomycin (**52**) and aclacinomycin A (**53**). Although the structures of these compounds are quite similar their biological



(**50**) R = Me, R′ = OH
(**51**) R = Me, R′ = H
(**52**) R = R′ = H

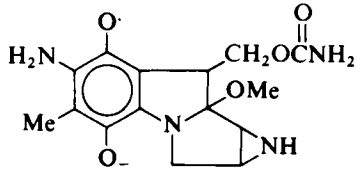


(**53**)

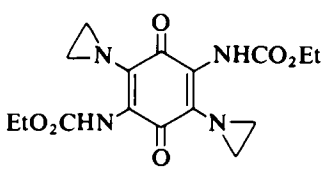
activities are diverse. Their pharmacological modes of action appear to be associated with suppression of nucleic acid and to some extent protein biosynthesis. This results in chromosomal defects in dividing cells. ESR studies of a spin-labelled derivative of adriamycin show that it forms a complex with DNA by intercalation between the purine and pyrimidine bases (Ref. 243 and references therein).

An alternative view of the molecular mechanisms of action of these compounds involves the formation of free radical intermediates. The possibility of either oxidation of the

hydroquinone moiety or reduction of the quinone may provide some selectivity in their biological effects (i.e. antitumour activity relative to toxicity). The radicals formed by reduction of the anthracycline antibiotics have been studied by ESR[243-245] and indeed at physiological pH spontaneous formation of semiquinone radicals has been observed. A variety of enzymes are also known to catalyse the formation of such semiquinone free radicals. Other quinone-containing antibiotics such as mitomycin C, carboquinone and bruneomycin are polyfunctional and may act as alkylating or cross-linking agents towards DNA in addition to their capacity to form semiquinone radicals. Indeed activation of the anthracyclines by reduction may foster covalent attachment to biomolecules. Reduction of mitomycin C in DMSO with sodium tetrahydroborate gives a 36 line ESR spectrum of a stable semiquinone radical (**54**) having $a_{NH_2} = 2.3$ G, $a_{N\,ring} = 1.7$ G, $a_H^{Me} = 1.0$ G, $a_H^{CH_2} = 0.65$ G and $g = 2.0046$[246]; the semiquinone radical is also generated in microsomes. The alkylating agent AZQ (**55**) can also be reduced to semiquinone radicals in microsomes[247].



(**54**)



(**55**)

Several quinones which are model compounds for the anthracycline antibiotics have been studied; their semiquinone radicals are stable in basic media in the absence of oxygen and give well resolved ESR spectra[244, 248].

There is considerable evidence that reactive oxygen species: superoxide, peroxide and hydroxyl radical are generated in vivo as a result of the metabolism or pharmacological activity of the anthracycline antibiotics, possibly as shown in reactions 67–70. Superoxide ion has been demonstrated by spin trapping in microsomal incubations of these drugs[249].

$$Q^{-\cdot} + O_2 \rightarrow Q + O_2^{-\cdot} \tag{67}$$

$$2O_2^{-\cdot} + 2H^+ \xrightarrow{SOD} H_2O_2 + O_2 \tag{68}$$

$$2H_2O_2 \xrightarrow{catalase} 2H_2O + O_2 \tag{69}$$

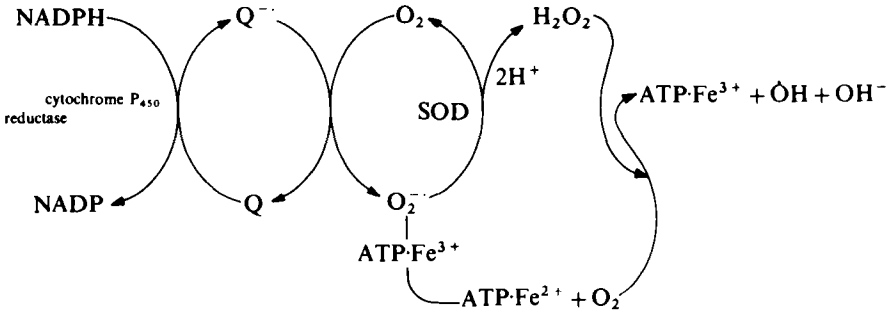
$$Q^{-\cdot} + H_2O_2 \rightarrow Q + OH^- + OH^{\cdot} \tag{70}$$

Superoxide and peroxide have been established as intermediates in the action of anthracyclines on DNA by their selective removal by the enzymes superoxide dismutase (SOD) and catalase respectively[250]. The cardiotoxicity of these antibiotics may be related to the reduced concentration of these cell protective enzymes as well as glutathione peroxidase in the heart relative to other organs[251, 252].

A scheme for intracellular enzymatic reductive activation of the anthraquinone antibiotics and subsequent generation of active oxygen species is shown below[243, 249].

C. Photosynthesis

Quinones also play important roles in photosynthesis and respiratory electron transport chains; their activities in these systems involve the intermediacy of semiquinone radicals. Although ubiquinone and the plastoquinones are the biologically important quinones



involved, chemical investigation of such biological systems has relied heavily on the use of model compounds in which simpler quinones are frequently incorporated. The literature on the chemical nature of both bacterial and plant photosynthesis is vast and complex and will not be discussed in detail here. Recent reviews are available[253–255]. Contributions of CIDMP to determination of the nature of the primary radical pairs involved in photosynthesis and the routes of subsequent electron transfer to other components of the reaction centre also have been discussed (Refs 254, 256–264, and references therein).

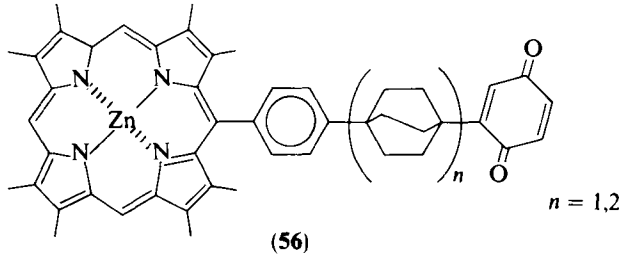
The primary event in photosynthesis involves oxidation of the lowest excited singlet state of a chlorophyll electron donor by a nearby electron acceptor. The distance between the two is restricted by a surrounding reaction centre protein. The initial reaction steps can be written as:

$$PIX \rightarrow P^*IX \rightarrow P^+I^-X \rightarrow P^+IX^- \rightarrow \ldots\ldots \quad (71)$$

where X is the first stable electron acceptor and P* is the first excited singlet state of the primary donor P. The primary photoreactants arise from an excited singlet state[265]. The lifetime of the initial radical pairs is approximately 200 ps but this can be lengthened to $\sim$ 15 ns by prereducing or removing the ubiquinone or menaquinone component X. The initial radical pair then decays by recombination of charges and the yields and reaction rates of the possible recombination processes can be affected by external applied magnetic fields (Ref. 266 and references therein).

Many model systems have been synthesized to study the intramolecular electron transfer processes between donors and acceptors fixed at certain distances and orientations relative to one another. Most often the donors are chlorophyll or porphyrin derivatives and the acceptors quinones (Refs 267–271 and references therein). For example, the photoinitiated electron transfer from tetratolylporphyrin to benzoquinone in a model compound linking these two moieties by a diester bridge was found to be most efficient when the bridge contained three methylene groups. A folded conformation minimizing the donor–acceptor separation was proposed for this structure[270]. A comparison of electron transfer rates in mesophenyloctaalkylporphyrins coupled to quinone via one or two bicyclo[2.2.2]octyl spacers (**56**) has been reported[272]. The effect of the second spacer in **56** is to decrease the electron transfer rate by a factor of 500–1600 depending on the solvent. In general electron transfer rates have been found to decrease with increasing solvent polarity in such porphyrin–quinone (P–Q) models.

Wasielewski and coworkers[270] have correlated rate constants for the forward electron transfer and recombination reactions with the free energies for the reactions using rigidly coupled P–Q complexes. The use of such complexes with constrained geometries can eliminate the problem of contributions from a variety of conformational isomers and provide better distance control between the donor and acceptor sites in the intramolecular electron transfer reactions.



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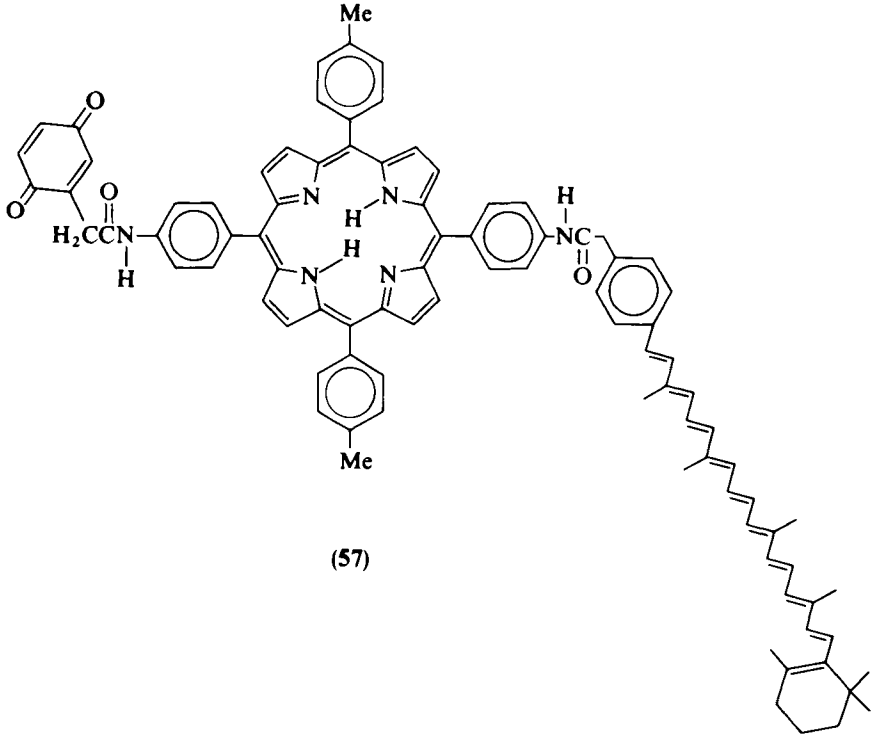
Further charge separation and sequential charge transfer can be studied in model compounds such as **57** in which a caroteneoid portion is linked to the porphyrin–quinone moiety[273]. Irradiation of this compound results in rapid electron transfer to $C\text{–}P^{+}\text{–}Q^{-}$ and then formation of $C^{+}\text{–}P\text{–}Q^{-}$, the charge separated intermediate. These reactions are extremely fast, occurring in less than 100 ps. The insertion of the neutral porphyrin molecule prolongs the lifetime to several μs and increases the quantum yield of the charged intermediate $C^{+}\text{–}P\text{–}Q^{-}$.



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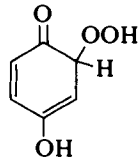
D. Interactions of Quinones with Active Oxygen Species

The interactions of quinones with oxygen and various reactive oxygen species such as $\dot{O}H$, $O_2^{-\cdot}$ and H_2O_2 may have considerable biological significance in a variety of systems. The toxicity of quinones has been suggested to be mediated by the formation of their semiquinone radicals and the subsequent production of reactive oxygen species[274, 275].

For example, menadione, which causes both DNA and cell membrane damage, is activated in hepatocytes to the semiquinone radical which can then be reoxidized to the quinone producing superoxide, peroxide and hydroxyl radical[276]. The neurotoxicity of 6-aminodopamine and 6-hydroxydopamine have been correlated with the reactions of their respective semiquinone or semiquinone–imine radicals[277] which produce activated oxygen species.

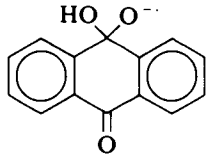
In addition to being produced by reactions of quinones with oxygen in biological systems, hydroxide ion, superoxide ion and singlet oxygen also can react with quinones and hydroquinones in a variety of ways. Superoxide ion has been suggested to react with catechols and hydroquinones first by protonation to form HO_2 followed by subsequent reactions which may involve charge transfer to form the semiquinone radical[278]. Pulse radiolysis of aqueous hydroquinones has been suggested to involve formation of the trihydroxycyclohexadienyl radical ($H_2\dot{Q}$–OH) which decays unimolecularly to the semiquinone radical ($H\dot{Q}$)[279]. An alternative mechanism for disappearance of $H_2\dot{Q}$–OH involving a peroxy intermediate such as **58** has also been proposed to occur[279,280]. Hydroperoxides have also been identified as intermediates in reactions of vitamin E and vitamin K_1, especially in reactions with $^1O_2$[281–284]. It has been suggested that



(58)

hydroperoxides of vitamin K_1 may be involved in the carboxylation of glutamic acid residues of blood proteins. Wilson and Tharp have shown that hydroperoxides of vitamin K_1 models can be readily formed from molecular oxygen and that subsequent ionic decomposition of these peroxides leads to active acylating species[285].

Reaction of hydroxide anion radical ($OH^{-\cdot}$) with anthraquinones in aprotic media has been shown to result in significant yields of the radicals ($AQ^{-\cdot}$) and the dioxygen species (H_2O_2, $^1O_2$ and $O_2^{-\cdot}$) through the initial formation of the addition complex [$AQ(OH)^{-\cdot}$] (**59**) which can react with additional AQ to give the semiquinone and the radical [$A\dot{Q}(OH)$][286]. Reactions such as these may be important in biomembranes.

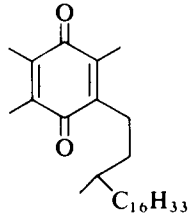


(59)

An ESR study of oxidation of a variety of catechols and naphthalenediols with H_2O_2 has shown that the oxidation occurs to give preferential introduction of the new oxygen centre *ortho* rather than *para* to the initial hydroxyl groups[287].

Although not itself a quinone vitamin E is known to react with quinones as well as a variety of biologically significant antioxidants such as vitamin C and glutathione. Although it functions primarily as an antioxidant, protecting lipids from peroxidation by scavenging

peroxyl and alkoxyl radicals, $^1O_2$, and superoxide anion radical, vitamin E also has a variety of less well established roles. Its oxygen scavenging properties may be involved in its ability to protect cardiac tissue from the toxicity of the antitumour quinones adriamycin and daunomycin[275]. Vitamin E can react with $^1O_2$ either by reaction to form hydroperoxydienones which subsequently hydrolyse to stable products, or by a physical quenching process (Ref. 288 and references therein). Gorman and coworkers have recently suggested that reversible formation of an exciplex intermediate is involved in this quenching[289]. Photolysis of vitamin E in the presence of $^1O_2$ has been shown to produce, among other species, the α-tocopherylquinone **60**[281]. This quinone may also have



(60)

considerable biological significance since it has been involved in the reactions of vitamin E with hepatotoxins such as CCl_4, and in the protection of lung tissue from airborne pollutants (Ref. 288 and references therein). The ESR parameters for the semiquinone radical derived from **60** have been described[21].

Photolysis of vitamin E in the presence of quinones such as benzoquinone results in its rapid oxidation to the chromanoxyl radical E . Time-resolved CIDEP experiments show total emissive polarization by the TM for this radical indicating that the oxidant is the triplet quinone and that the reaction is very fast[288, 290]. However, quinones such as menadione and vitamin K_1 which have lower redox potentials do not photooxidize vitamin E in alcohol solutions. Steenken has suggested a value of 0.48 V for the redox potential of vitamin E, similar to that measured for the model compound 2,2,5,7,8-pentamethylchroman-6-ol[226]. The presence of a variety of different quinones in lipophilic environments in which vitamin E is biologically active suggests that further investigation of their interactions might be productive.

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CHAPTER 17

Heterocyclic quinones

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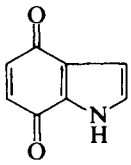
I. INTRODUCTION

This survey of the chemistry of heterocyclic quinones gives consideration to those compounds which have a quinonoid nucleus fused to a heterocycle. Thus, compounds such as **1** and **2** are included whereas **3** is not within the scope of this chapter except as an intermediate from which a heterocyclic quinone might be formed. A subgroup of



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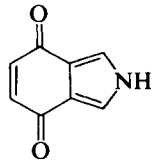

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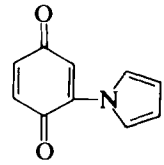
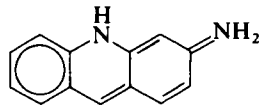


(3)

compounds in which the heterocycle is fused to a quinonoid nucleus and includes an atom of the heterocycle as part of the quinonoid system, e.g. **4**, have also been excluded from



(4)

consideration, except where they occur as intermediates or as the reaction products of a heterocyclic quinone as defined above. Compounds having a 1,2- or 1,4-dicarbonyl system in an unsaturated heterocycle as part of their structure have also been excluded from consideration since they do not display properties especially recognizable as quinonoid. On the other hand consideration is given to the chemistry of some representatives of quinone imines and quinone methides (see Section IV) and diazaquinones (see Section V).

Emphasis has been placed in this survey on recent developments in the field of heterocyclic quinone chemistry, and there have been many. The information which follows has been distilled from consultation of in excess of 450 references, the vast majority of which are later than 1970. Much of the stimulation for work in this area has come from the

discovery of naturally occurring heterocyclic quinones having potentially important biological properties. In one case, that of isoindole, the first representative of the heterocycle found in nature proved to be a quinone derivative. The occurrence of these compounds has encouraged synthetic work designed to produce the heterocyclic quinone system in an efficient manner in order to effect a total synthesis of the naturally occurring quinone or to produce a series of analogues of the bioactive compound for subsequent structure-activity analysis. In those cases where some understanding of the biochemical mechanism of action of a quinone has been established there has often been a surge of synthetic activity. This is well exemplified in the case of the antitumour antibiotic, mitomycin, and the idea of bioreductive activation of certain quinones (see Section III.D). The indole, quinoline, benzofuran and benzopyran quinones have been the most extensively investigated while very little work has been done on, for instance, cinnoline, phthalazine or benzoxazole quinones. In general, about half the recent work on heterocyclic quinones, as judged by the number of references, has been devoted to those containing one or more nitrogen atoms.

This survey of the preparations and properties of heterocyclic quinones is illustrative rather than comprehensive and is arranged so that the usefulness of reagents and reactions are considered in sequence rather than the alternative arrangement of giving consideration to each type of heterocyclic quinone system in sequence. We have endeavoured to take illustrative examples from a wide range of heterocyclic quinone types and to provide recent references so that we hope the reader will be able to find a useful lead reference to a particular quinonoid system of interest. The discussion here is mainly concerned with recent work and this does mean that earlier work may be neglected. A small number of reviews of earlier work is available and of particular interest at this point are the more widely based reviews of Baxter and Davis[1] who concentrate their attention on synthetic routes but also make mention of some applications of heterocyclic quinones and give references to earlier reviews; of Horspool[2] who describes the synthesis and thermal reactions of *ortho*-quinones including some heterocyclic quinones, though the emphasis is on carbocyclic systems; and of Sartori[3] who describes the heterocyclic quinones obtainable from 2,3-dichloro-1,4-naphthoquinone. It is worth mentioning here that some of the work quoted in Sartori's review has been shown recently[4] to contain erroneous structural assignments. In addition, monographs on particular ring systems may contain mention of the quinonoid derivatives.

II. PREPARATIVE ROUTES

A. Oxidation of Benzoheteroarenes

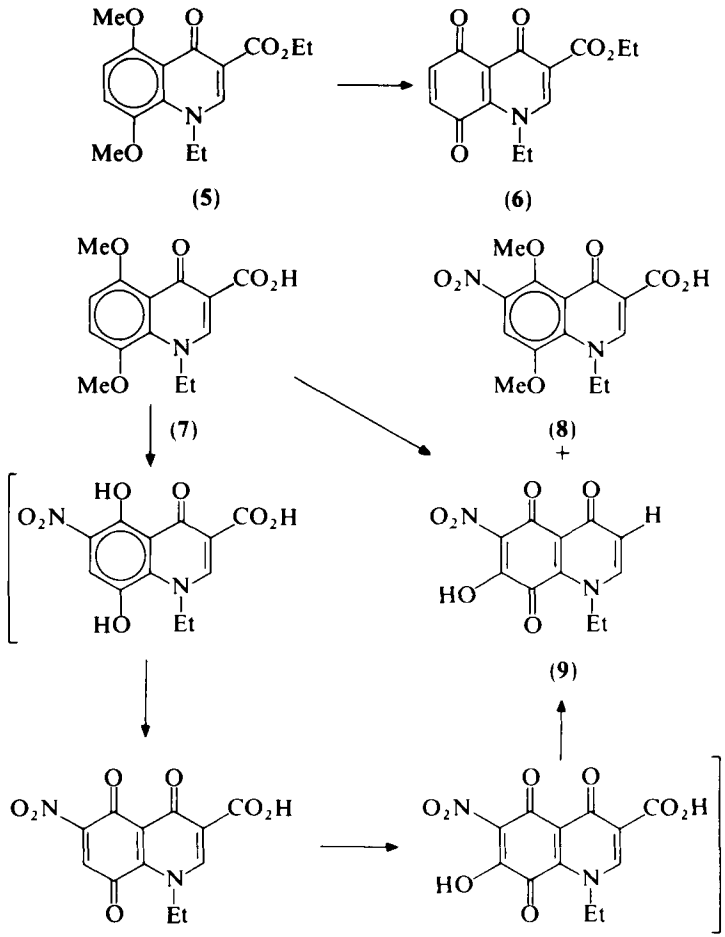
1. General

It is probably true to say that most preparations of heterocyclic quinones involve the oxidation of the suitably substituted carbocycle of a benzoheteroarene. The reagent of choice depends upon the ease of oxidation and stability of the particular heterocycle under investigation, but the classical reagents such as dichromate, Fremy's salt (potassium nitrosodisulphonate), and nitric acid still find wide application. The more recently introduced combination of silver(II) oxide and nitric acid and ceric ammonium nitrate (CAN) are finding increasing applications. Interestingly, the use of the supported reagent silver carbonate does not seem to have been reported in the heterocyclic quinone field though it is an efficient reagent for the formation of carbocyclic quinones[5] and has the virtue of ease of use. The uses of the frequently employed oxidizing agents are described briefly.

2. *Oxidants and their uses*

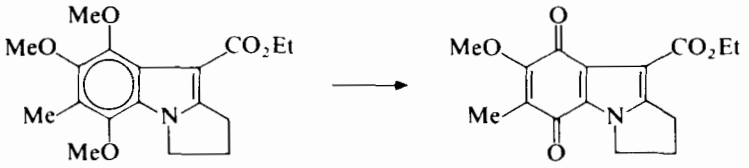
a. Dichromate This vigorous and strongly acidic reagent has obvious limitations on its usefulness but it has been found to be effective for the oxidation of 5,8-dihydroxy-[6] and 5,8-diamino-quinolines[7], in the latter case even in the presence of a 6-methoxyl group. Similar success was achieved with 5,7-diaminothiazole[8] but, on the other hand, strong nitric acid was found to be more useful than dichromate for the oxidation of a 8-hydroxy-5-methoxycoumarin[9].

b. Nitric acid or nitrous acid Nitric acid has been used extensively to oxidize coumarins (here it seems to be the reagent of choice[9]), quinolines, isoquinolines, benzimidazoles, benzothiazoles and benzothiophenes to *p*-quinones. The reagent can also produce *o*-quinones from the corresponding dimethoxy compounds[10]. Nitration of the benzene system is a possible complicating factor in these reactions when several electron-donating substituents are present. The oxidation of the quinoline ester **5** to **6** proceeds smoothly at room temperature in the presence of ceric ammonium nitrate, but at 0°C in the presence of nitric acid the hydroxynitroquinolone quinone **9** is the major product from the acid **7** together with **8** and a small quantity of a monodemethylated product[11]. However, 4,7-



dihydroxyindoles carrying an electron-withdrawing 3-substituent have been oxidized to the corresponding quinone with strong nitric acid[12].

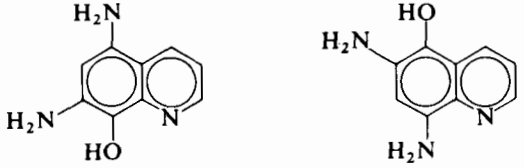
Nitrous acid has been used to obtain the mitosene derivative **11** by oxidative demethylation of the 4,5,7-trimethoxyindole derivative **10**. The *o*-quinone **12** was also produced in low yield[13]. The 2,5,6-benzimidazolintrione **13** was first prepared by the nitrous acid oxidation of 5,6-dimethoxy-2-benzimidazolinone[14].



(10) **(11)**

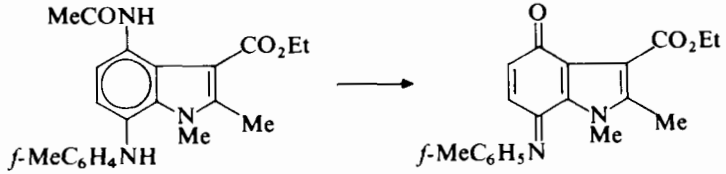
(13) **(12)**

c. Dioxygen (air) Air has been used to produce heterocyclic quinones from suitable precursors fairly infrequently but both **14** and **15** have been oxidized to *p*-quinones by the action of air and, in each case, the amino group *ortho* to a hydroxyl group was replaced by a hydroxyl group either in the oxidation process or the workup procedure. However, the subtle variation in structure between **14** and **15** caused major changes in the conditions



(14) **(15)**

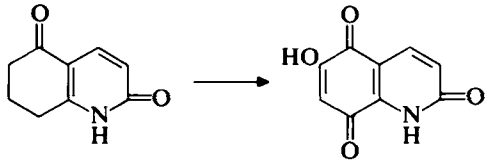
necessary for a successful oxidation: **14** required basic conditions whereas **15** yielded the quinone smoothly only under acidic conditions[15]. Copper(II) compounds were used by Russian workers[16] to promote the oxidation of 6-hydroxybenzothiazole to the corresponding 6,7-quinone and, in part of their extensive investigation of heterocyclic quinone imines, copper(II) acetate was used[17] in the oxidation of **16** to **17**. It is thought that 5,6-



(16) **(17)**

dihydroxyindoles are immediate precursors of the skin pigment, melanin, and this idea has stimulated a number of investigations of the autoxidation and oxidation of these compounds. This work has been reviewed[18].

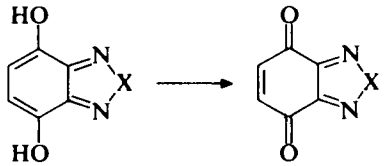
The tetrahydroquinoline-2,5-dione (**18**) has been oxidized with oxygen in the presence of potassium *tert*-butoxide to the hydroxyquinolinetrione (**19**); a similar reaction occurs in the naphthalene series[19].



(18) **(19)**

d. Fremy's salt (*potassium nitrosodisulphonate*) Probably the most widely used oxidizing agent in this field. For instance, 4-,5- and 7-hydroxyindoles and 4-aminoindoles have been converted into the corresponding 4,7-quinones. In the case of 7-hydroxy-2,3-diphenylindole, both the 4,7- and 6,7-quinone were formed but the *N*-methyl derivative gave only the 6,7-quinone[20]. The efficiency of the oxidation of amines may be markedly affected by the pH of the reaction mixture. The oxidation of 5-amino-6-methoxyquinazoline[21] or 6-methoxy-8-hydroxyquinolines[22] gave the corresponding 5,8-quinones. Interesting possibilities for the formation of isomeric quinones arise when the quinone precursor contains both 1,4- and 1,2-related oxidizable substituents in the carbocycle. There seems to have been no systematic study of the effects of either the presence of various groups or of the choice of oxidizing agents on the type of quinone formed in any heterocyclic system.

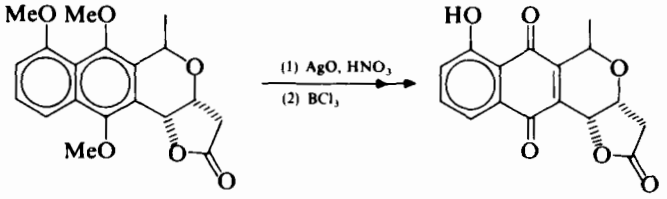
e. Silver oxides Silver(I) oxide has been used to convert 1,4-dihydroxy compounds into the *p*-quinones: for instance, the conversion of **20** to **21**[22]. The introduction of nitric acid



X = S or CH=CH

(20) **(21)**

and silver(II) oxide as a combination of reagents causing ether splitting and oxidation in a one-pot process was an important development[23]. The method has found increasing application in the area of heterocyclic chemistry and is illustrated here by the penultimate step in the synthesis[24] of kalafungin (**22**), a member of a growing number of pyranonaphthoquinone antibiotics which can be considered as derivatives of juglone. Kalafungin is the first example that has been mentioned here of a heterocyclic quinone where the heteroatom is β to the quinonoid nucleus and the heterocyclic moiety is not an aromatic nucleus. A similar oxidation step was also used in the synthesis of (+)-deoxygriseusin B, the characterization of which led to the revision of an earlier structure for (−)-griseusin B. The revised structure is **23**[25].



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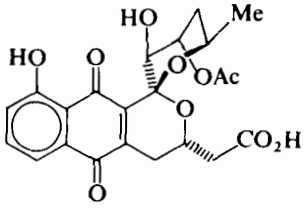
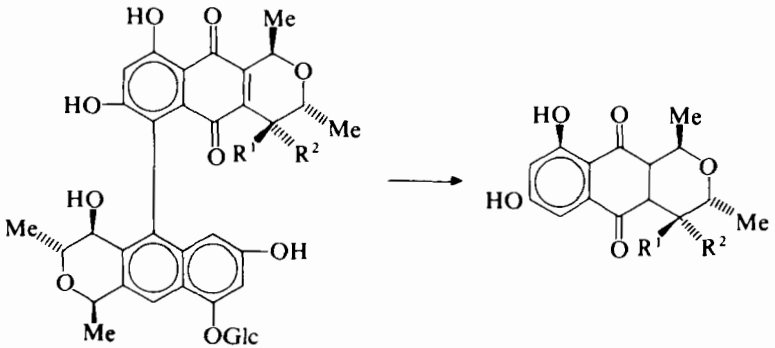


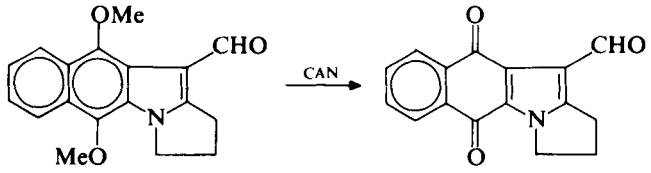
(23)

f. Ceric ammonium nitrate (CAN) This is another reagent which is useful for the direct conversion of 1,4-dimethoxyarenes into their corresponding quinones. The reagent has been employed extensively in heterocyclic quinone synthesis in the naphthopyran systems similar to those just described. Investigations of synthetic routes to the reduction products **25**, **27** and **29** from the β-pyranonaphthoquinone aphid pigments protoaphin *fb* (**24**), protoaphin *sl* (**26**) and deoxyprotoaphin (**28**) have shown that silver(II) oxide is a more useful oxidant than CAN when the naphthalene nucleus carries one or more methoxyl groups in addition to those oxidized in quinone formation[26]. In other cases where the nucleus is more stable to oxidation, for instance quinoline and benzimidazole, CAN has proved to be useful for the conversion of 1,4-dihydroxy derivatives to the corresponding quinones when other reagents have proved less effective[27]. The reagent is useful in the indole series provided that steps are taken to delocalize the nitrogen lone pair of electrons



(24)	$R^1 = OH, R^2 = H$	**(25)**
(26)	$R^1 = H\ R^2 = OH$	**(27)**
(28)	$R^1 = R^2 = H$	**(29)**

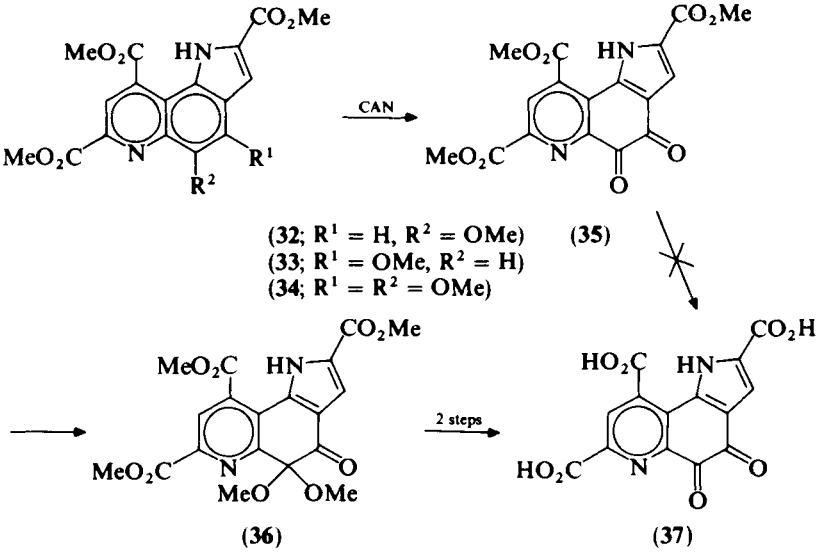
other than into the aromatic system prior to the attempt at the oxidation step. In this way the aldehyde **30**, where the carbonyl function is removing electrons from the pyrrole nucleus, was successfully oxidized to the quinone **31** in high yield[28]. A possible



(30) **(31)**

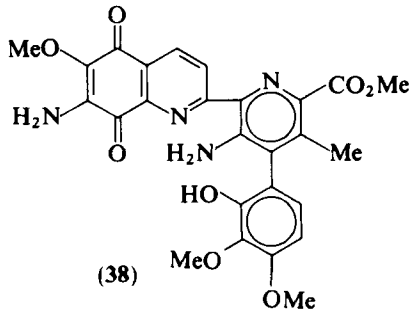
complicating factor when the 1,4-dimethoxyarene nucleus has an unsubstituted position is the formation of a nitro derivative rather than, or in addition to, quinone formation. The efficiency of the oxidation with CAN may be increased by the addition of pyridine-2,6-dicarboxylic acid *N*-oxide to the reaction mixture and this procedure has been used in the preparation of a range of quinoline- and isoquinoline-5,8-quinones from the corresponding dimethyl ethers[29].

CAN will also oxidize monomethoxy compounds having an unsubstituted *vic* position to the *o*-quinone in certain favourable cases. An interesting example here is the formation of the *o*-quinone **35** as an intermediate[30] in the synthesis of the unusual coenzyme **37**, which is used by bacteria such as *Methylophilus methylotrophus* in the oxidation of methanol. The *o*-quinone (**35**) formed smoothly from the monomethoxy compound (**32**), but hydrolysis of the three ester functions could not be brought about to produce the coenzyme, methoxatin (**37**), in one step. It was necessary to form the intermediate ketal (**36**) in order to allow efficient hydrolysis of the ester functions under basic conditions and then this product yielded **37** upon acidification. Interestingly, the isomeric monomethoxy compound **33** failed to react with CAN[31] and the dimethoxy compound **34** was conveniently oxidized with silver(II) oxide and nitric acid[32].

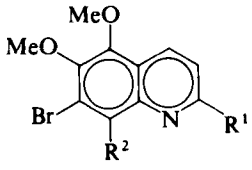


(36) **(37)**

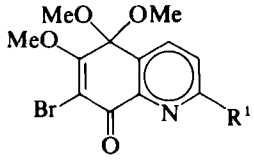
g. Periodate Sodium metaperiodate has been used in the quinoline series for the oxidation of 6-hydroxyquinolines to quinoline-5,6-quinones[33] and for the formation of 5,8-quinones from highly substituted quinolines. Much of this work has been directed towards the synthesis of the antitumour antibiotic, streptonigrin (**38**), and related compounds. The 8-hydroxy-5-methoxyquinoline (**39**) was oxidized by periodate to the ketal **41** which yielded the quinone **42** on acidification[10]. In the case of the corresponding amine **40**, oxidation with either periodate or CAN yielded both the *p*-quinone **42** and the *o*-quinone **43**[10]. Reports of attempts to use periodate in the formation of heterocyclic quinones are limited in number and types of heterocycle, and it does seem that its potential usefulness in this type of reaction may have been neglected.



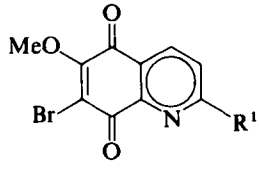
(**38**)



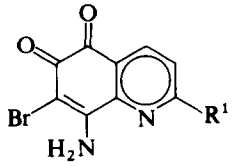
(**39**; $R^2 = OH$)
(**40**; $R^2 = NH_2$)



(**41**)



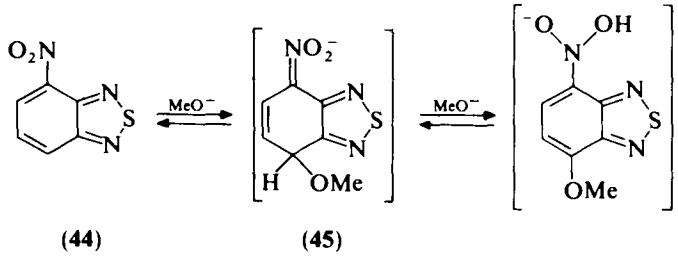
(**42**)



R^1 = substituted 2-pyridyl

(**43**)

h. Hydroxide or alkoxide ions The action of alkali upon certain nitrohetero aromatic compounds may lead to quinones. The formation of the quinone monoxime (**47**) by the action of sodium methoxide in methanol on 4-nitrobenzothiadiazole (**44**) has been explained in terms of the initial formation of the Meisenheimer complex (**45**) and the intermediacy of the oximinoketal (**46**)[34]. In a related reaction[35], the action of hydroxide ion upon 5-nitro-1,10-phenanthroline (**48**) yielded the oximino-*o*-quinone (**50**) by attack of hydroxide ion at the 6-position, formation of the tautomeric arylhydroxylamine **49** and elimination of a molecule of water.



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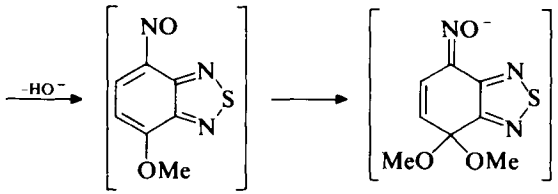

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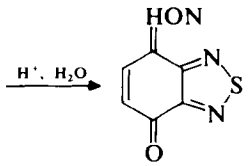

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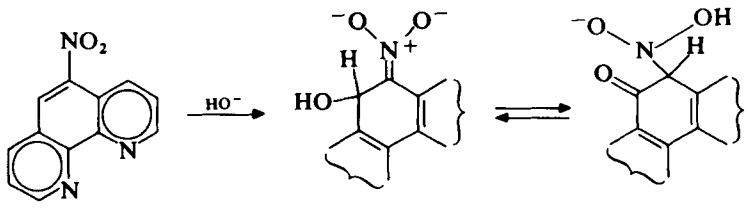
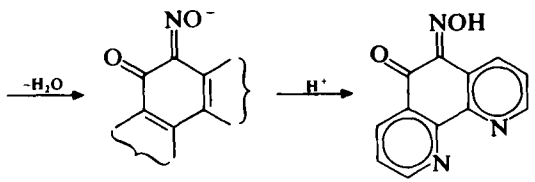


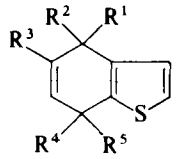
(48) (49)



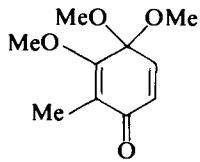
(50)

i. Miscellaneous methods Oxidizing agents which have been used rarely for the oxidation of hydroxyquinolines to the corresponding quinones include lead tetraacetate[36] and benzoyl *tert*-butyl nitroxide[31]; the latter was employed to provide the *o*-quinone, methoxatin (**37**), from a monohydroxy precursor. Oxidation of 8-hydroxy-5,6-dimethoxyquinoline with bromine yielded, perhaps surprisingly, the non-brominated 6-methoxyquinoline 5,8-quinone as the initial isolable product[10]. The same workers have used nitronium tetrafluoroborate to obtain a 5,6-quinone from a 2-substituted 8-acetamido-5,6-dimethoxyquinoline. Nitrosation at the *o*-position to a hydroxyl group has provided the mono-oxime of an *o*-quinone[37].

An excellent method for the formation of quinones from 4-methoxybenzothiophenes has been shown to be electrochemical anodic oxidation at a platinum electrode and at 65°C[38]. Under these conditions the bis-ketal **51** was formed in high yield and this was readily hydrolysed to the quinone **52** under acidic conditions. Similarly, 5- or 6-substituted derivatives of **51** were obtained from the corresponding substituted 4-methoxythiophenes



(**51**; $R^1 = R^2 = R^4 = R^5 = OMe$, $R^3 = H$)
(**52**; $R^1R^2 = O$, $R^3 = H$, $R^4R^5 = O$)
(**53**; $R^1 = R^2 = R^4 = R^5 = OMe$, $R^3 \neq H$)
(**54**; $R^1 = R^2 = OMe$, $R^3 \neq H$, $R^4R^5 = O$)



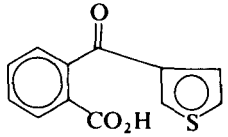
(**55**)

and yielded the quinones upon hydrolysis. Mild hydrolysis of the 5-substituted bis-ketals **53** produced the mono-ketal **54**, whereas under the same mild conditions hydrolysis of **51** afforded the two isomeric mono-ketals. Parker and coworkers[39] have recently utilized Swenton's electrochemical oxidation sequence to obtain an intermediate **55** in the synthesis of an isoindole quinone.

B. Cyclization Reactions Forming the Quinone System

1. Friedel–Crafts reaction

This reaction, which has been extensively applied to the preparation of anthraquinones, may be used for the formation of tricyclic and more extended heterocyclic quinones in those cases where the heterocycles are stable to the conditions of the reaction and are susceptible to electrophilic attack. In a tricyclic product the middle ring is quinonoid and one terminal ring is heterocyclic. The other terminal ring may be benzenoid. When these factors are considered, it is not surprising that the main applications of this method have been in the synthesis of benzothiophene, quinoline and isoquinoline quinones, but it is perhaps less immediately apparent that the method is useful for the preparation of some substituted isobenzofurans. For instance, *o*-(2-thienoyl)benzoic acid (**56**) yields **57** under Friedel–Crafts conditions. Similar type of reaction with thiophene 3,4-dicarboxylic acid chlorides[40] and the appropriate arene yield the isobenzothiophene quinones, **58**, **59** and **60**. Similarly, toluenes and xylenes can be diacylated with 2,5-dimethyl- and 2,5-diphenylfuran 3,4-dicarboxylic acids to give good yields of the quinones **61**[41]. It is necessary to consider the possibility that rearrangement of substituent groups may have



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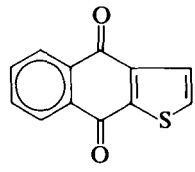

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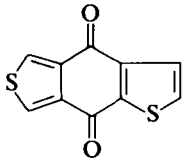

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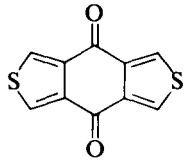

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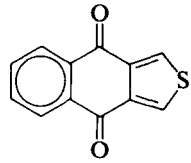

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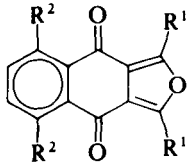

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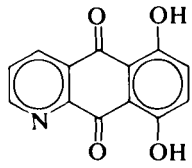

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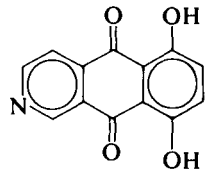
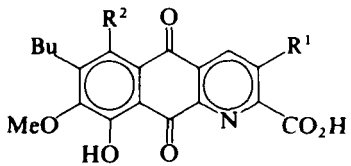
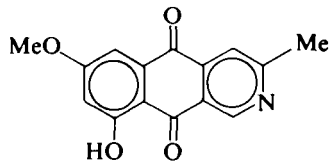


(63)

occurred prior to the cyclization process in reactions of this type[42]. Dihydroxy-1- and -2-azaanthraquinones (**62** and **63**) have been obtained by the action of quinolinic anhydride or cinchomeronic anhydride on 1,4-dimethoxybenzene[43]. However, attempts to use this approach for the synthesis of the pigments phomazarin (**64**) and isophomazarin (**65**) and the antibiotic bostrycoidin (**66**) were not successful, but this failure led to the development of a useful novel cyclization procedure[43] which is described next.



(**64**; R^1 = OH, R^2 = H)
(**65**; R^1 = H, R^2 = OH)

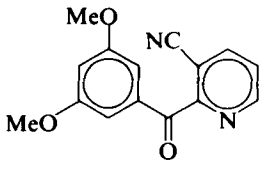


(66)

2. *Free radical cyclization*

Minisci and coworkers have shown that radicals generated from aldehydes by the action of iron(III) sulphate and *t*-butyl hydroperoxide behave as nucleophiles producing 2- and

4-acylated pyridines from protonated pyridines[44]. In this way it is possible to obtain 2- and 4-benzoylation of pyridine-3-carbonitrile and its derivatives[43]. Thus, 3,5-dimethoxybenzaldehyde and 3-cyanopyridine gave a mixture of **67**, **68** and **69**.



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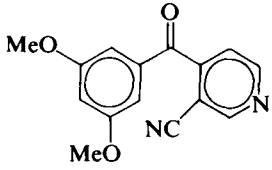

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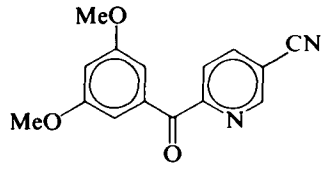
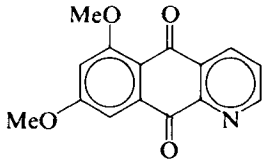


(69)

Cyclization of the cyano compounds **67** and **68** to the quinones **70** and **71** was achieved by the action of hydrogen chloride followed by ammonia under Houben–Hoesch reaction conditions. Bostrycoidin has been obtained using this approach to the heterocyclic quinone nucleus.



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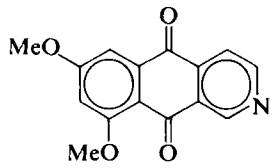
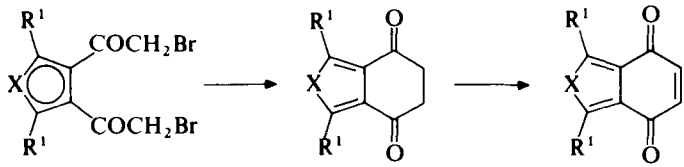
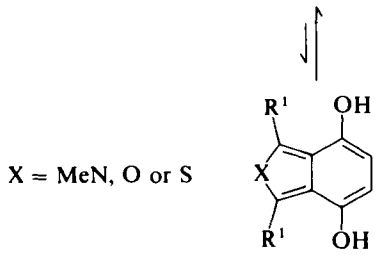


(71)

A reaction which is said to go by a radical mechanism has conveniently yielded examples of those quinones with a heteroatom in a five-membered ring at the position β to the quinonoid nucleus[45]. Attempts to apply the method to other systems do not appear to have been reported. The process requires an *o*-bis(bromoacetyl)heterocycle, e.g. **72**, which undergoes cyclization in the presence of a zinc–copper couple in aprotic medium to the



(72) (73) (74)



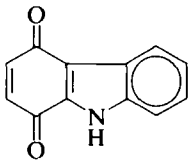
X = MeN, O or S

(75)

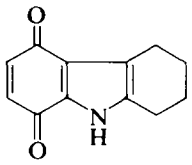
dihydroquinone, e.g. **73**. Oxidation to the quinone, e.g. **74**, occurs readily as might be expected since **73** is the tautomer of the quinol **75**. The tautomeric equilibrium appears to lie heavily towards the keto form **73**. It is suggested[45] that reductive cyclization occurs by a biradical mechanism since the corresponding diacetylpyrrole was obtained when **72** (X = MeN, R^1 = Me) was reduced in a protic medium.

3. Organometallic reagents

Surprisingly little work has been done on the quinones of tricyclic systems derived from indole. The carbazole quinones **76** and **77** are known but there appears to be no reference to quinones from the tricyclic carboline systems. In contrast several routes have been

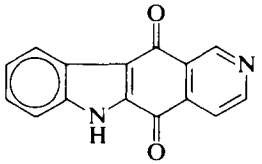


(**76**)

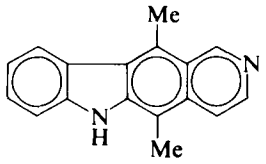


(**77**)

explored for the synthesis of tetracyclic systems derived from **78**. Such compounds have been used as intermediates in the syntheses of the antitumour alkaloid, ellipticine (**79**), and analogues. Convenient routes to the quinone **78** often utilize organometallic reagents.



(**78**)

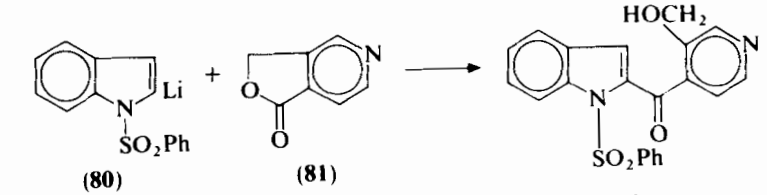


(**79**)

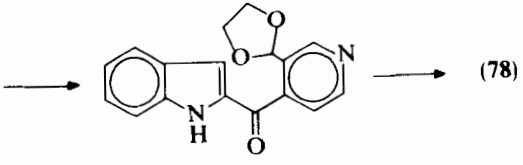
Excellent, high yield syntheses of **78** and the three isomeric compounds with the pyridyl nitrogen in the 1-, 3- or 4-positions have been developed by Joule's group[46]. Their method uses the ready 2-lithiation of 1-benzenesulphonylindole and the reaction of the lithiated species with pyridine lactones. For instance, the lithiated indole **80** undergoes reaction with the lactone **81** to provide the ketoalcohol **82**. Oxidation of the alcohol to the aldehyde, protection of this function as the acetal, followed by solvolysis of the *N*-protecting group in alkali yielded **83**, and this was cyclized to **78** in greater than 90% yield upon deprotection and oxidation. Later[47] it was found that the alcohol **82** takes part in a nucleophilic cyclization on to the 3-position of the indole nucleus in the presence of alcoholic base to give the oxepine **84**. This, in an excess of base and in the presence of oxygen yielded **78** via the oxirane **85**.

Saulnier and Gribble[48] have used the 3-iodoindole (**86**) to obtain lithiation in the 3-position, and subsequent reaction of the 3-lithioindole with cinchomeronic anhydride gave the 4-pyridyl ketone **87** which was converted to the ester **88**. Cyclization to the quinone **89** was achieved by utilizing the acidity of the 2-H on the 1-benzenesulphonylindole nucleus.

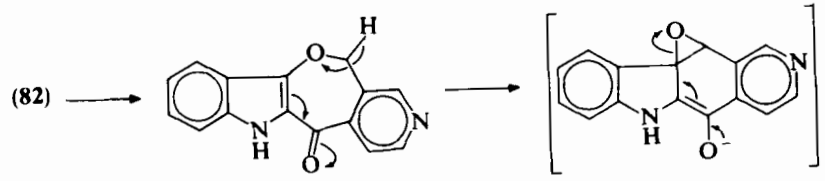
Watanabe and Sniekus[49] have used what they term 'tandem directed metalation reactions' in their syntheses of derivatives of ellipticine and other heterocyclic quinones. They used the established property of an *N*,*N*-diethylcarboxamide group to direct



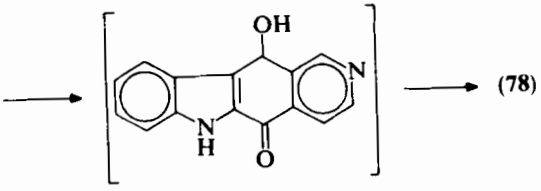
(80) (81) (82)

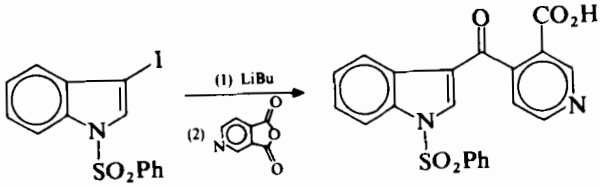


(83)

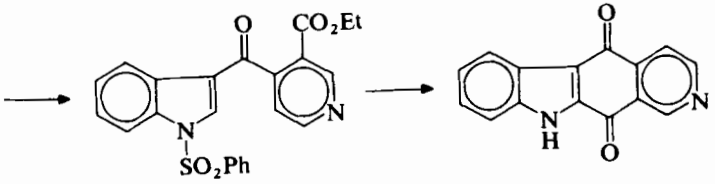


(84) (85)



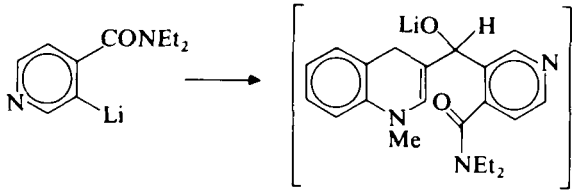


(86) (87)

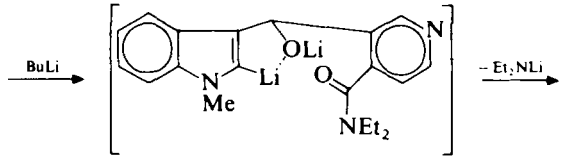


(88) (89)

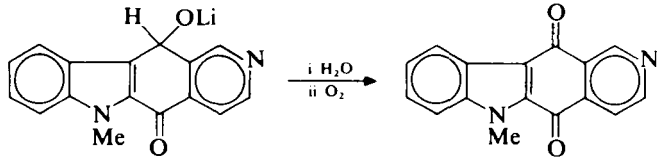
lithiation *ortho* to itself in order to obtain the pyridyl lithium **90**. This on reaction with 1-methylindole-3-carboxaldehyde yielded the lithium derivative of the alcohol **91**. Upon reaction of this with more butyllithium, lithiation at the 2-position of the indole nucleus is achieved because the lithium of the attacking organometallic reagent is coordinated to the alkoxide oxygen. The newly formed organolithium reagent then undergoes intramolecular cyclization with the dialkylamide group with elimination of lithium diethylamide. Workup of this one-pot reaction with water in the presence of air yielded the quinone **94** as a



(90) (91)

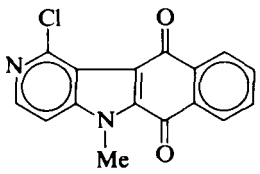


(92)



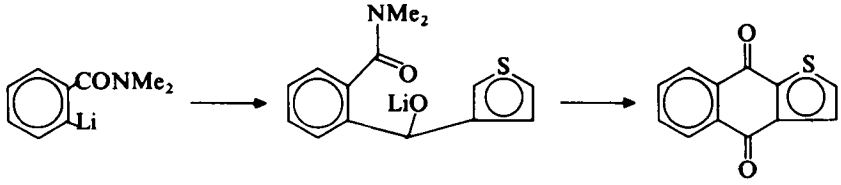
(93) (94)

product of oxidation. A similar reaction sequence but starting from *N,N*-diethylbenzamide to form the initial lithium aryl and subsequent reaction of this with 4-chloro-1-methyl-5-azaindole 3-carboxaldehyde gave an intermediate which was subjected to tandem directed metalation with butyllithium to give 5*H*-pyrido[4,3-b]benzo(f)indolo-6,11-quinone (**95**), a benzocarboline quinone, on oxidative workup of the reaction mixture[50].



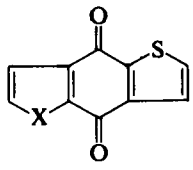
(95)

In a similar way the lithiated amide **96** upon reaction with thiophene 3-carboxaldehyde yielded **97**, which on tandem directed metalation of the heterocycle with butyllithium and subsequent oxidative hydrolysis gave the thiophene quinone **98**[49], though in only moderate yield. However, the process is essentially a multi-step but one-pot reaction from

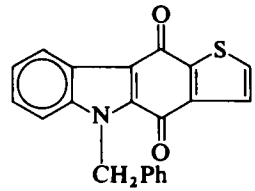


(96) (97) (98)

an aromatic (or heteroaromatic) dialkylamide and appears to be a versatile and convenient route to a range of heterocyclic quinones. Examples of further applications of the method are the preparations of **99**, **101**, **102**[49] and **100**[51].

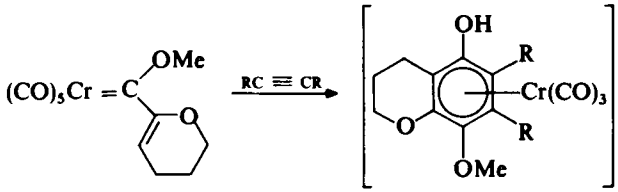


(**99**; X = O)
(**100**; X = S)
(**101**; X = – CH=N–)

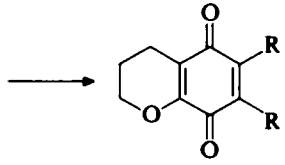


(**102**)

An interesting novel approach to the benzopyran system[52] utilizes the reaction of an alkyne with an α,β-unsaturated chromium carbene complex, e.g. **103**, for the controlled construction of the aromatic nucleus under neutral conditions. Oxidation of the arene–chromium carbonyl complex **104**, without prior isolation, produces demetalation and oxidation to give the quinone **105**.



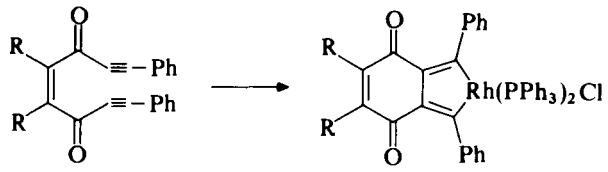
(**103**) (**104**)



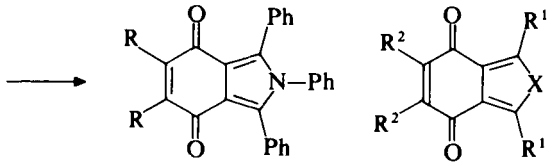
(**105**)

4. Diyne route

As part of an extensive investigation of diyne chemistry, Mueller has developed a useful route to certain heterocyclic quinones analogous to isoindole through the intermediacy of an organorhodium quinone. For example, the diyne **106** is cyclized in the presence of tris(triphenylphosphine) rhodium(I) chloride to the quinone **107**. The transition metal can be replaced by the action of nitrosobenzene to give the isoindole quinone **108**[53]. The two steps from **106** to **108** may be conducted as a one-pot reaction process[54]. By replacement of



(106) **(107)**



(108) **(109**; X = O)
(110; X = S)
(111; X = Se)

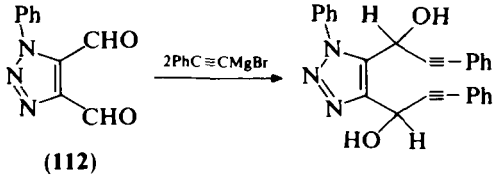
the nitrosobenzene by other reagents it is possible to obtain other heterocyclic quinones: *m*-chloroperbenzoic acid[54], sulphur[55] and selenium[54] separately yield compounds of types **109**, **110** and **111**, respectively. If the bisketoacetylenic system is in the form of vicinal substituents on a heterocycle, it is possible to use this general approach in order to obtain other types of heterocyclic quinone. So, for example, the vicinal dialdehyde **112**[53] yields the diyne **113** and hence the organorhodium quinone **114**, which on treatment with certain acetylenes yields the tricyclic triazole quinone **115**.

5. Intramolecular benzoin condensation

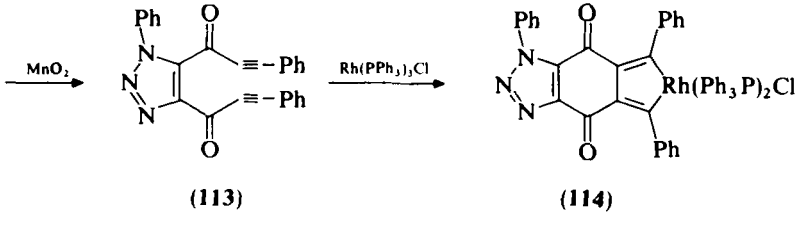
Three of the five possible thiophene analogues of phenanthraquinone have been obtained by an intramolecular benzoin condensation of diformylbithienyls followed by aerial oxidation of the product[56]. In this way, 2,2'-diformyl-3,3'-bithienyl (**116**) yielded **117**, and **118** was obtained similarly. The method is applicable to the isomeric compounds having the sulphur atom in the β-position: thus **119** yielded **120**. This approach has not been exploited extensively outside the field of thiophene chemistry.

6. Intramolecular nucleophilic displacement

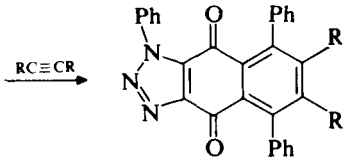
This method has been used to provide the novel *p*-quinone derivative which occurs in part A of the antitumour antibiotic known as CC-1065 (**121**). It seems likely that the already considerable interest in this type of quinone derivative will increase and it is worthy of note here that the heterocyclic quinone antibiotic mycorrhizin A (**122**) also contains a



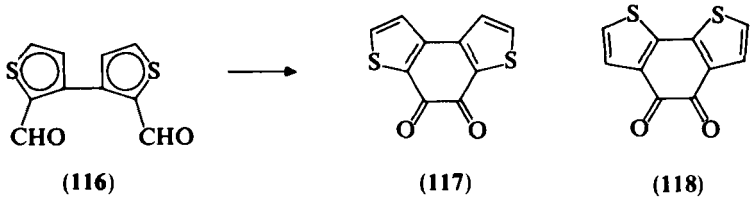
(112)



(113) (114)



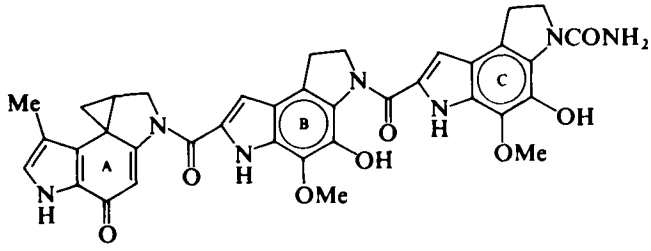
(115)



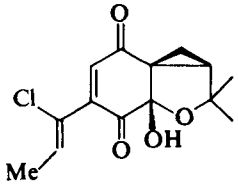
(116) (117) (118)

(119) (120)

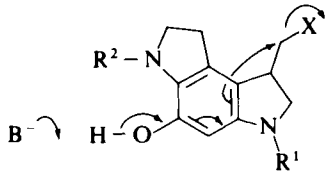
cyclopropane ring but not as part of the quinonoid system. Construction of the cyclopropane system at position 6 of the developing cyclohexa-1,4-dien-3-one system has been achieved by treatment of the tricyclic phenol **123** with base[57] or from **124** by use of an intramolecular Mitsunobo reaction with diethyl azodicarboxylate and triphenylphosphine[58].



(121)



(122)

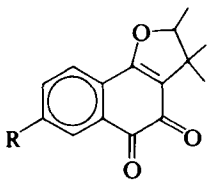


(123; $R^1 = SO_2Me$, $R^2 = H$, X = Br)
(124; $R^1 = COMe$, $R^2 = SO_2Ph$, X = OH)

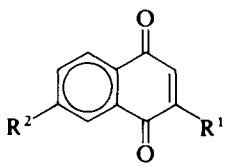
C. Methods which start from a Quinone

1. Cyclization of substituted benzo- and naphtho-quinones

Several naturally occurring 2,3-dihydronaphtho[1,2-*b*]furan 4,5-quinones have been isolated and found to be derivatives of dunnione (**125**). A recent synthesis of (±)-trypethelone (**126**) has involved the use of a substituted naphthoquinone and a rearrangement reaction[59]. The 2-methoxynaphthoquinone (**127**) was hydrolysed under basic conditions and the diol acetylated to give **128**. This, on treatment with silver(I) oxide and isoprenyl bromide in HMPT gave the allyl ether **129**. The substrate **128** is the vinylogue of an anhydride and is probably converted by the basic oxide to the silver salt

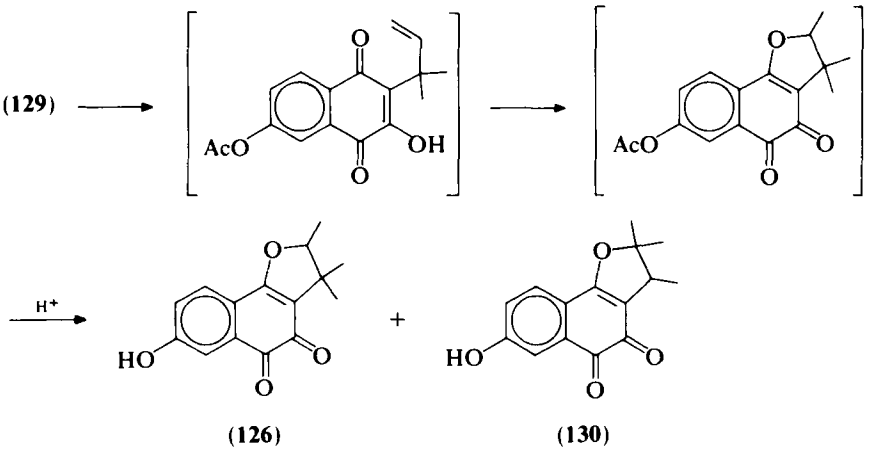


(**125**; R = H)
(**126**; R = OH)



(**127**; R^1 = OMe, R^2 = OH)
(**128**; $R^1 = R^2 = OAc$)
(**129**; $R^1 = OCH_2CH{=}CMe_2$, R^2 = OAc)

and then alkylated in the usual way. Refluxing **129** in ethanol was sufficient to cause two consecutive thermal rearrangements to give the acetates of trypethelone (**126**) and of the expected by-product β-isotrypethelone (**130**) which yielded **126** and **130** after acidification of the thermolysis product.



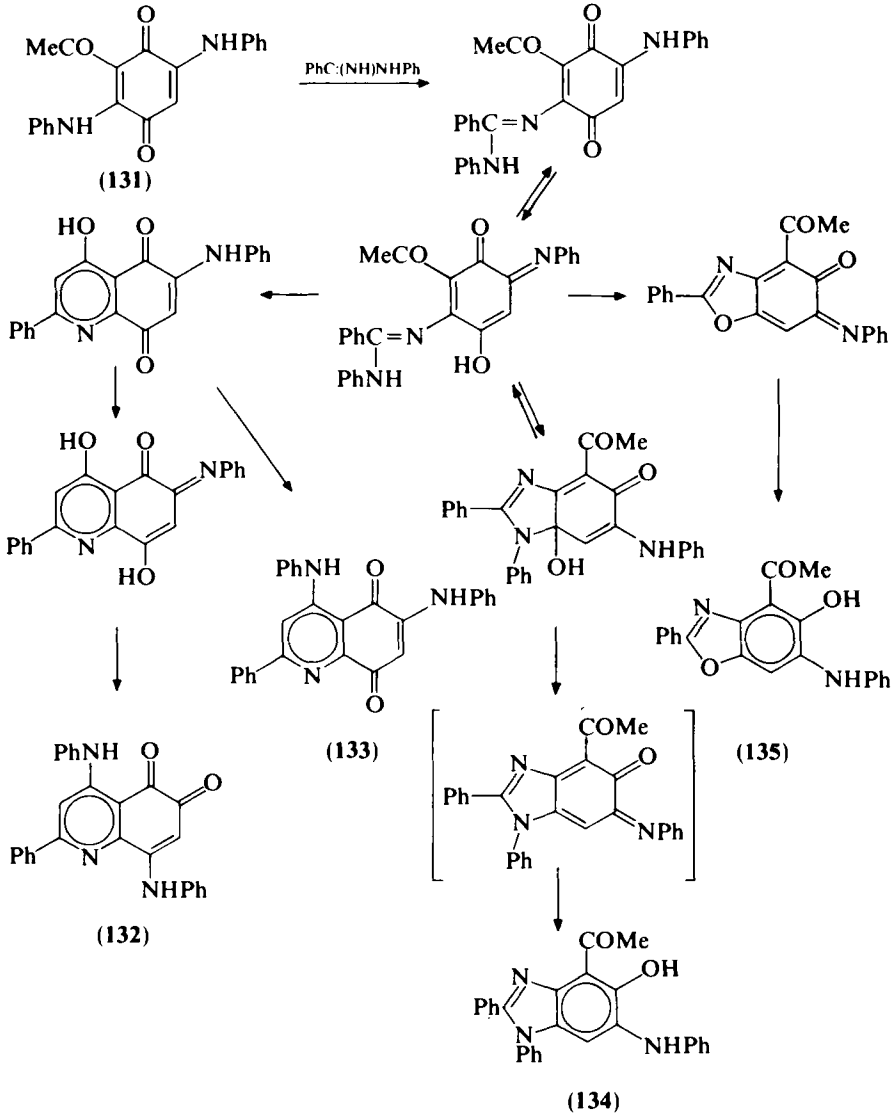
(126) **(130)**

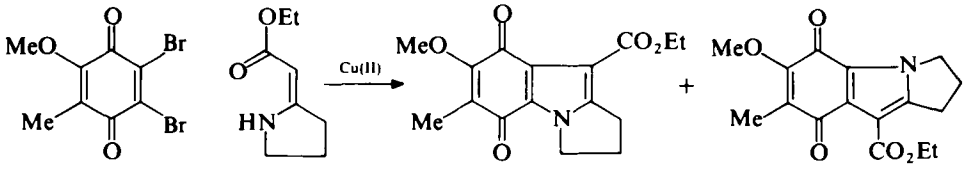
Schäfer and Falkner[60] have described the annelation of the trisubstituted benzoquinone **131** with *N'*-phenylbenzamidine to give mainly the trisubstituted quinoline 5,8-quinone **133** with the benzoxazole **135**, the benzimidazole **134** and the trisubstituted quinoline 5,6-quinone **132** as by-products. The proposed reaction scheme requires initial displacement of the 2-anilino group from the quinone **131** by the benzamidine followed by a variety of intramolecular cyclizations and intermolecular substitution reactions.

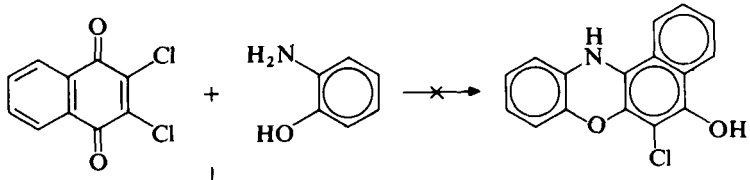
In a search for a simple route to the tricyclic mitosene nucleus **138** Rapoport has discovered a novel metal catalysed cyclization on to a quinone, although a similar copper(I) bromide catalysed cyclization on to arenes is known. Rapoport's route[13] involves the reaction of the dibromobenzoquinone **136** with the unsaturated amino ester **137** in the presence of copper(II) bromide to give a separable mixture of the mitosene derivative **138** and the linear isomer **139**.

2,3-Dichloro-1,4-naphthoquinone has been used extensively as a starting material in the synthesis of tricyclic and higher members of various types of heterocyclic quinones. The chemistry of quinones containing five-membered heterocycles has been reviewed[3]. Many of these compounds contain bridgehead nitrogen atoms; the syntheses are simple but the yields are often poor. As mentioned earlier, some of the data given in the review[3] has been corrected in the light of later investigations[4]. An example is the reported reaction of *o*-aminophenol with 2,3-dichloro-1,4-naphthoquinone to give the phenoxazine **140**. More recent work[61] has shown that a mixture is formed and among the products are **141** and **142** but **140** is not found (the methoxyl group in **141** is derived from the methanol solvent). The naphthoquinone analogues **143** of the more common benzoheterocyclic quinones **144** are often obtainable from dichloronaphthoquinone.

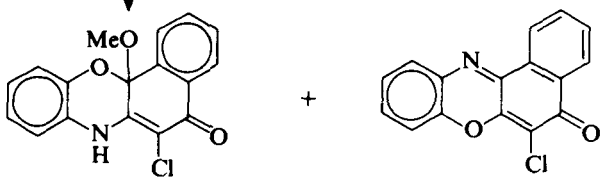
Kishi's group used a substituted benzoquinone in their approaches to the mitomycin nucleus. For instance, their 19-step total synthesis of deiminomitomycin A[62] from 2,4-dimethoxy-3-methylphenol included the hydrogenolysis of the highly protected **145** followed by treatment of the quinol with oxygen to yield the heterocyclic quinone **147** in reasonable yield, presumably by intramolecular addition of the amine to the quinone **146** despite the requirement to form an eight-membered ring. Conversion of the alcohol to a


MeCO
NHPh
PhNH
O
(131)
PhC:(NH)NHPh
PhC=N
PhNH
HO
Ph
N
COMe
NPh
OH
(133)
(135)
(132)
(134)

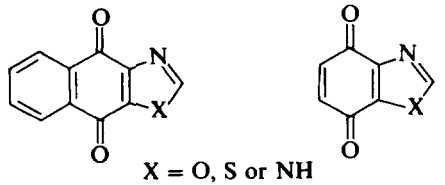

MeO
Br
Me
O
(136)
OEt
HN
(137)
Cu(II)
CO2Et
+
(138)
(139)



(140)



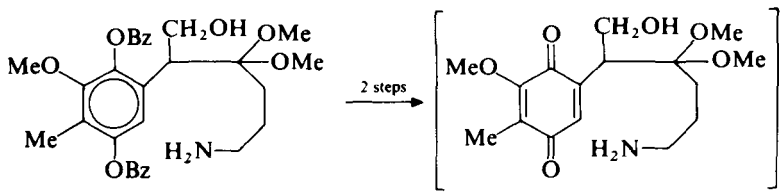
(141) (142)



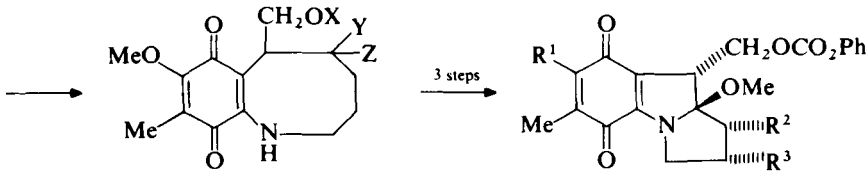
X = O, S or NH

(143) (144)

phenyl carbonate and of the ketal to a hemithioketal gave an intermediate (**148**) which underwent the crucial transannular cyclization in the presence of mercuric chloride and triethylamine to give a (1 : 1) mixture of the geometrical isomers of the tricyclic system, from



(**145**; Bz = CH_2Ph) (**146**)



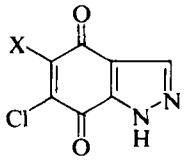
(**147**; X = H, Y = Z = OMe)
(**148**; X = CO_2Ph, Y = OMe, Z = SMe)

(**149**; R^1 = OMe, R^2 = R^3 = H)
(**150**; R^1 = NH_2, R^2,R^3 = NMe)

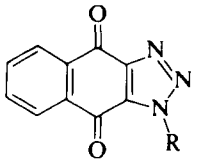
which the *trans* isomer **149** was isolated by thin-layer chromatography. A similar approach to the indoloquinone system was used in the same group's total synthesis of the related natural product, porfiromycin[63] (**150**).

2. *Cycloaddition reactions of quinones*

Dipolar cycloaddition to benzoquinone occurs readily and has been exploited in a number of ways to produce heterocyclic quinones. Recently, a number of novel aziridinyl-substituted 1(2*H*)-indazole-4,7-quinones have been synthesized this way and shown to have antitumour activity[64]. Diazomethane adds to the unsubstituted double bond of 2,3-dichloro-1,4-benzoquinone and the intermediate is oxidized by an excess of the benzoquinone to give the dichloroindazole quinone (**151**). The 5-chlorine atom is replaceable by aziridine to afford **152**.

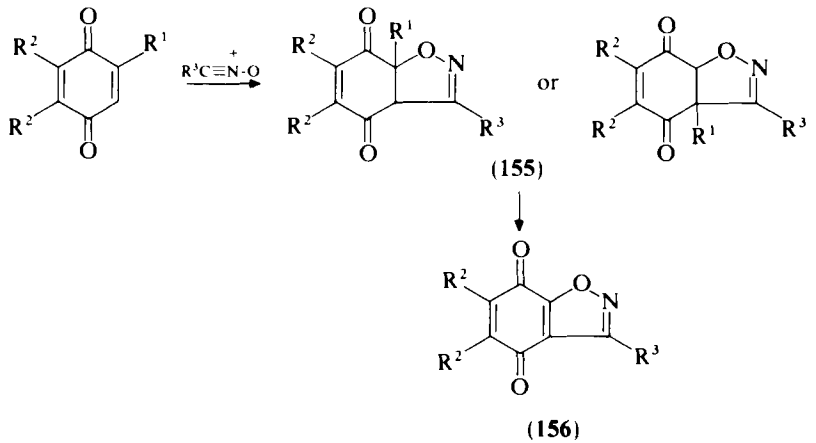


(**151**; X = Cl)
(**152**; X = –N⟨ ⟩)



(**153**; R = $CH_2C_6H_4OMe$-*p*)
(**154**; R = H)

Approaches to benzo- and naphtho-1,2,3-triazoles have included 1,3-dipolar addition of azides to 1,4-quinones. For example, the use of 4-methoxybenzyl azide with 1,4-naphthoquinone[65] produced a 1-substituted triazole **153** from which the unsubstituted quinone **154** was obtained by treatment with trifluoroacetic acid. In a similar way aliphatic[64] and aromatic nitrile oxides[66] add to substituted benzoquinones to give the isoxazoline addition products **155** which are readily converted into the isoxazoloquinones **156**. The site- and regioselectivity of the reaction has been examined in some detail[67].

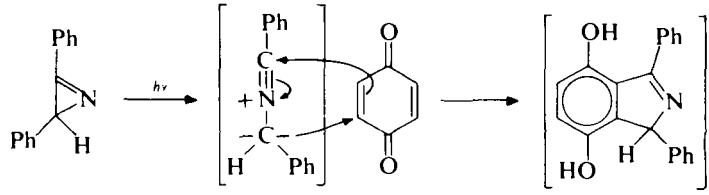


(**155**)

(**156**)

Preparative routes to isoindole quinones rely heavily upon dipolar cycloaddition reactions. 1,3-Diphenylisoindole-4,7-quinone (**158**) is conveniently obtained by photolysis

of a solution of benzoquinone and 2,3-diphenyl-2*H*-azirine in the presence of oxygen[68]. The process is thought to involve the intermediate **157**. Other cycloaddition reactions leading to isoindoles have utilized the mesoionic oxazolium oxides **159** which are readily



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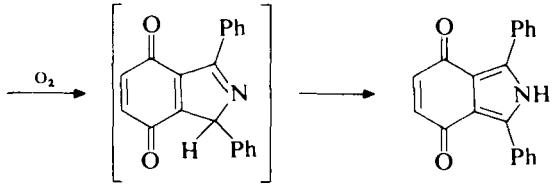
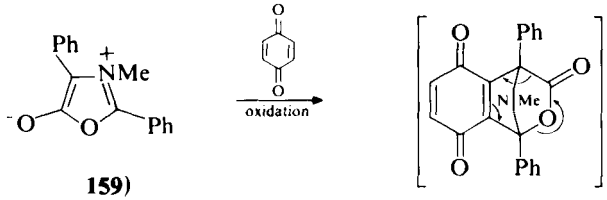


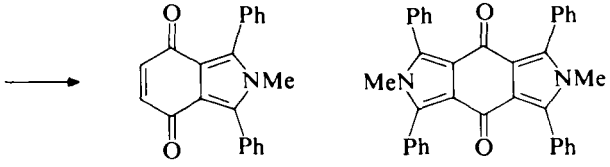
(158)

generated from *N*-acylglycine derivatives[69]. Addition to the quinone occurs across the 2,4-positions of the mesoionic system to give intermediates such as **160**, which on loss of carbon dioxide yield the isoindole **161**. This heterocyclic quinone may undergo further reaction to give the tricyclic **162**. Similarly, the reaction of the glycine derivative **163** gives the oxazolium oxide **164**, which yields the partially reduced indolizine quinone **165** upon reaction with benzoquinone[70]. Isobenzothiophene quinones such as **167** are obtained from cycloaddition reactions of benzoquinone with 1,3-dithiolylium-4-enolates (**166**) in a one-pot reaction[71].

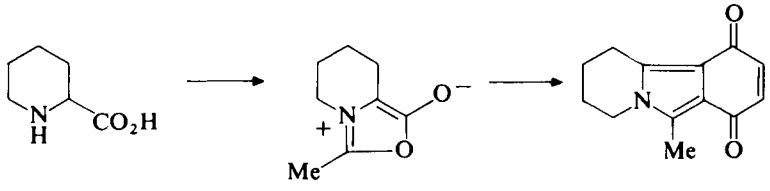


159)

(160)



(161) (162)



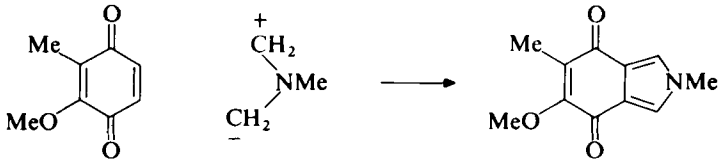
(163) (164) (165)

(166) (167)

The first naturally occurring isoindole to be isolated was obtained from the sponge *Reniera* and was identified as the quinone **171**. A synthesis of this and other isoindole quinones[39] uses non-stabilized azomethine ylides, e.g. **169**, formed from cyanomethyl trimethylsilylmethylamines, e.g. **168**, by the action of silver fluoride. The reaction of the ylide with 2-methoxy-3-methylbenzoquinone (**170**) gave **171** in one step.

$$NCCH_2NMeCH_2SiMe_3 \xrightarrow{AgF} CH_2 = \overset{+}{N}Me - \bar{C}H_2 \leftrightarrow \overset{+}{C}H_2 - NMe - \bar{C}H_2$$

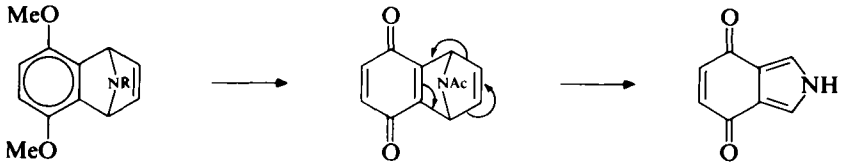
(168) (169)



(170) (169) (171)

3. *Retro-Diels–Alder reactions*

The parent isoindole-4,7-quinone (**175**) has been synthesized by subjecting **174** to a retro-Diels–Alder reaction in the presence of the ethyne scavenger, 3,6-di-(2-pyridyl)-*s*-

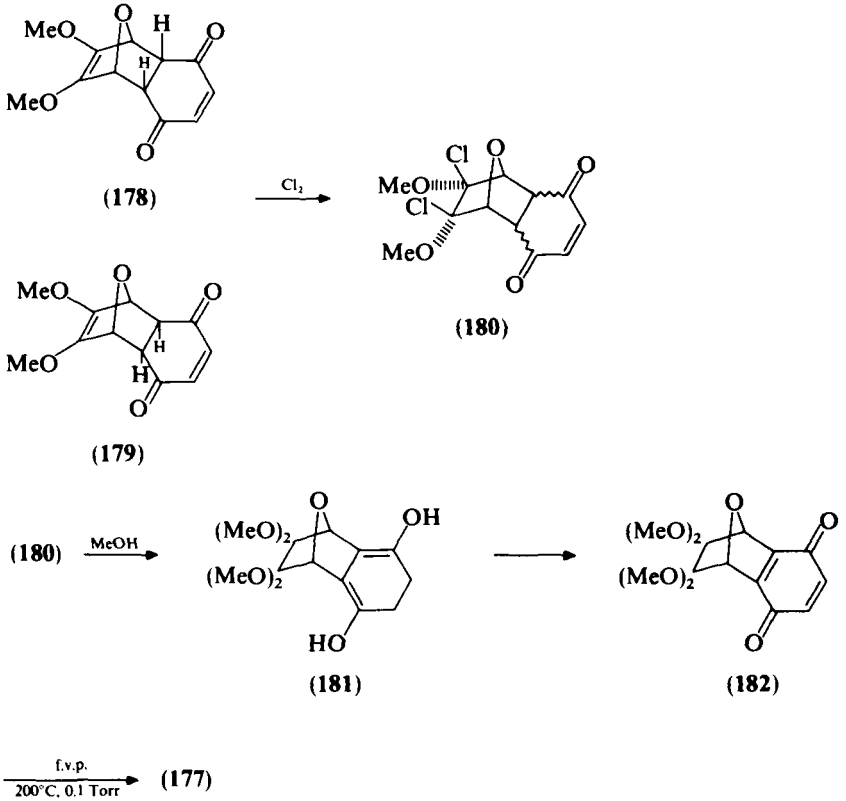


(172; R = CO_2Et)
(173; R = Ac) (174) (175)

tetrazine[72]. The heterocyclic quinone **174** was obtained by the action of 3,6-dimethoxybenzyne (from the appropriate dimethoxyanthranilic acid or 1-aminobenzotriazole) on *N*-ethoxycarbonylpyrrole to give **172**, conversion of this to the *N*-acetyl compound **173**, and subsequent oxidation to the quinone **174**. An analogous but simpler process from furan leads to **176** and thence to the parent isobenzofuran quinone (**177**) which is obtained as a

(176) **(177)**

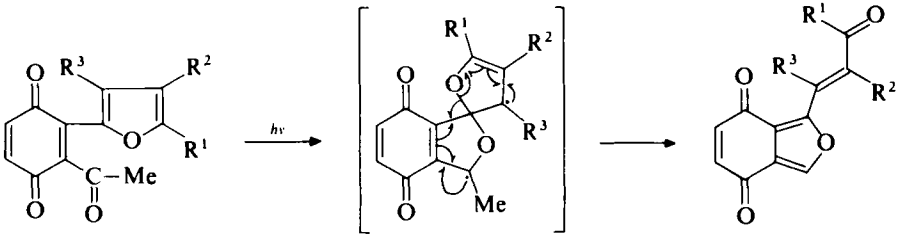
stable yellow solid in high yield[72]. An alternative and somewhat more complex route[73] to **177** starts with the reaction of 1,4-benzoquinone and 3,4-dimethoxyfuran to give the *endo*- and *exo*-Diels–Alder adducts **178** and **179**, respectively. The adducts add a molecule of chlorine in a stereospecific *cis* manner from the *exo* side to give **180**. Solvolysis with methanol then leads to the bis-dimethoxy derivative **181** which, on oxidation yields the



heterocyclic quinone **182**. Flash vacuum pyrolysis (f.v.p.) of this at relatively low temperature gives isobenzofuran quinone by a retro-Diels–Alder reaction.

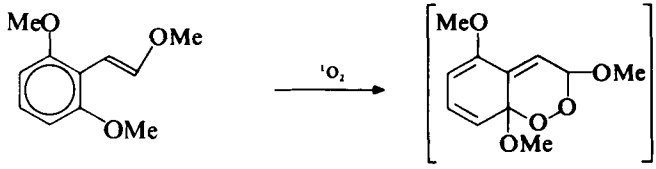
4. Photochemical reactions

Photolysis of 2-acetyl-3-(2-furyl)-1,4-benzoquinones (**183**) is suggested[74] to yield a diradical (**184**) through an $n \rightarrow \pi^*$ excitation of the acetyl group. Intramolecular rearrangement then gives the isobenzofuran products **185** in useful yields.

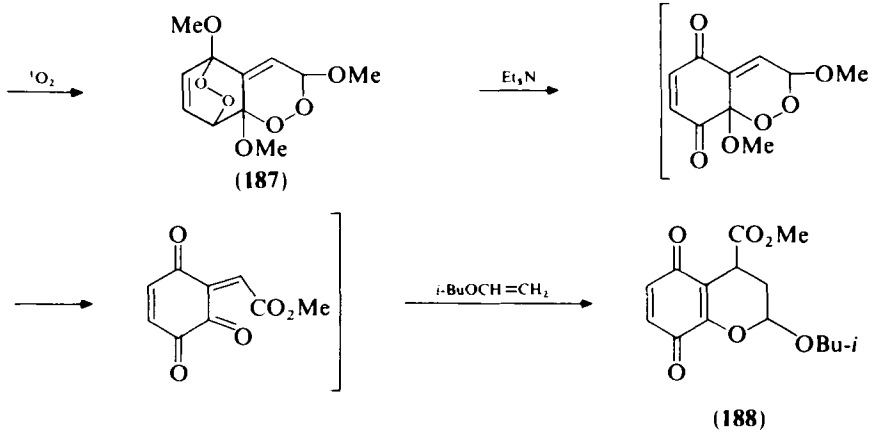


(**183**) (**184**) (**185**)

Sensitized photo-oxygenation with singlet oxygen of vinyl arenes in the presence of base and a vinyl ether has been shown to give benzopyran quinones[75]. It is suggested that the substituted vinyl arene, e.g. **186**, undergoes two attacks by singlet oxygen to yield the diperoxide **187**, this then decomposes in the presence of base to give the quinone methide which is trapped to yield the product **188**.



(**186**)



(**187**)

(**188**)

III. PROPERTIES OF HETEROCYCLIC QUINONES

A. General Considerations

Your reviewers have been impressed by the general lack of systematic investigations of the reactivity of heterocyclic quinones and their derivatives. There are very few cases where data are available from comparative studies of the reactivity of a series of heterocyclic quinones and one or more carbocyclic analogues. Therefore, quantitative data showing the effects of the presence of a particular heteroatom and of its position relative to the quinonoid nucleus are not available. Recently there have been some moves to rectify this situation, at least in a semiquantitative sense, with the publication of results from studies of the addition of dienes to heterocyclic quinones. An understanding of the factors which control the regioselectivity of these reactions has been gained for the relatively few heterocycles studied this far.

When we turn to substitution reactions the detailed knowledge is very sparse. What is known has been acquired almost entirely from the frustrations and successes of work primarily directed towards the synthesis of naturally occurring or potentially biologically active quinones. Because of these origins the information tends to be fragmentary and there are even less data of a comparative or quantitative nature than in the case of the addition reactions.

There has been, and there continues to be much interest in the potential use of heterocyclic quinones in medicinal chemistry. Some time ago the major interest was in the field of anti-malarials, now the activity is centred more on the development of heterocyclic quinones for use in cancer chemotherapy or as adjuvants in the radiotherapy of cancer. The finding of anticancer activity in compounds such as mitomycin, CC-1065 and streptonigrin, together with their novel structures, has stimulated much research activity. Studies of mitomycin and related compounds have produced interesting theories to explain their biological activity, and these ideas suggest that other heterocyclic quinones may have useful anticancer activity. The recent discovery that methylotrophic bacteria utilize a dehydrogenase enzyme which requires a coenzyme, methoxatin (**37**), having a novel heterocyclic quinone structure adds another facet to the importance of heterocyclic quinones.

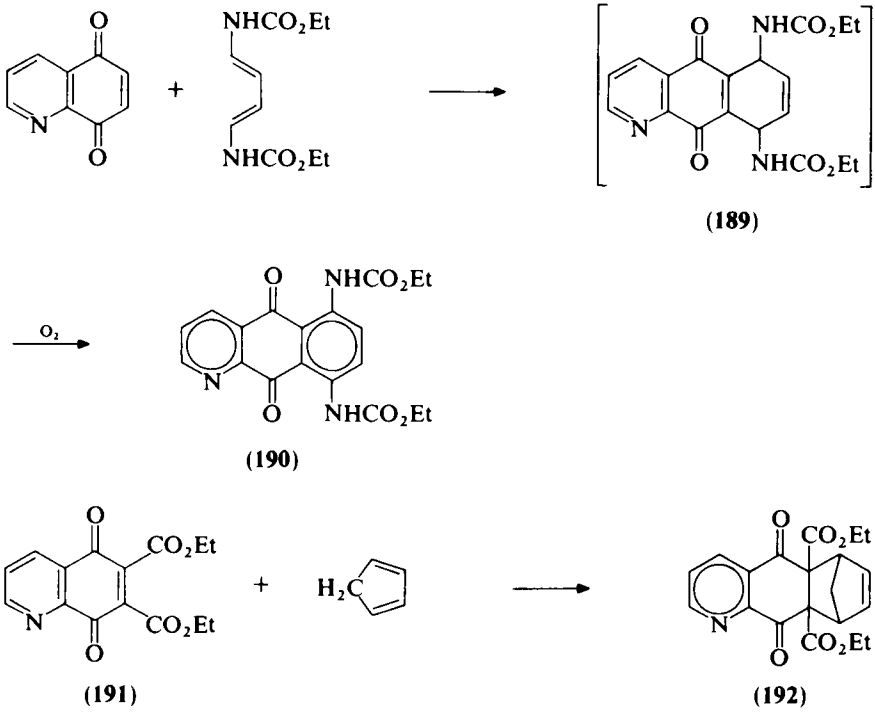
The industrial use of heterocyclic quinones has been small, presumably because the requirements can be satisfied with the cheaper carbocyclic quinones. The chemical properties, biological and medicinal interests and uses, and (briefly) industrial applications of heterocyclic quinones are discussed in more detail in the remainder of this chapter.

B. Addition Reactions

1. Addition of 1,3-dienes

Reactions of the Diels–Alder type present a useful method for the annelation of heterocyclic *p*-quinones. Clearly the reaction of an unsymmetrical heterocyclic quinone and/or an unsymmetrical diene may lead to more than one product. Studies of factors influencing regioselectivity in this type of reaction with quinoline- and isoquinoline-5,8-quinones have been completed recently. The use of other heterocyclic quinones has been studied much less in these reactions.

The electron-rich diene, *trans*, *trans*-1,4-bis(ethoxycarbonylamino)-1,3-butadiene adds to quinoline-5,8-quinone (conveniently[76] obtained from 8-hydroxyquinoline) to give the addition product **189** which is oxidized[77] in air to the aromatic system **190**. Similar reactions occur with isoquinoline and quinazoline quinones. The quinone 6,7-diester **191** undergoes addition of cyclopentadiene to give the adduct **192** which cannot become fully aromatic[36].



(189)

(190)

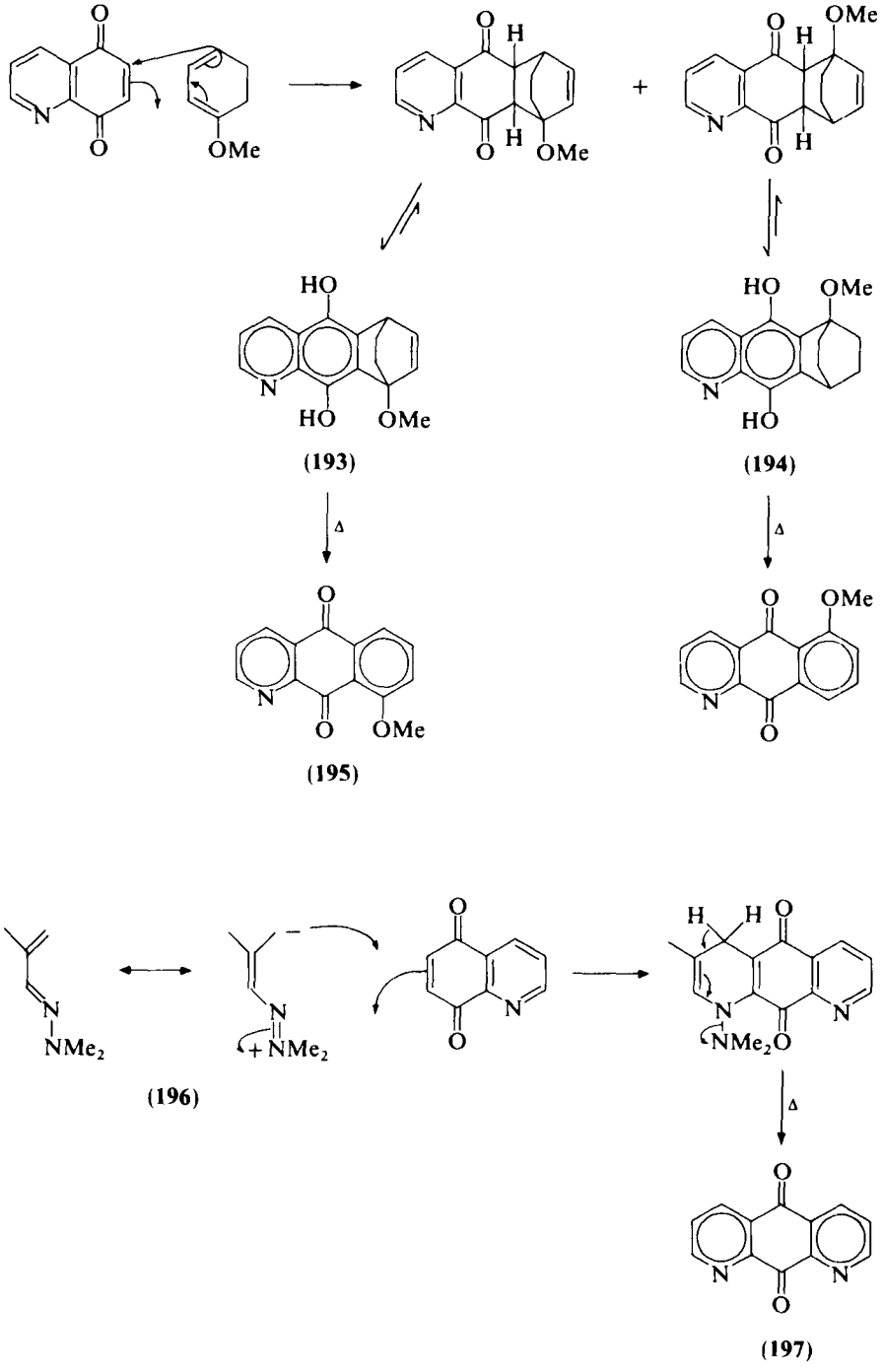
(191)

(192)

Recent investigations with unsymmetrical dienes have produced results which allow some discussion of the factors which influence regioselectivity in these reactions. The addition of 1-methoxycyclohexa-1,3-diene to quinoline-5,8-quinone yielded compounds which exist mainly in the dihydroxy forms **193** and **194**. Pyrolysis of the mixture gave a product from which the major component **195** was readily separated[78]. These results taken together with studies of similar reactions of isoquinoline-5,8-quinone[78] indicate that the position of substitution of the carbonyl group on the pyridine nucleus determines the site of attack and can produce what is, for preparative purposes, a regiospecific reaction. In the reaction shown, the 6-position of the quinoline quinone is the one affected most by the carbonyl group bonded to the electron-withdrawing 2-position of the pyridine nucleus, while the 7-position is affected by the 5-carbonyl group which is bonded to the much less electron-demanding 3-position of the pyridine ring. Hence, overwhelmingly, the preferred site for nucleophilic attack in the cycloaddition reaction is the 6-position. This is in line with the findings for the substitution reactions of these quinones and seems to indicate that the reactions are probably not concerted and certainly not synchronous. In agreement is the finding that methacrolein *N,N*-dimethylhydrazone (**196**) adds to quinoline-5,8-quinone in a regioselective way to give the diazaanthraquinone **197**[78].

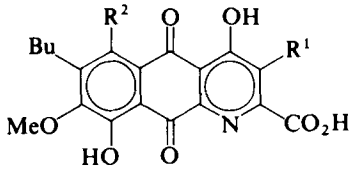
2. Addition of olefins and isocyanides

Interest in the aza- and diaza-anthraquinones is stimulated by the occurrence of the fungal pigments phomazarin (**198**) and isophomazarin (**199**)[79] and the antibiotic diazaquinomycin (**200**)[80]. In reactions of quinoline-5,8-quinone with two molar equivalents of 1,1-dimethoxyethene, the product is a mixture of isomeric 1-azaanthraquinones,

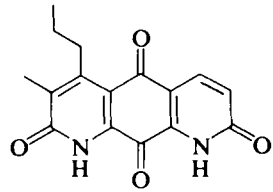


(193) (194) (195)

(196) (197)



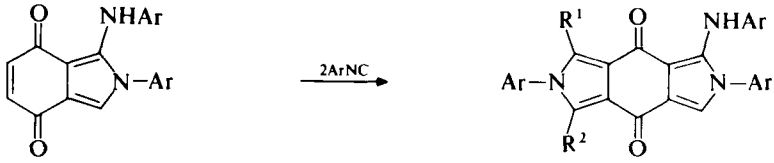
(**198**; R^1 = OH, R^2 = H)
(**199**; R^1 = H, R^2 = OH)



(**200**)

in a ratio of 4:3. In this type of reaction, whose mechanism is uncertain, the quinoline quinone shows much less regioselectivity than the corresponding isoquinoline quinone[76].

Isoindole quinones **201**, which can be formed from benzoquinone and an aryl isocyanide, undergo further reaction with the aryl isocyanide to give the isomeric, dark blue quinones **202** and **203**. A mechanism for the reaction has been proposed[81].

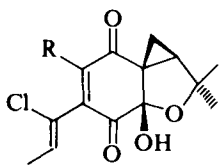


(**201**)

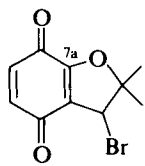
(**202**) R^1 = NHAr, R^2 = H
(**203**) R^1 = H, R^2 = NHAr

3. Miscellaneous addition reactions

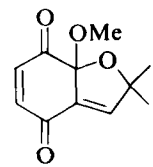
A group of compounds which may be considered as the products of addition to benzofuran 4,7-quinone are produced by the fungus *Gilmaniella humicola* Barron. Two of these, mycorrhizin A (**204**) and chloromycorrhizin A (**205**) are strongly inhibitory to the root rot fungus *Fomes annosus* (Fr.) Cke. In a recent approach to this nucleus, R. F. C.



(**204**; R = H)
(**205**; R = Cl)



(**206**)

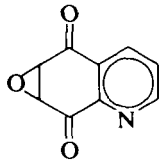


(**207**)

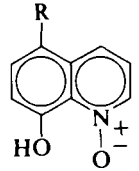
Brown's group have found an unusual addition of methanol to 3-methyl-2,2-dimethylbenzofuran-4,7-quinone (**206**) in the presence of silver oxide to give **207**[82]. It is suggested that the process involves kinetically preferred addition of methanol at the 7a-position of the allylic cation formed on loss of bromide ion from **206**.

The products of the formal addition of oxygen to either the carbon–carbon bond of a heterocyclic quinone to give an epoxide or to an azine nitrogen atom in such a compound to give an *N*-oxide are almost unknown. A start has been made recently to uncover their

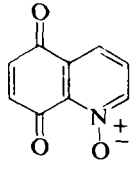
chemistry in the quinoline- and isoquinoline-5,8-quinone series[83]. The epoxides such as **208** are formed readily using conditions similar to those used in order to form naphthoquinone epoxide. The quinone *N*-oxide **211** was obtained by *N*-oxidation of 5-acetamido-8-hydroxyquinoline with hydrogen peroxide in the presence of sodium tungstate to give **209**. Acidic hydrolysis of the acetyl group and oxidation of the 5-amino-8-hydroxyquinoline 1-oxide (**210**) gave **211**.



(**208**)

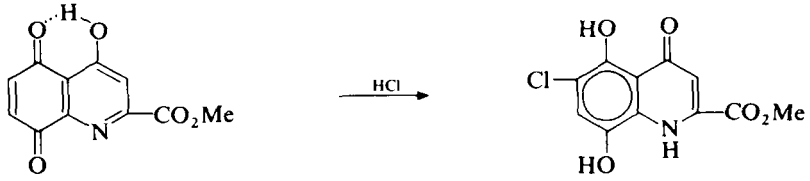


(**209**; R = NHCOMe)
(**210**; R = NH_2)



(**211**)

Addition of hydrogen chloride to the quinone **212** affords the chloroquinol **213**[27]. Probably the most commonly used addition reaction in this series is the hydrogenation of quinones to quinols but there appears to be nothing remarkable about this reaction in the heterocyclic series.

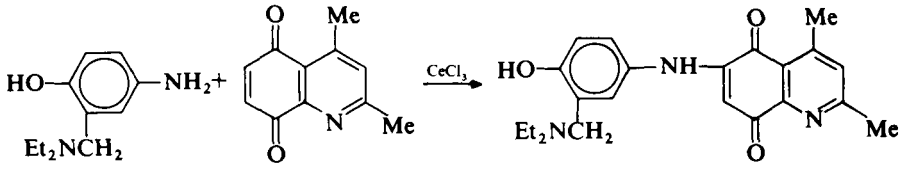


(**212**) (**213**)

C. Substitution Reactions

1. Replacement of a hydrogen atom

We have already seen (Section III.B.1) that the 6-position in quinoline-5,8-quinones is the most susceptible to nucleophilic attack. Aniline derivatives react with quinoline quinones to give products such as **214** when the reaction is catalysed by cerium(III) chloride[84]. Presumably the cerium(III) ion coordinates with the pyridyl nitrogen atom so promoting attack by the nucleophile. Replacement of a hydrogen atom in the 7-position is possible even when there is an electron-releasing substituent in the 6-position of a quinoline 5,8-quinone. For instance, a 7-alkylthio substituent may be introduced into 6-

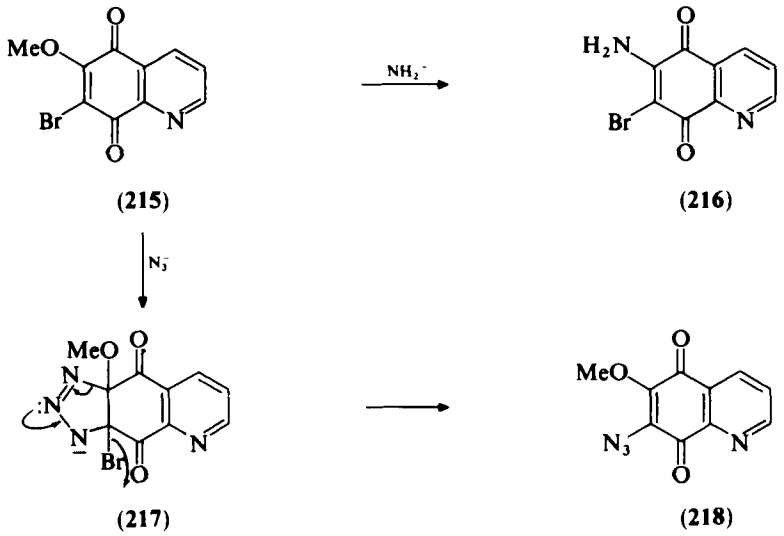


(**214**)

hydroxyquinoline-5,8-quinone and the same hydroxyquinone undergoes a modified Mannich reaction to give a 7-alkylaminomethyl derivative[85]. The presence of a 6-hydroxyl substituent on the quinoline-5,8-quinone[86] or the benzothiazole-4,7-quinone[8] nucleus allows the introduction of an alkyl group into the 7- or 5-position, respectively, by the generation of alkyl radicals from diacyl peroxides. Much of this type of work was done in the 1960s and 70s in the search for an effective antimalarial based on heterocyclic quinones. Other important work involving *vic*-alkylhydroxyquinones is to be found in the α- and β-lapachone series of benzopyran quinones, but the alkylation reactions themselves are on naphthoquinones. Little seems to have been done with heterocyclic quinones in this area of substitution chemistry.

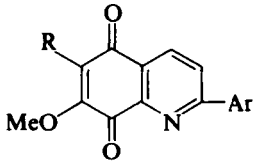
2. *Replacement of groups or atoms other than hydrogen*

The displacement of halogen or methoxyl have been the most used reactions. The 5-chlorine atom is readily replaced by amines from 5,6-dichloroindazole-4,7-quinone[64,87] whereas 6,7-dichloroquinoline-5,8-quinone gives the 6,7-bis-imidazole derivative[87]. Regiospecific substitution in the 6-position is often achievable[88] in this series by nucleophilic displacement of a 6-methoxyl group even when a 7-bromine is present. At first sight, the azide ion appears to be exceptional as a nucleophile in this reaction because the action of azide ion on **215** is to give the bromine displaced product **218**. However, it is

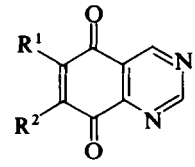


(215) **(216)** **(217)** **(218)**

thought that the reaction goes by initial nucleophilic addition at the 6-position followed by cyclization to give the triazole **217**. Subsequent displacement of bromine in a ring-opening process gives **218**. Reduction of **218** gives the corresponding amine, and this procedure complements the action of amide ion on **215** to give the aminobromoquinone **216**. In this connection it is interesting to note that treatment of a 7-methoxyquinone of the type **219** with azide ion in DMF gives the corresponding 6-amino-7-methoxy compound (**220**) directly[88]. As would be expected, the 6-methoxyl group of the quinazoline **221** is readily replaceable by a secondary amine. Vigorous treatment of **221** with aziridine gives **223**, presumably via the intermediate **222**[21].

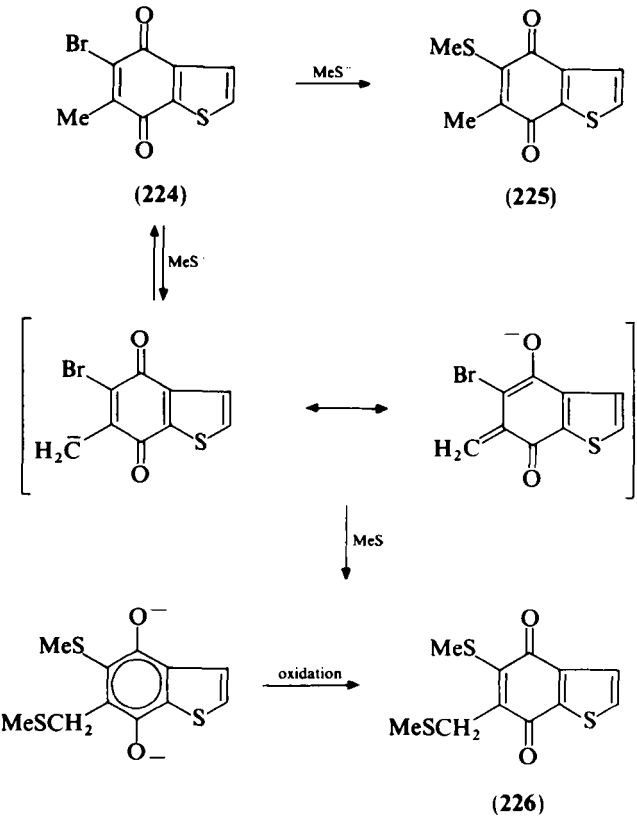


(219; R = H)
(220; R = NH_2)



(221; R^1 = OMe, R^2 = H)
(222; R^1 = 1-aziridinyl, R^2 = H)
(223; R^1 = R^2 = 1-aziridinyl)

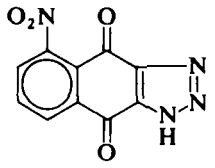
The reaction of 5-bromo-6-methylbenzothiophen-4,7-quinone (**224**) with methylthiolate ion gave the expected 5-substituted derivative **225** as the major product but the minor component of the reaction mixture was shown to be **226**. The mechanism suggested for the formation of **226** involves an intermediate anion with some *o*-quinone methide character[89].



(226)

Nucleophilic displacement of nitro groups from the carbocyclic and non-quinonoid ring of tricyclic heterocyclic quinones had been found to occur in both the systems represented by the triazole quinone **227**[90] and the thiadiazole quinone **228**[22]. Thermal replacement of

a methoxyl group from the related tricyclic system **229** by primary amines was successful only under vigorous conditions. However, on irradiation with light the reaction proceeded smoothly to give mainly the monosubstitution product **230** in the presence of methylamine, together with a smaller proportion of **231**[91].



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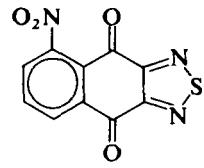

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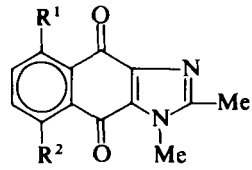
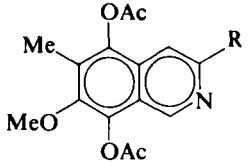


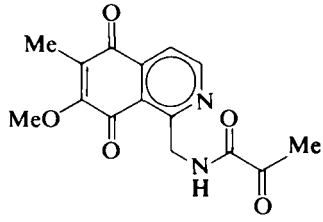
(229; $R^1 = R^2 = OMe$)
(230; $R^1 = NHMe$, $R^2 = OMe$)
(231; $R^1 = OMe$, $R^2 = NHMe$)

D. Reactions at the Carbonyl Groups

Probably the most common reaction of heterocyclic quinones is their reduction, either when they are used in a one molar excess in order that the quinone may oxidize the initially formed quinol in an addition reaction or when the quinone is reduced to give a quinol product. The latter type of reaction appears to proceed smoothly with no especially



(232; R = H)
(233; R = 1-morpholino)



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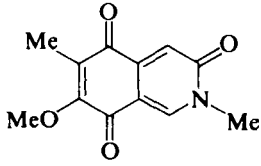

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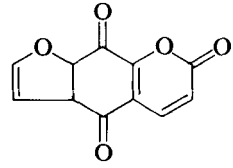
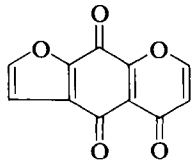


(236)

noteworthy features. Of course the quinol may present manipulation problems and it is sometimes more convenient to form a derivative of the hydroxyl groups *in situ*. An example of this procedure is the formation of **232** and **233** by reduction with zinc dust and acetic acid in the presence of acetic anhydride of the corresponding quinones. These quinol derivatives were used as intermediates in synthesis yielding the antibiotics mimocin (**234**)[92] and mimosamycin (**235**)[93], first isolated from the culture medium of *Streptomyces lavendulae*. The reduction of a quinone and the formation of derivatives of the quinol by the action of di- and trimethyl esters of phosphorous acid upon the quinone, psoralen (**236**) have been investigated[94]. The chromone quinone (**237**) yielded **238** with trimethyl phosphite[94].



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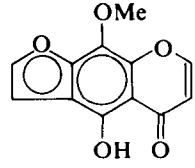
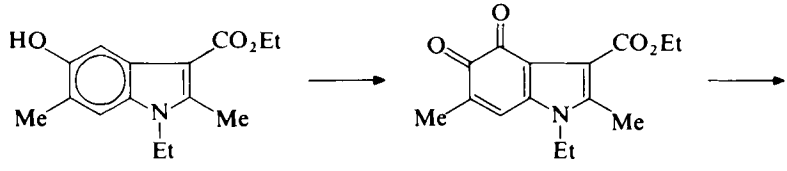
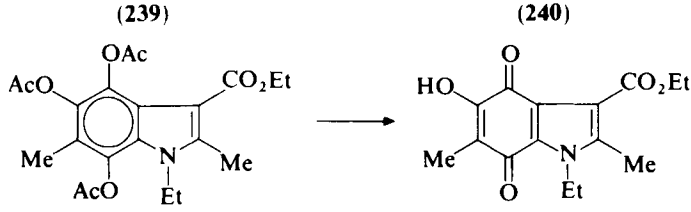


(238)

Thiele acetylation has been used in the heterocyclic series of quinones in order to introduce a 2-acetoxy group into a 1,4-quinone. Perhaps a more unusual use of the reaction is shown in the conversion of the *o*-quinone **240**, which is obtained from the Nenitzescu reaction derived 5-hydroxyindole **239**, into the triacetyl derivative of the *p*-quinol **241** and then into the *p*-quinone **242**[95].

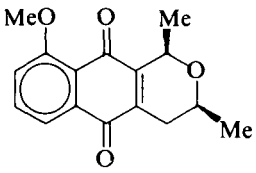


(239) (240)



(241) (242)

Intramolecular cyclization of 3-alkyl-2-hydroxy-1,4-quinones, where the alkyl group carries a reactive function (usually hydroxyl or olefin) in the γ-position, is an extensively used route (the Hooker reaction) to pyran-containing quinones. There are many examples where the starting quinone is a 1,4-naphthoquinone and the product is a naphthopyran quinone but there seem to be very few examples of the reaction where the initial quinone is heterocyclic. An important and increasingly numerous group of naturally occurring naphthopyran quinones with the heteroatom in the β-position is being identified. Eleutherin (**243**) and isoeleutherin (**244**) are the simplest representatives of the group and



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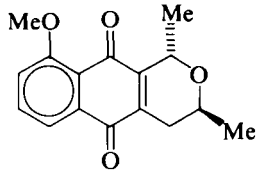
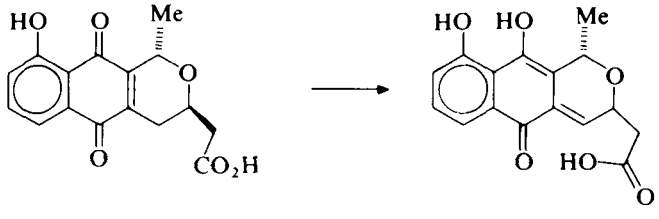
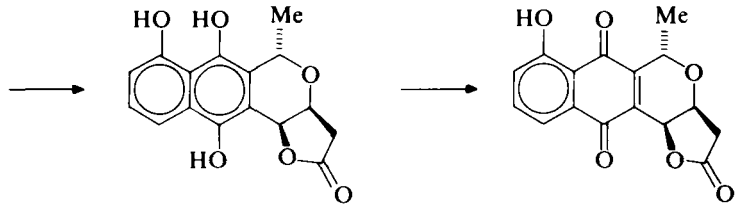


(244)

illustrate that the compounds may be considered to be derivatives of juglone. The aerial oxidation of nanaomycin A (**245**) to a mixture of nanaomycin D (**248**) and its enantiomer, kalafungin[96] has been explained by postulating the quinone methide **246** and the quinol lactone **247** as intermediates[97].

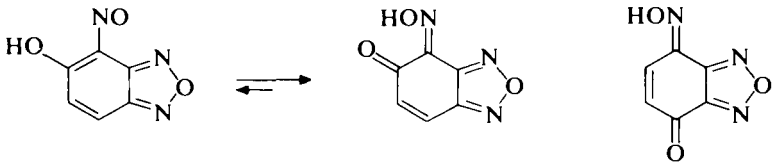


(245) (246)



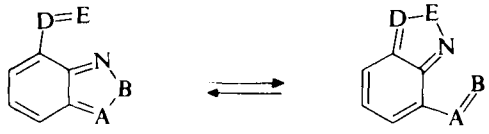
(247) (248)

Extensive studies have been made of the mono- and dioximes of 2,1,3-benzothiadiazolediones and 2,1,3-benzofurazandiones[98] and configurations assigned to geometrical isomers on the basis of NMR evidence. 5-Hydroxy-4-nitroso-1,3,2-benzofurazan (**249**) is the minor component of an equilibrium mixture with the quinone monoxime **250**. A similar relationship exists between the 7-hydroxy-4-nitroso-1,3,2-benzofurazan and the *p*-quinone monoxime **251**[99]. In their nitroso form these compounds can take part in the



(249) (250) (251)

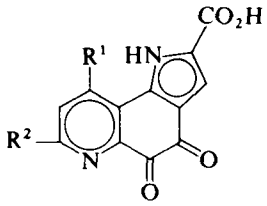
Boulton–Katritzky rearrangement, **252** to **253**, so that in organic solvents the major form of **249** is **250**, while in aqueous solvents the *p*-quinone derivative **251** is the major isomer[99]. Similar conversions from *o*- and *p*-quinones occur with 1,3,2-benzofurazan-4,5-quinone dioximes[100], presumably through the 5-hydroxyamino intermediate in this case. Some tricyclic 1,2,3-thiadiazole quinone derivatives form complexes with tetrathianaphthacene having high electrical conductivity[101].



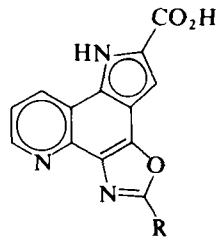
(252) (253)

Studies have been made of the interaction of thiophene quinones with metals and of the autoxidation of coumarin quinones. Electron spin resonance has been used to investigate the nature of the species formed when dithienobenzoquinones react with organometallic derivatives of group IVB[102] and VB elements[103] and of ions formed by reduction of these quinones with alkali metals[104]. ESR studies of the photoreactions of a range of quinones, including a dithienobenzoquinone, with phosphorus derivatives show that some derived phosphorus radicals add to both carbon–carbon and carbon–oxygen double bonds whilst others are regioselective and add to the latter only[105]. The autoxidation of hydroxycoumarins in aqueous alkali has been studied by ESR spectroscopy. 6,7-Dihydroxycoumarins undergo normal autoxidation through semiquinone radicals in dilute alkali to give the corresponding *o*-quinone. In stronger alkali the pyrone ring is cleaved to produce hydroxylated cinnamic acid semiquinones[106]. The inhibition of succinate oxidase activity by oxidized 6,7- and 7,8-dihydroxycoumarins is thought to be due to the activity of the semiquinone radicals formed in the oxidation[107].

The coenzyme, methoxatin (**254**), isolated from the methanol dehydrogenases of methylotrophic bacteria, has been mentioned earlier (Section II.A.2.f). It has been found to serve as a covalently bound coenzyme for bovine serum amine oxidase and it may be required as a cofactor for other mammalian enzymes. Indeed, methoxatin may be a vitamin. Methoxatin has been synthesized (see Section II.A.2.f) but it is not a readily available compound. Recently, the more accessible 7,9-didecarboxymethoxatin (**255**) has been prepared and shown to have electrochemical properties indistinguishable from those of methoxatin. Comparisons have been made of both the redox and amine oxidizing abilities of a series of related tricyclic quinones. The monocarboxylic acid **255** oxidizes primary but not secondary amines and, under certain conditions in the presence of oxygen



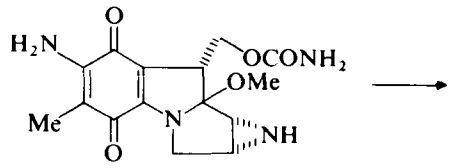
(**254**; $R^1 = R^2 = CO_2H$)
(**255**; $R^1 = R^2 = H$)



(**256**; R = Ph)
(**257**; R = H)

and primary amines, **255** is converted into oxazoles; for example **256** from benzylamine and **257** from glycine, presumably by decarboxylation following oxazole formation[108] in the latter case.

The naturally occurring antibiotic, mitomycin C (**258**) is an antineoplastic agent but, unfortunately, is highly toxic. The anticancer action of mitomycin is known to require an initial reduction step; perhaps in the first place to the semiquinone radical (**259**) and then to the quinol (**260**). This compound is now activated to form the vinylogue of a quinone methide (**261**) which is attacked by a nucleophile (DNA in the cell) to give **262** and this may subsequently cross-link by displacement of the carbamate to yield **263**. The mechanism of the biological activity of the mitomycins is being explored extensively[109].



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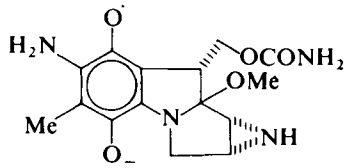
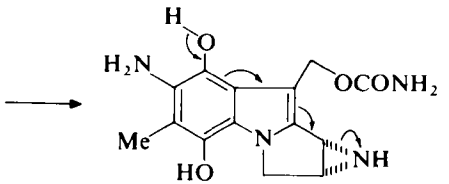


(259)



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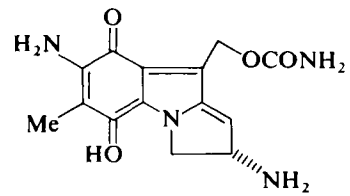
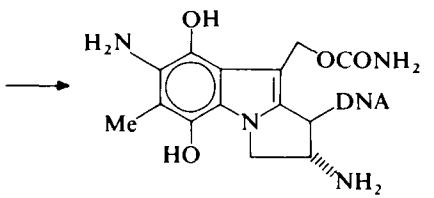
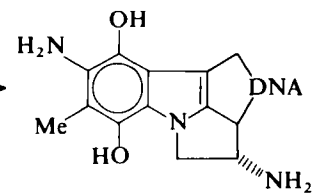


(261)

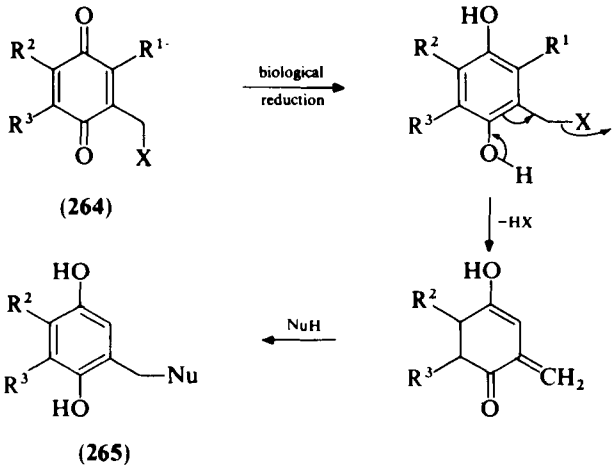


(262)



(263)

The proposed mode of action of mitomycin described above is a fairly complex example of an antitumour agent taking part in a process that has become known as bioreductive alkylation[110]. Support for this mechanism occurring in chemical systems has been obtained with mitomycin C[111,112]. It has been suggested that the principle of bioreductive activation to yield a highly reactive quinone methide may be usefully exploited in compounds which would be expected to show selective toxicity to oxygen-deficient (hypoxic) cells in solid tumours. These cells are known to be resistant to killing by X-rays and may also be resistant to chemotherapeutic agents. In a simple example, the principle of bioreductive activation and subsequent alkylation can be illustrated by the conversion of **264** through to **265**. The idea of quinone methide formation in biological systems has been



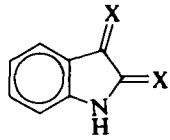
(264)

(265)

extended to include routes involving reductive phenolic deoxygenation and quinone–quinone methide equilibration. Nearly 200 naturally occurring quinones, many of them heterocyclic, have been shown to possess the structural features necessary for quinone methide formation by one of the three mechanisms[113]. In most cases the medicinal applications of these quinones have not been evaluated.

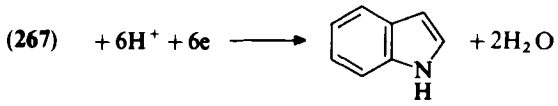
IV. QUINONE METHIDES

Heterocyclic quinone methides are a little investigated group of compounds, and this is particularly so for methides derived from those heterocyclic quinones which fall within the definition and limitations set in the introduction to this chapter. However, quinone methides which can be considered to be derived from compounds having a 1,2-dicarbonyl system as part of the heterocyclic moiety are well recognized and are the subject of considerable interest. The most extensively investigated example is indole-2,3-quinodimethane (**266**), a derivative of isatin (**267**) which is not usually considered to be a quinone and certainly was not recognized as such in the previous part of the chapter. Perhaps some justification for considering here such compounds as **266** is necessary.



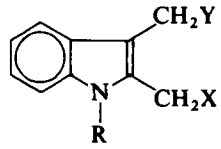
(**266**; X = CH_2)
(**267**; X = O)

In a discussion of carbocyclic non-benzenoid quinones, Turney[114] quotes a definition due to Trost of non-benzenoid quinones as any dicarbonyl species whose two-electron reduction product would generate a non-benzenoid aromatic system. If the scope of the definition is widened to include heterocyclic systems, then isatin falls into the category of a quinone, since two electrons are used in order to reduce the dicarbonyl system. In this way, **266** can be seen as a methide derived from a quinone. Probably the most important

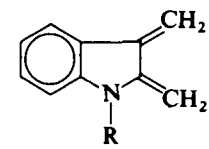


justification for a brief discussion of these compounds in this chapter is that they are useful synthetic intermediates whose importance is likely to increase.

The major interest in heterocyclic quinone methides is as synthetic intermediates which can either be trapped in intermolecular reactions with dienophiles or can undergo intramolecular reactions with a suitably disposed unsaturated system within the same molecule. The ease with which the heterocyclic quinone methides can be generated is crucial in the development of their use, and several routes have been devised. For example, the 2,3-bisbromomethylindole **268** yields **270** on treatment with sodium iodide[115] and the quaternary ammonium salt **269** gives **271** upon treatment with fluoride ion[116]. The

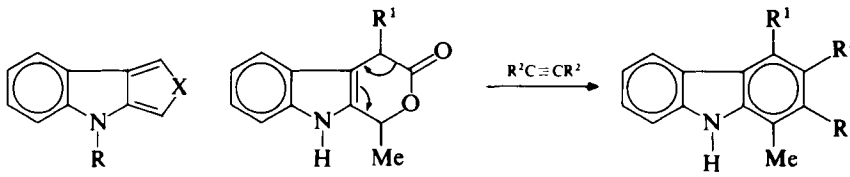


(**268**; R = COPh, X = Y = Br)
(**269**; R = Me, X = $SiMe_3$, Y = $\overset{+}{N}Me_3\bar{I}$)



(**270**; R = COPh)
(**271**; R = Me)

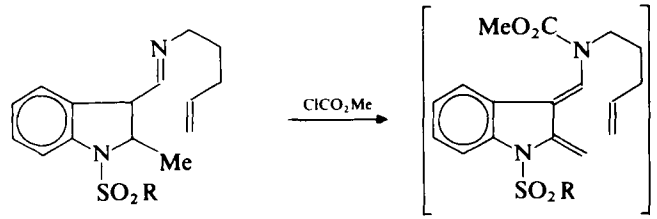
reactive methides such as **270** or **271** are readily trapped with dimethyl acetylenedicarboxylate to yield carbazoles or with *N*-phenylmaleimide or *p*-benzoquinone to give tetracyclic compounds. Similar intermolecular Diels–Alder reactions have been used to trap methides generated from tricyclic systems of the type **272**, where X is the heteroatom O, S or Se or the group NR^1. All these methods require that the indole nitrogen atom be protected. However, mild thermolysis of the readily available and unprotected pyrano[3,4-6] indole-3-ones (**273**) in the presence of acetylenes yield carbazoles **274**[117].



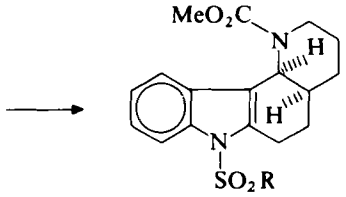
(**272**) (**273**) (**274**)

The concept of forming and trapping a heterocyclic quinodimethane has been taken one stage further by the inclusion of a dienophilic group within the quinodimethane structure at such a position that trapping by an intramolecular Diels–Alder cyclization occurs. This elegant approach to certain indole alkaloids has been exploited particularly by Magnus and coworkers[118]. The use of the intramolecular Diels–Alder process is illustrated by the route from **275** to the heterocyclic **277** via the quinodimethane intermediate **276**.

Some discussion of additional aspects of quinone methide chemistry is to be found in Section III.D and quinone imines are mentioned in Section II.A.2.C and occur in a reaction scheme in Section II.C.1.



(275) (276)

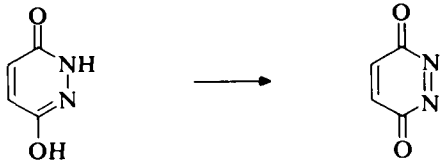


(277)

R = C_6H_4OMe-*p*

V. DIAZAQUINONES

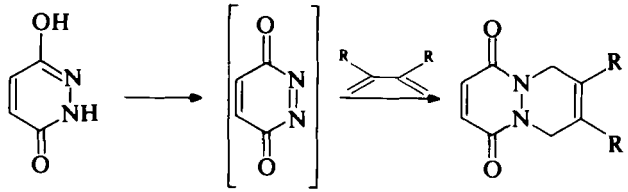
One of the few simple heteroaromatic systems not mentioned this far is phthalazine. This is because phthalazine quinones of the types so far discussed do not appear to have been recorded. However, 6-hydroxypyridazin-3(2*H*)-one (maleic hydrazide) (**278**), 4-hydroxy-1(2*H*)-phthalazinone and other heterocycles containing the cyclic hydrazide system are potentially capable of undergoing oxidation to the reactive diazaquinone: for example, the formation of **279** from **278**. The usual oxidizing agents are *t*-butyl



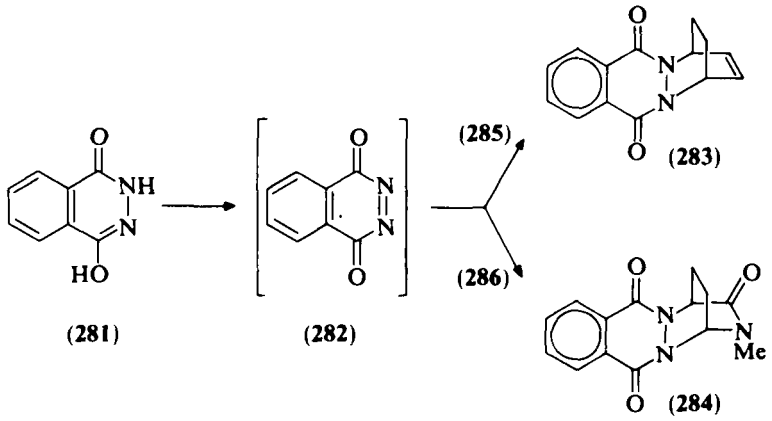
(278) (279)

hypochlorite or lead tetraacetate[119,120] but chlorine and nickel peroxide have been used. The first of these reagents has been used in the formation of a number of diazaquinones from the cyclic hydrazides derived from a range of heterocyclic 1,2-dicarboxylic acids[121].

Diazaquinones are generated *in situ* in the reaction mixture but some can be isolated at low temperature[121]. They readily undergo addition reactions and, indeed, are among the most powerful dienophiles. As expected then, diazaquinones undergo [4 + 2] cycloaddition reactions of the Diels–Alder type with a wide range of dienes to form cyclic systems having two bridgehead nitrogen atoms. Thus, maleic hydrazide (**278**) reacts with 2,3-disubstituted butadienes in the presence of an oxidizing agent to give products of the type **280**. Similarly, 4-hydroxy-1(2*H*)-phthalazinone (**281**) yields **283** and **284** with cyclohexa-1,3-diene (**285**) and 1-methylpyridin-2(1*H*)-one (**286**) via the diazaquinone **282**[122].

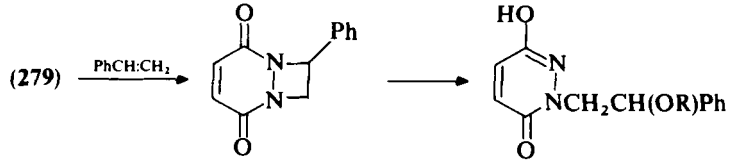


(280)

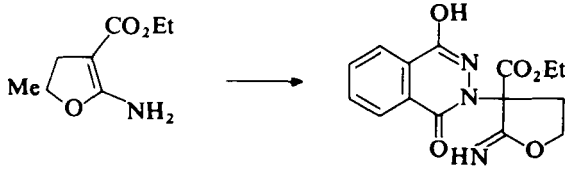


(281) (282) (283) (284)

Diazaquinones also undergo [2 + 2] cycloaddition reactions with olefins. For instance, diazaquinone **279** reacts with styrene to give the diazacyclobutane **287** which produces the ring-opened product **288** on treatment with water or *t*-butanol. A similar reaction occurs with enamines. For instance, the enamine **289** reacts with phthalazinedione **282** to give **290**[123].

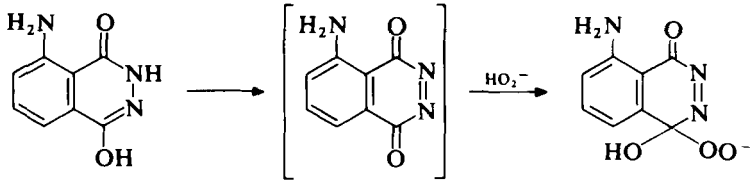


(287) (288)



(289) (290)

The mechanistic interpretations of the chemiluminescence of luminol (**291**) under oxidizing conditions have included the formation of the intermediate diazaquinone **292** at an early stage in the reaction process[121, 124]. Evidence in support of this includes the fact that the presence of cyclopentadiene in the reaction mixture prevents chemiluminescence as does the presence of 2- or 3-substituents on hydroxyphthalazinone nucleus. Recent studies of the reaction kinetics[125] lend weight to earlier suggestions that a carbon-centred peroxide (**293**) is formed from the diazaquinone (**292**). The peroxide **293** decomposes



(**291**) (**292**) (**293**)

through several steps to the aminophthalate ion with the emission of light. The mechanistic details of the chemiluminescent processes under both protic and aprotic conditions have yet to be firmly established.

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CHAPTER 18

Polymerization and polymers of quinonoid compounds

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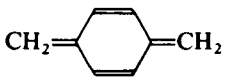
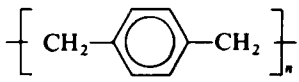
I. INTRODUCTION

Benzoquinone is a stable, yellow solid at room temperature and benzoquinone methides in general are far more reactive to dimerization and polymerization unless stabilized by appropriate substituents. Thus 1,4-benzoquinone dimethide (QM)* is so reactive that it gives poly(*p*-xylylene) spontaneously at room temperature, and 7,7,8,8-tetracyano-1,4-

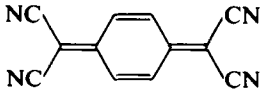




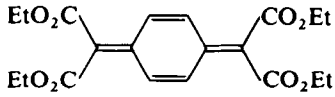
1,4-benzoquinone dimethide, *p*-quinodimethane, *p*-xylylene (QM)

poly-(*p*-xylylene) poly-QM

quinodimethane (TCNQ) and 7,7,8,8-tetrakis(ethoxycarbonyl)-1,4-quinodimethane (TECQ) stabilized by four strongly electron-withdrawing substituents are stable indefinitely and scarcely or sparingly homopolymerizable. However, these electron-



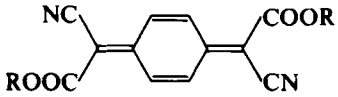
TCNQ



TECQ

accepting derivatives are copolymerizable readily and alternatingly with an electron-donating monomer such as styrene.

Unexpectedly, 7,8-bis(alkoxycarbonyl)-7,8-dicyanoquinodimethane (ACQ) is considered to occupy an intermediate position in physical and chemical properties between those of TCNQ and TECQ, is homopolymerizable via free radical and anionic initiation, the latter of which gives the high polymer with molecular weight above some millions, and is



ACQ

R = CH_3 (MCQ)
R = C_2H_5 (ECQ)
R = C_4H_9 (BCQ)

copolymerizable in random fashion with styrene. This unexpected polymerization behavior is believed to be useful both for the chemistry of quinonoid compounds and for polymer chemistry. In this chapter, polymerization and polymers of quinonoid compounds are described with emphasis on the usual polymerization behavior since the comprehensive review of Errede and Szwarc[1] mainly for unsubstituted quinonoid compounds and others[2] are already published.

*The IUPAC nomenclature for *p*-xylylene (*p*-quinodimethane, 1,4-benzoquinone dimethide) is 1,4-dimethylene-2,5-cyclohexadiene. However, since in this review reference is frequently made to the original papers, the trivial names are retained.

II. FLASH PYROLYSIS OF *p*-XYLENE

In 1947 Szwarc prepared a white polymeric material by a rapid flow (flash) pyrolysis of *p*-xylene under reduced pressure[3]. Since *p*-xylylene diiodide was detected among the pyrolysis products with iodine gas[4] he proposed the formation of *p*-xylylene (*p*-quinodimethane) (QM) in this pyrolysis [3,5]. He claimed the polymeric material to be poly-*p*-xylylene (poly-QM)[3] and proposed a mechanism for its formation[4] which involves thermal cleavage of carbon–hydrogen bonds of *p*-xylene to yield *p*-xylyl radicals, which in turn collide with each other to give *p*-xylene and QM through disproportionation. QM condenses and polymerizes to produce poly-QM, a high melting point substance which is inert to organic and inorganic reagents. Subsequently this material has been extensively studied on account of its unusual chemical and physical properties[6–11]. It has also attracted the interest of many quantum chemists[12–15]. Coulson and coworkers[12] calculated the energy difference of the QM molecule between the singlet ground state and the triplet excited state of QM to be 8–9 kcal mol^{-1}. The corresponding value for ethylene was determined by Evans to be 82 kcal mol^{-1} [16]. This unusually low energy difference is responsible for the very high reactivity of the QM molecule. In a series of studies on QM derivatives[17–27], Errede and Landrum prepared a 0.12 molar solution of the QM monomer. Rapid flow pyrolysis of *p*-xylene was carried out under reduced pressure of 4 mmHg at 1000°C and the pyrolysis product was condensed at −78°C to obtain solutions of monomeric QM up to 0.12 molar concentration[17]. In addition to QM, toluene, styrene, *p*-ethylstyrene, 1,2-di-(*p*-tolyl)ethane, a diarylmethane, anthracence and 4,4-dimethylstilbene were produced as by-products[21]. Even when kept at −78°C the solution of the pyrolysis product polymerizes very slowly. When an aliquot is drawn up into a warm pipet and allowed to flow back into the solution, the polymerization rate is markedly increased as shown in Figure 1, presumably due to formation of diradicals with *n*-mers. The

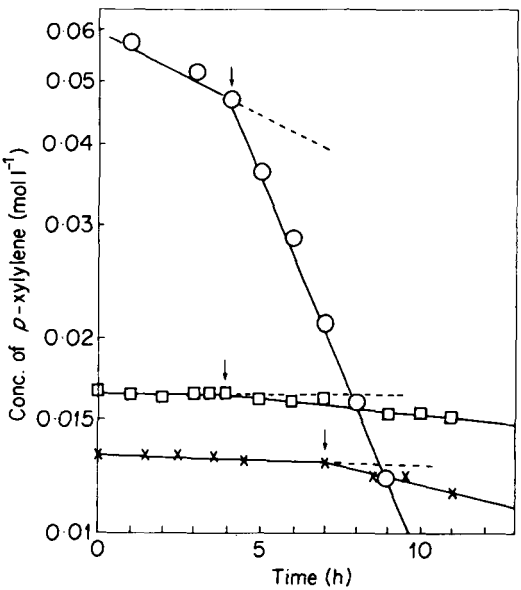


FIGURE 1. Polymerization of *p*-xylylene at −78°C: arrow indicates time when solution was disturbed by contact with object at room temperature. *Reproduced with permission from Ref.* 22. *Copyright* (1960) *American Chemical Society*

polymerization of QM takes place by successive addition of QM monomer until all the monomer is consumed or the polymeric free radical ends are entrapped in the polymer mesh. A linear polymer with molecular weight above 2×10^5 (obtained by measuring the number of radioactive iodine end groups incorporated into the polymer when the polymerization mixture is quenched with radioactive iodine after the polymerization has proceeded to 95% completion) is obtained[22]. Errede and coworkers have found that solutions which polymerize with apparent first-order rate constants of $9 \pm 1 \times 10^{-6}\ s^{-1}$ could be reproduced fairly consistently if the solution of the pyrolysis product was filtered through a bed of crystalline *p*-xylene using an apparatus that was prechilled to $-78°C$. Such solutions were used to determine the rate of polymerization at various temperatures above $-78°C$. The rates were found to obey a first-order law with respect to monomer as shown in Figure 2. The Arrhenius plot of the apparent first-order rate constants was linear and from its slope the activation energy for the polymerization was calculated to be 8.7 kcal mol^{-1}. The first-order plot of polymerization at $-78°C$ appears to be linear for the first 10 h but the deviation from the first-order kinetics becomes appreciable at longer reaction times as shown in Figure 3, corresponding to the slow but steady decrease in apparent rate constants. A plot of the reciprocal of the apparent rate constants against time is linear (Figure 4), indicating that the disappearance of the polymerization active sites is second-order with respect to the sites[20]. This treatment gives the ratio of apparent rate

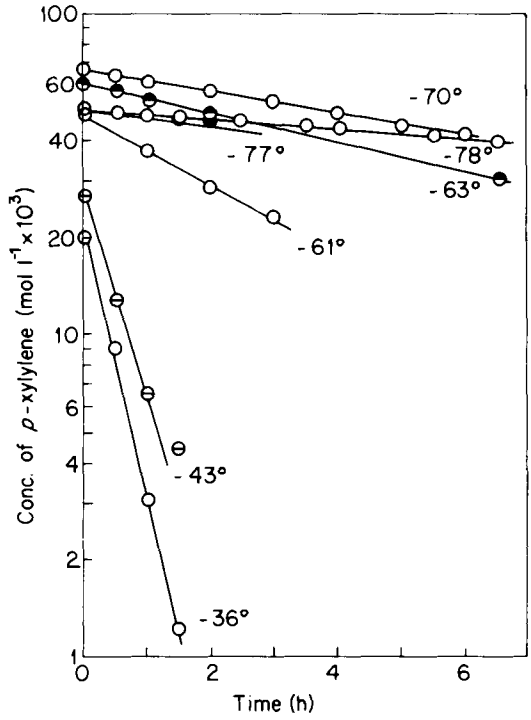


FIGURE 2. Polymerization of *p*-xylylene solution having as apparent rate constant (k_p) = $9 \pm 1 \times 10^{-6}$ at $-78°C$ as a function of temperature. *Reproduced with permission from Ref.* 22. *Copyright* (1960) *American Chemical Society*

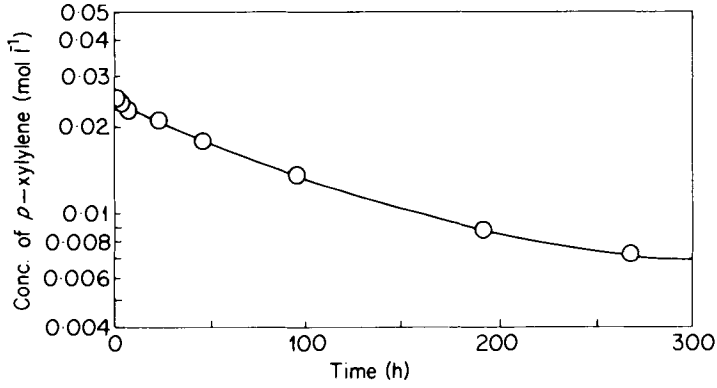


FIGURE 3. Polymerization of *p*-xylylene at −78 °C. *Reproduced with permission from Ref.* 22. *Copyright* (1960) *American Chemical Society*

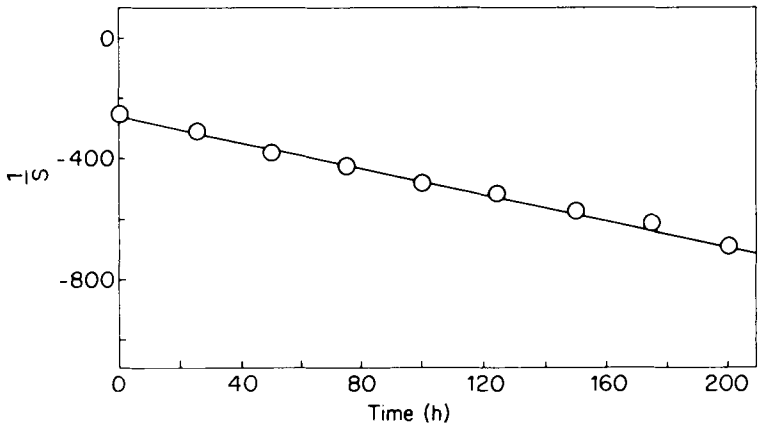


FIGURE 4. Reciprocal of the apparent rate constant (k_P) of *p*-xylylene polymerization at −78 °C as a function of time. $1/S - 1/S_0 = \frac{4.6\,K_t}{k}$ where $S = \frac{k_P}{2.3}$, then $\frac{2K}{k} = 0.904$. K is the specific rate constant for coupling of one insoluble free radical end-group with another. *Reproduced with permission from Ref.* 22. *Copyright* (1960) *American Chemical Society*

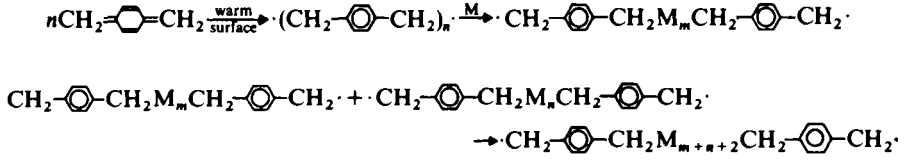
constant of disappearance of the polymerization active site to that of the polymerization to be 0.45, in sharp contrast to the conventional free radical vinyl polymerization in which termination is about $10^4 \sim 10^6$ times faster than propagation. Interestingly, one characteristics of QM polymerization is that the propagation, a radical addition reaction between a very stable polymer radical and a very reactive monomer, takes place with a rate similar to that of the termination, which is a radical coupling reaction between very stable polymer radicals.

QM does not copolymerize with conventional olefinic monomers at −78 °C in the usual way that both monomers are mixed, but the homopolymer of QM is obtained[19]. However,

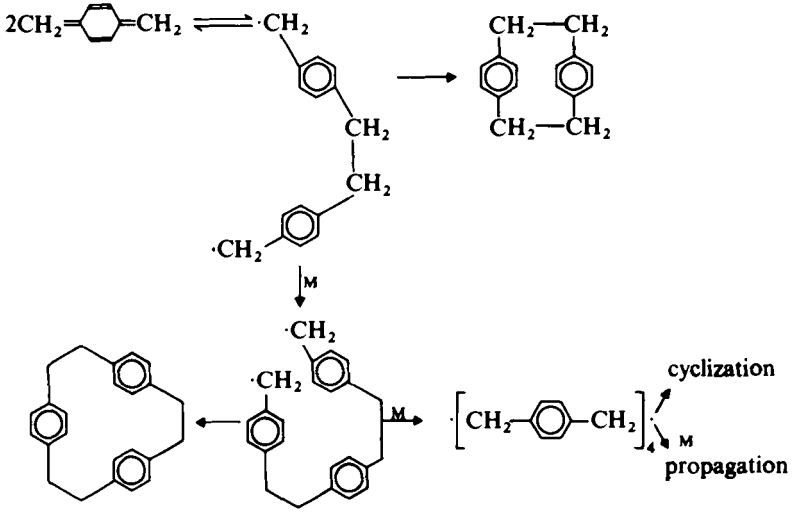
when a solution of QM at −78°C is added to a solution of a conventional monomer maintained at about 100°C, a copolymer can be produced[19]. On the other hand, QM is copolymerizable in the usual way with pseudomonomers such as sulfur dioxide[19], nitroso compounds[19] and phosphorous trichloride[25]. When oxygen or air is bubbled through a solution of QM, QM is copolymerized with oxygen to yield poly-QM peroxide with an oxygen content ranging from 1 to 23% (molar ratios of QM to oxygen from 31:1 up to 1:1)[18]. The polymerization of QM is not influenced by conventional chain transfer agents such as carbon tetrachloride, chloroform, *p*-cumene, nitrobenzene and hydroquinone[19]. When a three-fold excess of thiophenol, a highly reactive chain transfer agent, is added to a solution of QM, a telomer with a 21:1 ratio of QM to thiophenol units is obtained, i.e. the chain transfer reaction takes place with difficulty[19].

When a solution of QM is heated at a temperature higher than −78°C, in addition to the insoluble high molecular weight polymer, some soluble low molecular weight products such as a cyclo-trimer, cyclo-tetramer, 1,4-bis(2′-*p*-tolylethyl)benzene and oligomers are obtained[22]. Furthermore, when a solution of QM at −78°C is added dropwise to a hot inert solvent such as toluene at 100°C a cyclo-dimer is obtained in good yield[22]. The reaction scheme proposed by Errede and coworkers is shown in Scheme 1[22].

(a) Isothermal polymerization at low temperature

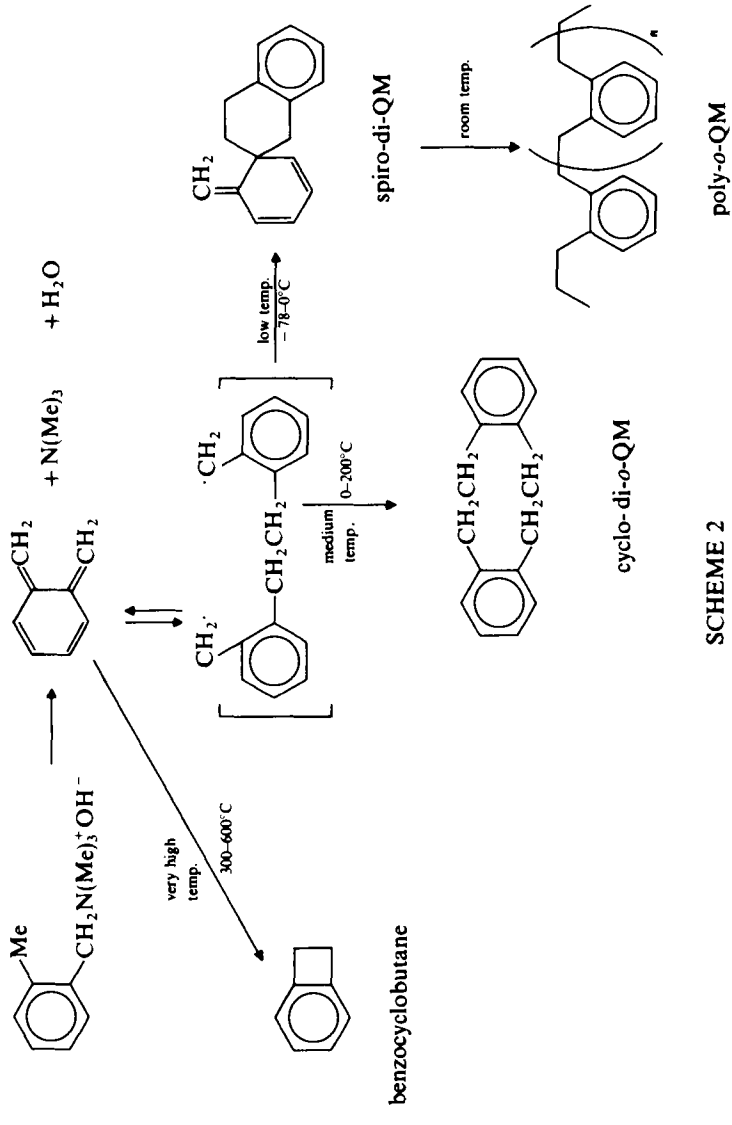


(b) Non-isothermal polymerization



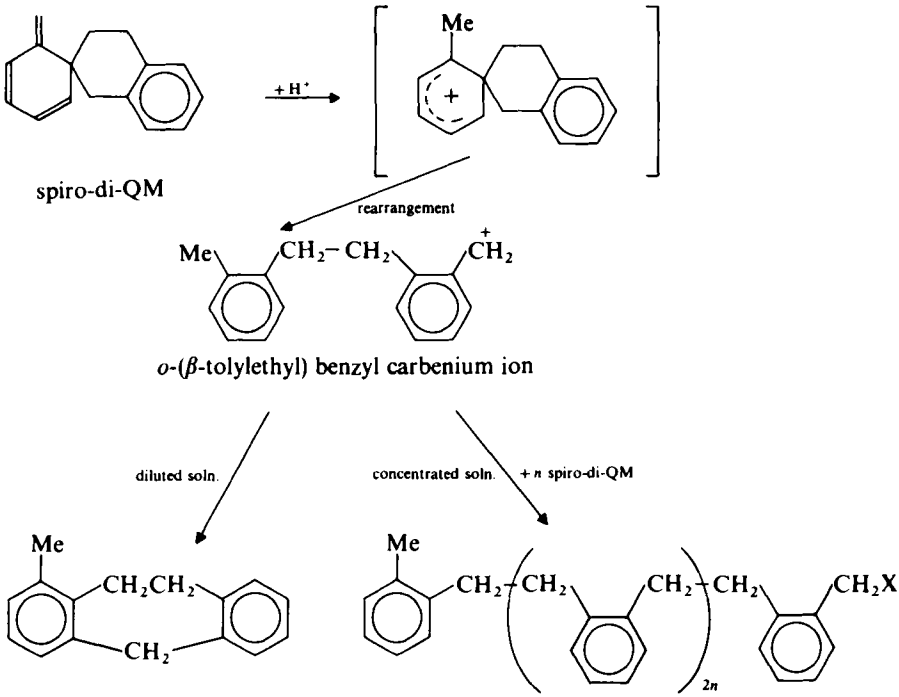
M: QM monomer

SCHEME 1


Me
CH2N(Me)3+OH−
+ N(Me)3
+ H2O
very high temp.
300–600°C
benzocyclobutane
medium temp.
0–200°C
low temp.
−78–0°C
spiro-di-QM
room temp.
cyclo-di-o-QM
poly-o-QM

SCHEME 2

Furthermore, Errede successfully prepared *o*-xylylene(*o*-quinodimethane) (*o*-QM) by Hofmann degradation of *o*-methylbenzyltrimethylammonium hydroxide at low pressure using a modified flow process[24]. Bis(*o*-methylbenzyl)ether and *o*-methylbenzyl alcohol were formed as by-products. When *o*-QM is warmed from $-78°C$ to room temperature, spiro-(5,5)-2,3-benz-6-methyleneundeca-7,9-diene(spiro-di-QM) is obtained in a good yield (Scheme 2). When *o*-QM is heated at temperatures from 0 to 200°C, cyclo-di-*o*-QM is obtained (Scheme 2). Furthermore, at 300–600°C, benzocyclobutane is predominantly formed (Scheme 2). Apparently, the formation of the spiro compound is favored at temperatures lower than 0°C. Spiro-di-QM can be preserved without any change at $-15°C$. It solidifies slowly when cooled to $-20°C$ and remelts at -5 to 0°C. When it is warmed to room temperature, it polymerizes very slowly to give high molecular weight poly-*o*-QM with an intrinsic solution viscosity of about 0.6 dl g^{-1} and glass temperature of 9°C[24]. Spiro-di-QM is copolymerized with conventional olefinic monomers such as styrene, acrylonitrile, methyl methacrylate, vinylidene fluoride and 1,3-butadiene[24]. In its polymerization an effective chain transfer with conventional reagents such as mercaptans and carbon tetrahalides[24] takes place in contrast to QM polymerization. When an acid catalyst is added to a concentrated solution of spiro-di-QM in hexane, poly-*o*-QM is obtained (Scheme 3). When the catalyst is added to a dilute solution of spiro-di-QM, 1-



1-methyl-dibenzo (a,d) cycloheptа-1,4-diene

poly-*o*-QM

X = terminal group

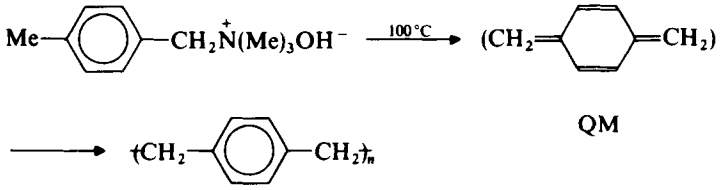
SCHEME 3

methyl-dibenzo (a,d) cyclohepta-1,4-diene is produced in good yield via intramolecular aromatic substitution of *o*-(*β*-tolylethyl)benzyl carbenium ion, formed in turn by rearrangement of the carbenium ion formed by addition of proton to the spiro-dimer[27] (Scheme 3). Spiro-di-QM is copolymerized with formaldehyde in the presence of an acid catalyst to give the corresponding polymeric ether[27].

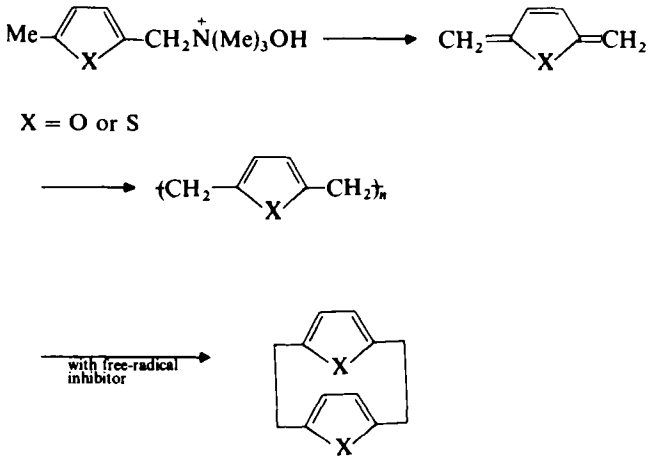
III. HOFMANN DEGRADATION AND OTHER METHODS

It was pointed out that the flash pyrolysis method of *p*-xylene has several limitations[28], i.e. (1) At most 25% yields of QM are obtained at the extreme pyrolysis temperature of 1150°C[6]; (2) the polymers obtained are loosely cross-linked[7,8] and (3) the vapor-deposited polymeric products formed by this method are contaminated with 10–20% of low molecular weight by-products[6,8].

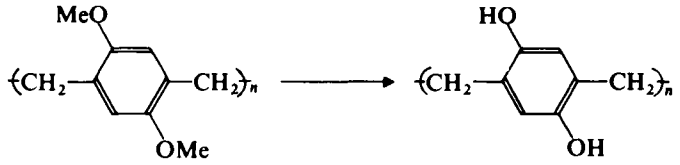
Fawcett[29] found that degradation of *p*-xylyltrimethylammonium hydroxide can take place at temperature as low as 100°C, and the immediate and concurrent polymerization of the monomer affords linear, soluble poly-QM in high yield. This method was successfully



applied to 5-methyl-2-furfuryltrimethylammonium hydroxide and 5-methyl-2-thienyltrimethylammonium hydroxide to obtain 2,5-dimethylene-2,5-dihydrofuran and -thiophene, respectively[30]. Both monomers are very reactive and they either polymerize readily, or in the presence of polymerization inhibitors form a heterocyclophane, crystalline cyclic dimer[30]. The furan monomer can be isolated at −78°C[30]. This method is

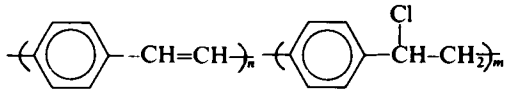


widely applicable to the synthesis of other QM polymers substituted with groups which are insensitive to the strongly basic medium; e.g. poly-2,5-dimethoxy-QM, which can be hydrolyzed to poly-2,5-dihydroxy-QM of redox properties[31]. In a modified process, *p*-

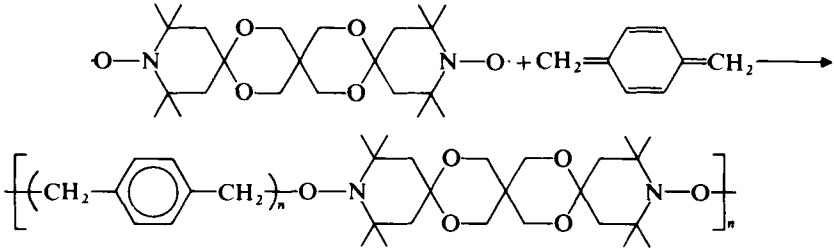


[(trimethylsilyl)methyl] benzyl trimethyl ammonium iodide can decompose with tetrabutylammonium fluoride in acetonitrile at room temperature to give poly-QM (51% yield) and cyclo-di-QM (6% yield), or at refluxing temperature to give 50% cyclo-di-QM[32].

Amorphous, low molecular weight (~ 3000) poly-*p*-xylylene (poly-QM) was synthesized by the Wurtz–Fitting reaction of 7,8-dibromo-*p*-xylene with sodium or magnesium metal[32]. This reaction was improved in various ways to give satisfactory yield of the crystalline polymer[9,34]. Thus, different dehalogenation agents such as reduced iron and cobalt powder suspended in water[35], Urushibara Nickel[35], naphthalene–alkali complex[36] and tin(II) chloride[37] were used. Electrolytic reduction was also applied[38]. When strong bases such as sodium amide[39,40], potassium *t*-butoxide[41] and sodium methoxide[42] are used, 7,8-dihalo-*p*-xylenes are converted to a copolymer of xylylidene and halo-QM with the following structure:



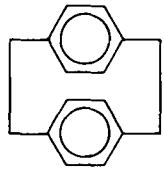
The reaction of 7-chloro-*p*-xylene with potassium *t*-butoxide in *p*-xylene in the presence of stable *N*-oxy biradicals such as 2,2,6,6-tetramethylpiperidinoxy-4-spiro-2′-(1′,3′-dioxane)-5′-spiro-5″-(1″,3″-dioxane)-2″-spiro-4″-(2‴,2‴,6‴,6‴-tetramethyl-piperidinoxy) gives the



corresponding copolymer[43] indicating the formation of QM as a reaction intermediate. The Friedel–Crafts reaction of benzene with 1,2-dichloroethane affords non-linear polymer since it is insoluble in any solvent and does not melt[44,45]. The same reaction of (2-chloroethyl)benzene likewise yields only an intractable polymer[45]. Di-azo-*p*-tolylmethane may undergo a cationic rearrangement to poly-QM[46].

IV. VAPOR-COATING PROCESS: GORHAM'S STUDY

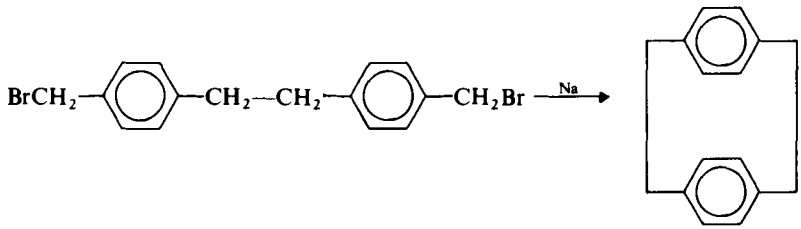
Gorham[28,47,48] had developed the vapor-coating process in which [2,2]-paracyclophane, cyclo-di-xylylene(cyclo-di-QM), is pyrolyzed in vacuum at 600°C and the pyrolyzed gas is



cyclo-di-QM

condensed on glass or metal surface to yield a tough, transparent polymeric film. This pyrolysis of cyclo-di-QM under milder and more readily controlled conditions than described by Szwarc and Errede results in almost quantitative preparation of the polymer containing less than 1% carbon tetrachloride extractable material, most of which is unreacted dimer. The polymer film obtained is readily soluble in hot chlorinated biphenyls and benzyl benzoate, indicating that it is free from cross-linking. This process has much greater advantages than the Szwarc–Errede direct pyrolysis of *p*-xylene. Due to the milder pyrolysis temperature the vapor-coating process may be applied to the preparation of a variety of substituted QM polymers.

Cyclo-di-QM was identified first by Brown and Farthing[11,49,50]. In the Szwarc's pyrolysis of *p*-xylene under reduced pressure at 680–850°C, the products obtained in 10–20% yield were mainly polymeric materials which were found to contain a small portion of low molecular weight compounds soluble in chloroform. Thus, 4,4'-dimethyldibenzyl was detected in the chloroform extract[9] together with traces of acetone insoluble compound[9] which was identified as [2,2]-paracyclophane by X-ray diffraction measurement[50]. Independently, Cram and Steinberg prepared a cyclic dimer in a poor yield by Wurtz–Fitting reaction of 4,4'-dibromomethyl dibenzyl[51]. Due to its distorted structure



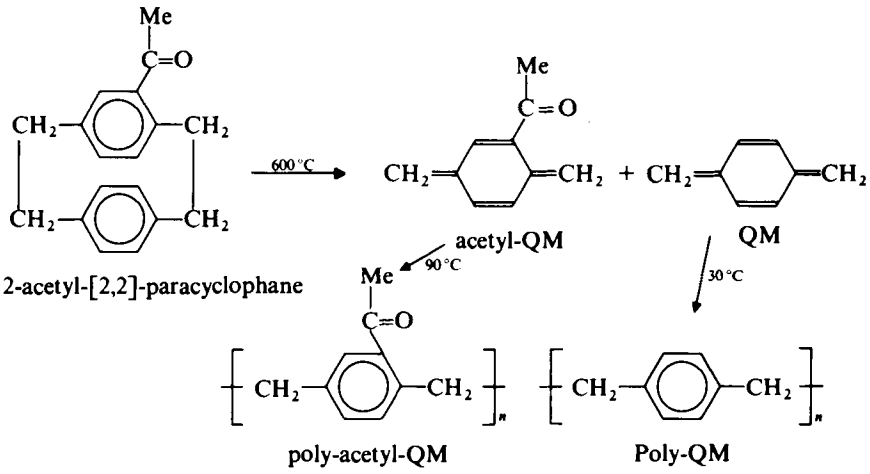
this dimer is sterically hindered and is generally referred to as cyclophane. It has been widely studied[52,53]. Errede and coworkers selectively prepared cyclo-di-QM by adding dropwise a 0.1 M QM solution in hexane maintained at −78°C to toluene heated at 100°C[22]. Pollart had developed a solvent quenching technique for the synthesis of cyclo-di-QM[54,55]. The condensation of QM vapor directly into an organic solvent at a temperature of 50–200°C results in the formation of cyclo-di-QM in a yield higher than 90%[54]. The rapid pyrolysis of a mixture of steam and *p*-xylene at 850–900°C followed by condensation of the vapor in an organic solvent such as *p*-xylene at 50°C gives cyclo-di-QM in 8–10% yield with only 0.1% polymeric material[55].

Gorham prepared about 30 types of substituted paracyclophanes including the dichloro, dibromo, dicyano, dimethyl, diethyl and tetrachloro derivatives[28] for the preparation of polymers of the respective substituted QMs.

The various substituted QM monomers condense and polymerize on the surface at temperatures lower than the threshold condensation temperature which is related to the

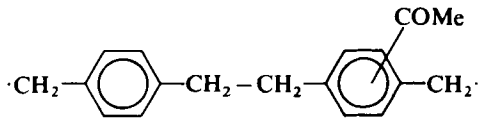
molecular weight and volatility of the respective monomer. The threshold condensation temperature is defined as the highest temperature of the surface on which the QM monomers condense and polymerize at an appreciable rate. At normal pressure (about 0.1 mmHg) the threshold temperatures are 30°C for QM, 60°C for 2-methyl-QM, 90°C for 2-ethyl- and 2-chloro-QM, and 130°C for 2-cyano-, 2-bromo-, and dichloro-QM.

The mechanism of the vapor-coating process of unsymmetrically substituted cyclo-di-QM has been studied[28]. The pyrolysis gas from mono-acetyl-cyclo-di-QM is initially led through a glass tube maintained at 90°C and subsequently through another glass tube kept at 20°C. The polymer deposited at 90°C has been identified as poly-acetyl-QM on the basis of its elemental analysis and IR spectrum. The second polymer obtained at 20°C has been characterized as poly-QM by its IR spectrum and by properties such as its melting point of 400°C and the insolubility in any organic solvent below 250°C. These results reasonably



SCHEME 4

suggest that acetyl-cyclo-di-QM is cleaved to two species, QM and acetyl-QM, (Scheme 4) instead of to a ring-opened biradical product such as



The subsequent fractional polymerizations which then take place depend upon the threshold condensation temperatures of these fragments.

Immediately after its preparation by the vapor-coating process, the poly-QM was found to be paramagnetic (radical concentration of $5\text{–}10 \times 10^{-4}$ mol g^{-1})[28]. When the polymer is annealed at an elevated temperature, the ESR signal disappears. It was therefore concluded that this polymerization takes place via a free radical mechanism similar to the scheme of Errede[22]. The polymer films deposited at room temperature in the vapor-coating process are always formed in the metastable α-polymorph, which transforms to the stable β-modification upon heating to 220°C or higher[47]. The irreversible transformation

was originally observed by Brown and Farthing[11]. Niegish found that single crystals of the poly-QM are prepared by heating a 0.05% (w/v) α-chloronaphthalene solution to 238°C, followed by slow cooling to 208°C[56]. These single crystals give two entirely different morphological structures. One is the pseudorectangular crystal due to the α-polymorph of monoclinic structure with parameters $a = 5.92$ Å, $b = 10.64$ Å, c (chain axis) $= 6.55$ Å, and $\beta = 134.7°$ and the other is the hexagonal crystal due to the β-hexagonal polymorph with parameters $a = 20.52$ Å and c (chain axis) $= 6.58$ Å[57]. Niegish stated that the α-polymorph is metastable because of irreversible α to β transition. However Wunderlich and coworkers mentioned that α-polymorph is stable[58]. They studied the crystallization during the polymerization of poly-QM in the vapor-coating process at temperatures ranging from −196 to 200°C and made the following qualitative observations[58, 59]. The monomer is weakly absorbed on the surface, and at temperatures of 26 to −17°C, its concentration is high enough and the mobility is sufficient to initiate polymerization which can be fast if the monomer is available. Before the polymerization is terminated, successive crystallization starts to take place. Since the glass temperature of the polymer is at 80°C, crystallization from the bulk polymer should not be possible in this temperature range. The necessary mobility of the molecular chains is maintained since the chains are on the surface and are swollen within the monomer. Under these conditions, folded-chain crystals of the stable α-polymorph oriented epitactically with chain axis in the crystal surface are grown with a rate determined by temperature (preferential orientation of the chains on the surface is observed). A steady-state separation between polymerization and crystallization sites might be established. At a low temperature, the polymerization rate would be determined by the higher monomer concentration while the crystallization rate would slow down due to decrease in chain mobility, resulting in the further separation between both sites. At higher temperatures, the polymerization rate decreases due to decrease in monomer concentration in the surface. At temperatures lower than −78°C, the surface concentration increases to such an extent that the monomer is immobilized due to surface condensation, yielding a change in the mechanism. The monomer either crystallizes first in the solid state and polymerizes and crystallizes then in the solid state or it polymerizes and immediately crystallizes to the polymer crystal, which is irregularly folded and unoriented with metastable β-polymorph. In either case, polymerization and crystallization are simultaneous. At temperatures higher than the glass temperature, the polymer is produced in a two-stage process where initially a small amount of the polymer (seed material) is deposited at a temperature lower than the threshold condensation temperature of 30°C and the second-stage polymerization is carried out at high temperatures. The crystallization rate is thought to increase rapidly with temperature while the polymerization rate decreases due to the lower monomer concentration on the surface, probably leading to an approach of the crystallization site to the polymerization site (i.e. simultaneous polymerization and crystallization). The crystals obtained are of the β-polymorph as at the lower temperature. Beach[60] developed a reaction model for the vapor-coating process of QM in which the temperature, pressure and rate of growth variables are correlated with the molecular rate constants, diffusional mass transport and molecular weights. The parameters obtained by numerical analysis in his model are: a propagation rate constant $k_p = 6.11 \times 10^3\ \mathrm{cm^3 g^{-1} s^{-1}}$ at 20°C from Errede's data[22], an initiation rate constant $k_i = 6.34 \times 10^2\ \mathrm{cm^6 g^{-2} s^{-1}}$ at 20°C and a diffusivity between monomer and polymer of $D = 1.13 \times 10^{-9}\ \mathrm{cm^2 s^{-1}}$. The initiation is the step of a formation of a trimer diradical with activation energy of 24.8 kcal mol^{-1}. The rates of consumption of the monomer by initiation at −30 and 20°C are calculated to be 100 000 times and 320 times, respectively, slower than by propagation.

The vapor-coating process was developed by Union Carbide Corporation which commercially manufactures the unusual polymers under the trade name Parylene; Parylene N refers to unsubstituted poly-QM and Parylene C to poly-2-chloro-QM.

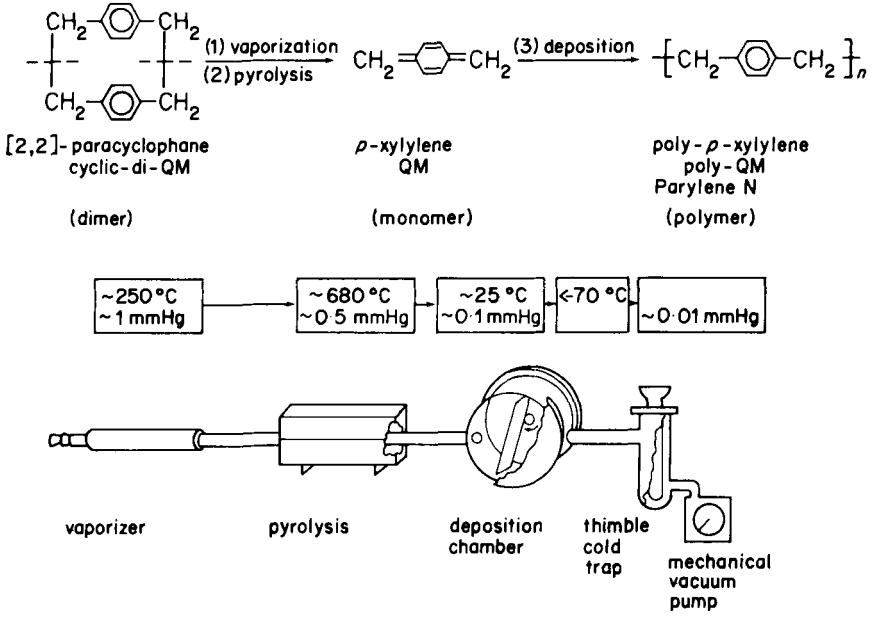


FIGURE 5. Schematic representation of the vapor-coating process, using [2,2]-paracyclophane as an example

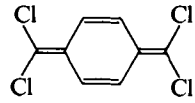
The process involves three steps as outlined in Figure 5 for Parylene N. The film deposited on the surface in this process is free of pinhole and can be adjusted to a thickness of several submicrons to several millimeters. The physical and electrical properties of these polymers are compiled in Table 1. They exhibit high moduli at room temperature and tensile moduli above 300 000 psi. Their glass transition temperatures are in the range of 60–90°C and their melting points are as high as 290–400°C. These polymers have low gas-permeability characteristics especially of Parylene C. Parlylene N is a dielectric exhibiting a very low dissipation factor, a high dielectric strength and a dielectric constant invariable with frequency. It is used as a dielectric of a plastic-film capacitor. Parylene C additionally exhibits a very low permeability to moisture and other corrosive gases and is especially useful for the coating of critical electric assemblies.

7,7,8,8-Tetrafluoro-QM polymer was prepared by a similar process starting from the corresponding paracyclophane derivative[61,62]. This polymer also exhibits physical and electrical properties similar to those of Parylene polymers (Table 1). It is extremely resistant to sunlight even after exposure for 3600 h while Parylene N is changed to a brittle material after exposure for 535 h[61].

V. POLYMERIZATION OF HALO-*p*-XYLYLENES

A. 7,7,8,8-Tetrachloro-*p*-xylylene

7,7,7,8,8,8-Hexachloro-*p*-xylene is dechlorinated on a copper mesh under reduced pressure (0.1–1.0 mmHg) at 300–600°C to 7,7,8,8-tetrachloro-*p*-xylylene (TCX) in yields up to 90%[63]. The pyrolysis product is absorbed in toluene maintained at −78°C and the



TCX

resulting yellow colored suspension is cooled down to give yellow solid. Repeated recrystallization from tetrahydrofuran under nitrogen at temperatures ranging from −60 to 0°C gives yellow needles. When these crystals are kept at room temperature, their yellow color gradually fades and poly-TCX is formed. For example, a tetrahydrofuran solution of 0.0244 M TCX polymerizes at 20°C for 30 min up to a conversion of 50%[63]. When the gaseous pyrolysis product is condensed on the surface maintained at a temperature above 120°C, a transparent film of poly-TCX is formed[64]. The freshly prepared film still contains monomeric TCX and exhibits a strong ESR signal, indicating the presence of free radicals. Polymerization is completed by annealing of the film at 190°C for 30 min[64]. When the pyrolysis gas is deposited on the surface below 90°C, crystalline monomeric TCX is formed and then gradually polymerizes[64].

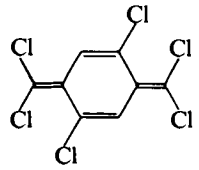
At 100°C, both crystals and a large amount of a transparent film are obtained simultaneously[64]. Poly-TCX displays a tensile modulus of 480 000 psi, a tensile strength of 8000 psi, a softing range of 280–290°C, a dielectric constant of 2.81, and a dissipation factor 2.6×10^{-4} at a frequency range of 60 cycles to 100 kilocycles[64]. TCX may be recrystallized and kept at temperatures below −10°C without polymerization. It is therefore clearly more stable than QM but is much more reactive than conventional olefinic monomers.

TABLE 1. Physical and electrical properties of poly-QMs

	Poly-*p*-xylylene (Parylene N)[28]	Polychloro-*p*-xylylene (Parylene C)[28]	Poly-7,7,8,8-tetrafluoro-*p*-xylylene[61]
Tensile properties (at room temperature)			
Tensile strength (psi)	6800	10 600	6200
Tensile modulus (psi)	350 000	460 000	360 000
Elongation at break (psi)	10–15	220	100
Tensile modulus at 200°C (psi)	25 000	25 000	—
Thermal properties			
Crystalline melting point (°C)	400	290	
Glass transition temperature (°C)	80	80	90
Permeability at 77°F (cm^3 (STP) mil/100 in^2 24 h)			
H_2	250	200	
CO_2	225	21	
O_2	30	8	
N_2	9	1	
H_2O (g mil/100 in^2 24 h)	6.0	0.6	
Electrical properties (1–3 mil film)			
Dielectric constant (1 kc/s^{-1})	2.65	3.2	2.36
Dissipation factor (1 kc/s^{-1})	0.0002	0.04	0.0008
Dielectric strength (v/mil^{-1})	7000	5000	5250

B. 2,5,7,7,8,8-Hexachloro-*p*-xylylene

2,5,7,7,8,8-Hexachloro-*p*-xylylene (HCX) is prepared by passing 2,5,7,7,7,8,8,8-octachloro-*p*-xylene vapor over a copper mesh at 500°C at reduced pressure[65]. Pure yellow

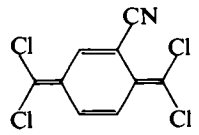


HCX

crystalline HCX is obtained by the same recrystallization method used for the isolation of TCX. HCX can be kept without any change below 0°C for a long time, but at room temperature it changes gradually to a white powder which has been identified as poly-HCX on the basis of its elemental analysis. The change of HCX crystals to its amorphous polymer on standing was examined by X-ray diffraction in order to follow the rate of the solid state polymerization of HCX. The height (or intensity) of the X-ray diffraction profile, corresponding to the crystalline portion (monomer) in the probe, decreased linearly with time, indicating the zero reaction order of the spontaneous solid state polymerization. After 66 h the X-ray diffraction of the monomer disappeared completely. The zero reaction order can be explained in terms of the effective monomer concentration in the solid state. Thus, when an active site migrates into a crystal in the course of polymerization, the number of HCX monomers around the active site, which are susceptible to polymerization, is considered to be constant. The polymer chain already formed does not influence this number because it always exists just in the near of the active site and is excluded from the HCX crystal. In addition, the formation of the active sites is regarded to be independent of the number of HCX monomers in the volume unit of the crystal. The rate of spontaneous polymerization of HCX in benzene follows first-order kinetics with respect to monomer concentration with apparent first-order rate constants of $5.56 \times 10^{-5}\ s^{-1}$ at 30°C and $13.33 \times 10^{-5}\ s^{-1}$ at 50°C. The linear Arrhenius plot gives an apparent activation energy of 8.2 kcal mol^{-1} for the polymerization of HCX. The temperature at which the apparent first-order constant for the polymerization of QM in toluene is $5.56 \times 10^{-5}\ s^{-1}$ is calculated to be −68°C by using an apparent first-order rate constant of $9 \times 10^{-6}\ s^{-1}$ at −78°C and the apparent activation energy of the polymerization of 8.7 kcal mol^{-1} [22]. Since the corresponding temperature for HCX is 30°C, QM is much more reactive than HCX, i.e. HCX is a much more stable monomer than QM.

C. 2-Cyano-7,7,8,8-tetrachloro-*p*-xylylene

2-Cyano-7,7,8,8-tetrachloro-*p*-xylylene (CTCX) is prepared similarly by gas-phase dechlorination of 2,5-bis(trichloromethyl)benzonitrile on a copper mesh[66]. CTCX also



CTCX

readily undergoes spontaneous polymerization with approximately first-order kinetics with respect to monomer at monomer concentrations higher than $2–3 \times 10^{-3}$ mol l^{-1} whereas it is second order below this monomer concentration. The apparent first-order rate constant at an initial monomer concentration of 0.01 mol l^{-1} is 1.3×10^{-4} s^{-1} at 30°C and the apparent activation energy is 8.8 kcal mol^{-1}. The apparent rate constant is 5.6×10^{-5} s^{-1} at 15°C. Consequently, the tendency of CTCX for homopolymerization is higher than that of HCX (30°C) and much lower than that of QM (−68°C).

D. Copolymerizations with Styrene

In contrast to QM, the three monomers TCX, HCX and CTCX have been found to undergo spontaneous copolymerization with various vinyl monomers such as styrene (St), isoprene, vinyl acetate, acrylonitrile and methyl methacrylate[60–62].

For the copolymerization systems of TCX–St, HCX–St, CTCX–St (Figure 6), CTCX–HCX (Figure 7) and CTCX–TCX (Figure 8) the following monomer reactivity ratios have been obtained; r_1 (TCX) = 85 and r_2(St) = 0 at 22°C[65], r_1(HCX) = 3 ± 0.8 and r_2(St) = 0.02 ± 0.05 at 50°C[63], r_1(CTCX) = 12 ± 6 and r_2(St) = 0.03 ± 0.02 at 20°C[64], r_1(CTCX) = 0.8 and r_2(HCX) = 0.95 at 20°C and r_1(CTCX) = 0.25 and r_2(TCX) = 1.7 at 20°C[66]. The relative reactivities of TCX, HCX and CTCX toward the active site of the polymer chain with a terminal St unit have been estimated from comparison of the reciprocals of r_2(St) of the TCX–St, HCX–St and CTCX–St systems: TCX($1/r_2 = 1/0$) > HCX(1/0.02) ≧ CTCX(1/0.03). The monomer reactivity ratios are thereby assumed to remain essentially unchanged in the temperature range of the polymerization (20–50°C). A comparison of the reciprocals of r_1 (CTCX) of the TCX–CTCX and HCX–CTCX systems gives another order of the relative reactivities of the monomers toward the active site of the polymer chain with a terminal CTCX unit: TCX (1/0.25) > HCX (1/0.8) ≧ CTCX (1/1). Both reactivity orders are in good agreement. In addition, the relative reactivities have been

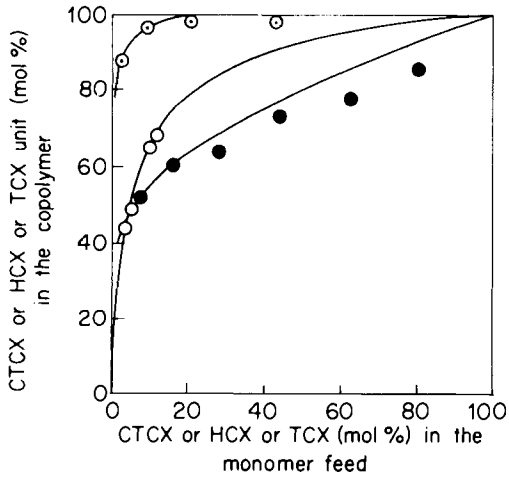


FIGURE 6. Composition of the copolymerization of CTCX with styrene (St) (O), copolymerization of HCX with St (●), and the copolymerization of TCX with St (O). The lines are obtained by a theoretical equation using the monomer reactivity ratios; r_1 (CTCX) = 12 and r_2 (St) = 0.03 for the CTCX–St system, r_1 (HCX) = 3.0 and r_2 (St) = 0.02 at 50°C for the HCX–St system and r_1 (TCX) = 85 and r_2 (St) = 0 at 22°C for the TCX–St system

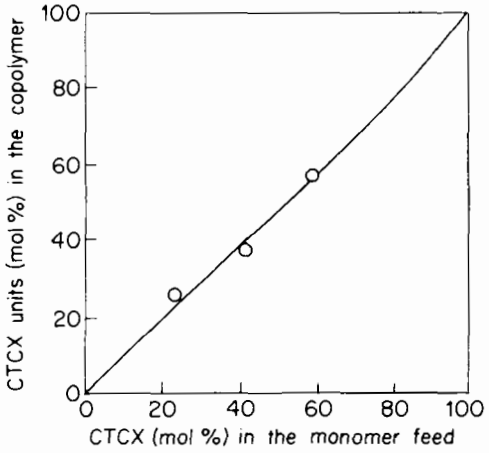


FIGURE 7. Composition of the copolymerization of CTCX with HCX. (O) refers to experimental value, and solid line is calculated from the theoretical equation using r_1 (CTCX) = 0.8 and r_2 (HCX) = 0.95

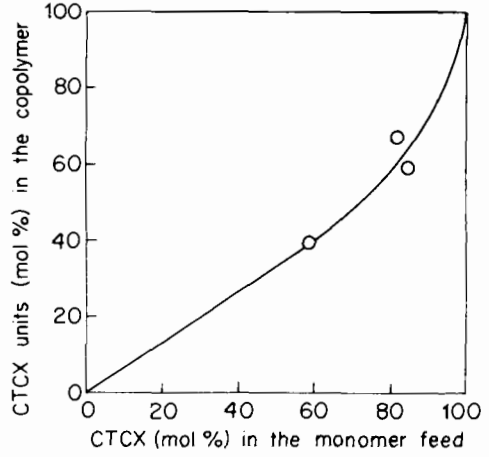


FIGURE 8. Composition of the copolymerization of CTCX with TCX. (O) refers to experimental value and solid line is calculated from the theoretical equation using r_1 (CTCX) = 0.25 and r_2 (TCX) = 1.7

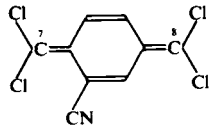
compared with some parameters estimated by quantum chemical calculations such as π-electron density, frontier electron density, and the free valence at the exocyclic carbon (Table 2). CTCX has different values at the two exocyclic carbons because of its unsymmetric structure. The results are in agreement with the relationship of Kooyman and Farenhorst[68] between the relative reactivity of the trichloromethyl radical toward the aromatic hydrocarbons (such as benzene, naphthalene, anthracene, pyrene, etc.) and the highest free valence index of the hydrocarbon and also with the relationship of Hush[14]

TABLE 2. π-Electron density, frontier density and free valence at the exocyclic carbon of CTCX, HCX and TCX[a]

		π-Electron density			
		Ground state	Singlet excited state	Frontier density	Free valence
CTCX[b]	C(7)	0.9642	1.0169	0.4048	0.412
	C(8)	0.9556	1.0675	0.4598	0.421
HCX		0.9691	1.0676	0.4469	0.424
TCX		0.9869	1.0716	0.4620	0.440

[a] Calculated by the ASMO–SCF method.

[b]



between the polymerizability of QM compounds and the free valence at their corresponding exocyclic atom.

Another interesting phenomenon has been found in the copolymerization of HCX with St starting with a high St monomer feed such as 92.3 mol%. A change of the content of the

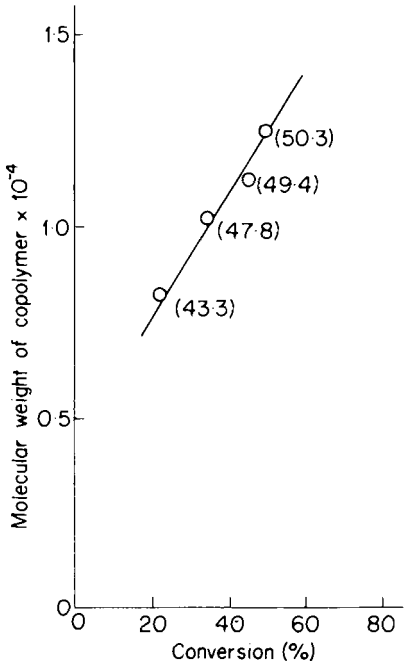
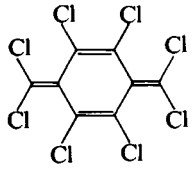


FIGURE 9. Relationship between the molecular weight of the copolymer and conversion in the copolymerization of HCX with St starting with high St monomer concentration (92.3 mol%). Figures in parentheses refer to the content of the St unit in mol% in the copolymer obtained

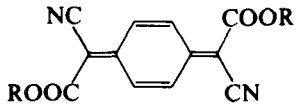
St unit in the copolymers with conversion can be observed similarly as in common vinyl copolymerization but its magnitude is very small (see Figure 9). The molecular weight of the obtained copolymers increases significantly with conversion as shown in Figure 9. This implies that this polymerization partially proceeds by a stepwise addition mechanism, i.e. it exhibits a somewhat 'living character' which is in sharp contrast to a conventional free radical vinyl polymerization. Therefore, it may be presumed that the active site of a polymer molecule with a terminal HCX unit reacts not only with St and HCX monomers via the radical addition mechanism but also with HCX via radical coupling.

Perchloro-*p*-xylylene prepared by Ballester and coworkers[69] exhibits no tendency for polymerization and is very stable even at elevated temperatures.



Perchloro-*p*-xylylene

VI. POLYMERIZATION OF 7,8-BIS(ALKOXYCARBONYL)-7,8-DICYANOQUINODIMETHANE



ACQ

R = Me (MCQ)
R = Et (ECQ)
R = Bu (BCQ)

Preparation and polymerization of 7,8-bis(alkoxycarbonyl)-7,8-dicyanoquinodimethane (ACQ) with ethoxy (ECQ) and methoxy groups (MCQ) as the alkoxy group has been briefly reported independently by Hall and coworkers[70] and Iwatsuki and coworkers[71] in 1982. On the basis of the chemical structure, ACQ was expected to occupy an intermediate position in physical and chemical properties between 7,7,8,8-tetracyanoquinodimethane (TCNQ)[72,73] and 7,7,8,8-tetrakis(alkoxycarbonyl)quinodimethanes with methoxy (TMCQ)[72,74] and ethoxy (TECQ)[75] groups as the alkoxy group. On the other hand, ACQ was also expected to have properties different from those of TCNQ, TMCQ and TECQ, in which the substituents at the 7 and 8 positions are identical, because ACQ has two different substituents at the 7 and 8 positions.

The polymerization behavior of 7,8-bis(butoxycarbonyl)-7,8-dicyanoquinodimethane (BCQ) was investigated in detail as a representative of ACQ[76]. Some physical properties of its high polymer were also studied because BCQ could be prepared more easily than other ACQ monomers and because its polymer is more soluble in many conventional organic solvents[76]. The electron-accepting character of BCQ was measured by means of the charge transfer complex method by using an empirical relationship[77] between the electron affinities of the acceptors and the energy of the intermolecular charge transfer absorption

(ν_{CT}) of the corresponding complexes with a given donor such as hexamethylbenzene (HMB). The solvent used was benzene. *p*-Chloranil (PCA) which was reported to have an electron affinity of 2.48 eV[78] was employed as a reference acceptor compound. Table 3 gives the intermolecular charge transfer absorption (λ_{max}^{CT}) and the electron affinity of BCQ as well as of TMCQ, TECQ, MCQ, ECQ, TCNQ, PCA and maleic anhydride (MAnh). It is apparent that ACQ is intermediate in electron-accepting character between TMCQ and TCNQ, as expected from their chemical structures.

TABLE 3. Electron-accepting ability of ACQ and other related quinodimethanes, PCA and maleic anhydride (MAnh)

				ACQ				
	MAnh	TMCQ,	TECQ	Me	Et	Bu	PCA	TCNQ
Reduction potential[a]/V		−0.83		−0.65				−0.20
CT band[b] HMB (nm)		< 440–550[c]		500	497	496	516	594
EA (eV)				2.16[d]	2.10[d]	2.07[d]	2.48[e]	2.87[e]
CT band[f] DMA(nm)	422		457					
EA (eV)	1.33[e]		2.27[g]					

[a] Measured by cyclovoltammetry. In MeCN Ag/Ag^+.
[b] λ_{max} of CT band with hexamethylbenzene (HMB).
[c] CT bands are overlapped seriously with absorption of TMCQ and TECQ.
[d] Calculated by using the equation; $h\nu = Ip - EA + C$, and 2.48 eV for *p*-chloranil[78].
[e] Cited from literature[78].
[f] λ_{max} of CT band with dimethylaniline (DMA).
[g] Calculated by using the equation $h\nu = Ip - EA + C$, and 1.33 eV for MAnh[78].

TABLE 4. Homopolymerizations[a] of BCQ initiated by various catalysts at 0°C

Run no.	Catalyst, 1	[BCQ]/[1]	Solvent	ml	Time h	$\bar{M}n/10^4$[e]
1	Et_3N	103	$CHCl_3$	5	1.0	9.5
2	Et_3N	103	$(CH_2Cl)_2$	5	1.0	35.0
3	Et_3N	100	Toluene	10	1.0	21.5
4	Proton sponge[b]	102	$CHCl_3$	5	1.0	10.6
5	Pyrrolidine	108	$CHCl_3$	5	1.25	5.6
6	Pyridine	93	$CHCl_3$	5	0.5	No polymer
7	Ph_3P	101	$CHCl_3$	5	1.0	No polymer
8	TPP–Al[c]	59	CH_2Cl_2	5	56	10.1
9	BuLi	106	Toluene	10	0.7	103.0
10	EtMgBr	6	Toluene	10	0.5	1.9
11	AIBN[d]	8	$CHCl_3$	5	5.5	4.4
12	$BF_3 \cdot Et_2O$	101	CH_2Cl_2	5	1.0	No polymer

[a] [BCQ] = 28 mM for runs 1, 2, 4–8, 11 and 12 and [BCQ] = 14 mM for runs 3, 9 and 10.
[b] Proton sponge: 1,8-bis(dimethylamino)naphthalene.
[c] TPP–Al: 5,10,15,20-tetraphenylporphine–Et_2AlCl. Reaction at room temperature.
[d] Azobisisobutyronitrile to which one drop of AcOH was added.
[e] Number-average molecular weight, $\bar{M}n$, determined by GPC, THF eluent.

Table 4 summarizes the results of the polymerizations of BCQ with various anionic, cationic and free radical initiators. It is obvious that BCQ is homopolymerizable with anionic and free radical initiators but not polymerizable with cationic ones. On the other hand, TCNQ[72,73] and TECQ[75] were reported to be not homopolymerizable with any initiators, though they react as powerful electron-accepting monomers.

The fact that BCQ carries two different kinds of substituents (cyano and butoxycarbonyl) at the 7 and 8 positions whereas TCNQ and TECQ have identical substituents at the 7 and 8 positions, is considered to be responsible for the high homopolymerizability of BCQ.

The copolymerization of BCQ with styrene was found to be really in random fashion as shown by the shape of the copolymerization composition curve (Figure 10) and the fine straight lines for its Kelen–Tüdös and Fineman–Ross plots. The monomer reactivity ratios were obtained as r_1(BCQ) = 0.9 ± 0.3 and r_2(St) = 0.02 ± 0.02 at 60°C. TCNQ and TMCQ were reported to copolymerize with styrene alternatingly and spontaneously even though TMCQ is a weaker acceptor monomer than BCQ. The random behavior of the copolymerization of BCQ with styrene was thought to be closely associated with the homopolymerizability of BCQ, due to the lack of identity of both substituents either at the 7 or at the 8 position. Monomer reactivity ratios of the copolymerization of BCQ with styrene allow one to calculate the monomer reactivity parameters such as Alfrey–Price's Q and e values of BCQ as 9.9 and +1.20, respectively. When these values are compared with values of maleic anhydride (MAh) (Q = 0.23, e = 2.25)[79] and ethyl α-cyanoacrylate (Q = 2.14, e = 0.78)[79], it is found that BCQ has the higher electron affinity but the lower e value than MAnh. On the other hand, the e value of BCQ seems to be in good agreement with that of ethyl α-cyanoacrylate, which has a similar substitution pattern at the terminal carbons.

When BCQ was dissolved in some conventional basic solvents, the yellow color of the solution changed rapidly to colorless, indicating a rapid conversion of the BCQ monomer to its polymer. Table 5 summarizes the results of the polymerization of BCQ in five basic solvents. As shown in Table 4, most amine compounds except pyridine are capable of initiating the polymerization of BCQ in chloroform or toluene. The basicity of the basic

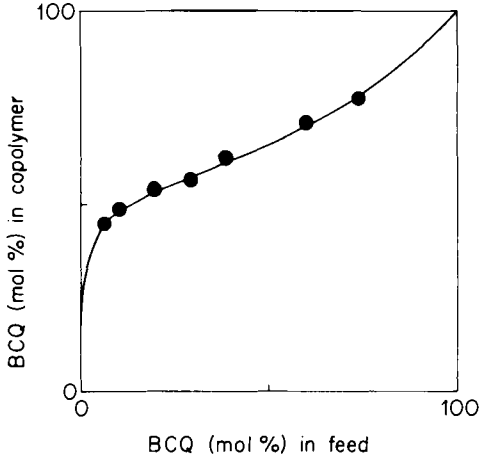


FIGURE 10. Copolymerization composition diagrams of BCQ with styrene

TABLE 5. Spontaneous homopolymerizations[a] of BCQ in various solvents

Solvent	$\Delta\nu_{OD}$[b]	$\bar{M}n/10^4$[c]	$\bar{M}w/\bar{M}n$[c]
Acetonitrile	49	410	1.72
Acetone	64	455	1.94
THF	93	86	1.80
DMF	107	340	1.89
DMSO	141	360	1.76

[a] BCQ 5.5 mg; solvent 1 ml; temp., room temp.
[b] OD stretching frequency shift of MeOD-base hydrogen bonding.
[c] Number-average and weight-average molecular weight, ($\bar{M}n$) and ($\bar{M}w$), determined by GPC using THF as eluent.

compounds could be expressed in terms of the strength of the hydrogen bond formed between a proton-donating alcohol such as methanol-d and the basic compounds[80]. In this respect, pyridine is a weaker base ($\nu_{OH} = 168\ cm^{-1}$) than triethylamine ($\nu_{OH} = 238\ cm^{-1}$)[81] and indeed pyridine is incapable of initiating the polymerization, but triethylamine is capable. Thus basicity is apparently related to the capability of initiating the polymerization of BCQ. However, even solvents such as acetonitrile and acetone, which are much less basic than pyridine, are capable of initiating the polymerization of BCQ, suggesting that additional factors other than basicity also exert an influence on the initiation of the anionic polymerization of BCQ. The relationships of the ratio of the concentration of the monomer to the initiator vs. the molecular weight of the polymers ($\bar{M}n$) in polymerizations with various amounts of butyllithium and triethylamine as initiator at an almost fixed concentration of BCQ as the monomer in toluene are shown in Figure 11.

In almost all the experimental runs with butyllithium the yellow color of the reaction systems disappeared within 0.5 h, suggesting that a complete conversion to the polymer is reached rapidly. However, when the concentration of butylithium was very small especially for [BCQ]/[BuLi] > 100, the polymerization was found to become slow and the reproducibility of the experiments to become poor. It is likely that the ratio of the concentration of the monomer to that of the initiator is linearly related to the molecular weight of the polymer produced. The results of the polymerization with additional monomer additions are shown in Figure 12. Apparently, after all the monomer additions, the polymers exhibit one fairly sharp peak in their gel permeation chromatography, even though their peak widths become a little bit broader with each monomer addition. The peak positions move to the higher molecular weight side with each monomer addition, indicating that the polymeric species produced after the monomer has completely polymerized is still able to react with added monomer molecules and to grow to a polymeric species with a higher molecular weight. Hence, the polymerization of BCQ with butyllithium is a living-like type process.

The polymerization with triethylamine was also found to give a polymer with high molecular weight. In the concentrated range of triethylamine, e.g. for [BCQ]/[triethylamine] < 5, the polymerization reaches completion within 0.5 h and the molecular weight of the polymers obtained increases with a decrease in the concentration of triethylamine in the monomer feed, as expected. However, in the more dilute range of triethylamine, i.e. for [monomer]/[initiator] > 6, the polymerization cannot be completed within an hour and molecular weight of the polymer obtained decreased with a decrease of the triethylamine concentration in the monomer feed. In spite of the low concentration of

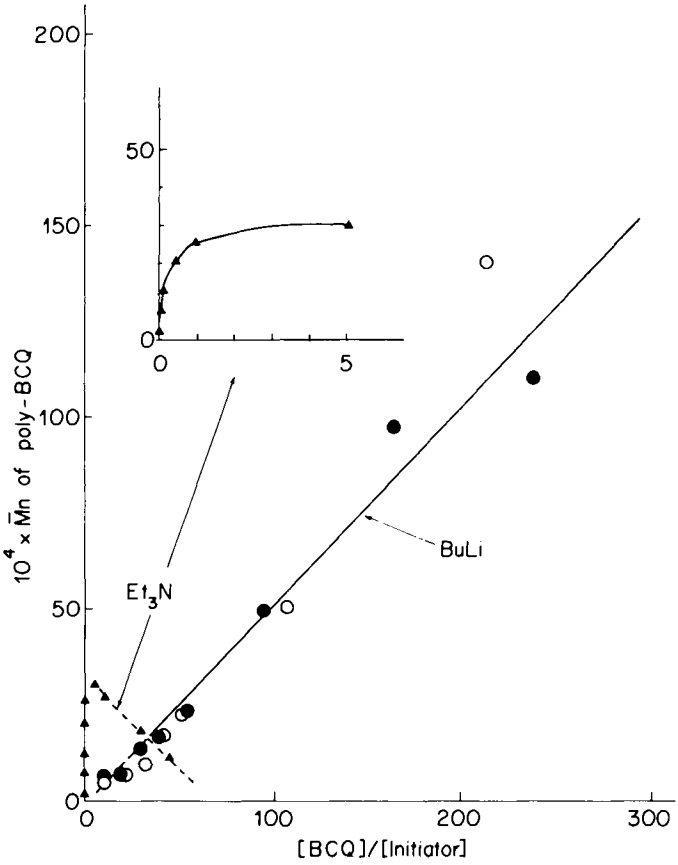


FIGURE 11. Relationships of the molecular weight of the polymer vs. the concentration ratio of monomer to initiator in polymerizations of BCQ with butyllithium ((O and (●) correspond to duplicated series of runs) and triethylamine (▲) at 0 °C in toluene (monomer concentration, 10 mM: solution volume, 10 ml)

triethylamine, a polymer with a lower molecular weight is produced, contrary to the general behavior in a living type of anionic polymerization. The calculated values of the initiator efficiency were found to increase extensively with the ratio of monomer to initiator. At the moment no satisfactory mechanism has been given for the polymerization with triethylamine, especially for the decrease in the molecular weight of the polymer with a decrease in initiator concentration in the monomer feed.

When pyrrolidine was employed as an initiator (i.e. [BCQ]/[I] = ca. 10^{-3}) a 1 : 1 adduct was formed, while triethylamine gave a polymer with high molecular weight of the order of 10^4 under the same experimental condition of high initiator concentration. Therefore, it is conceivable that an electron transfer reaction takes place between pyrrolidine and BCQ to give a zwitterion with positive and negative charges on the pyrrolidinium and α-cyano-α-(butoxycarbonyl)benzyl moieties, respectively. The latter moiety is considered to be able to add a BCQ monomer. When excess pyrrolidine is present, it is conceivable that the

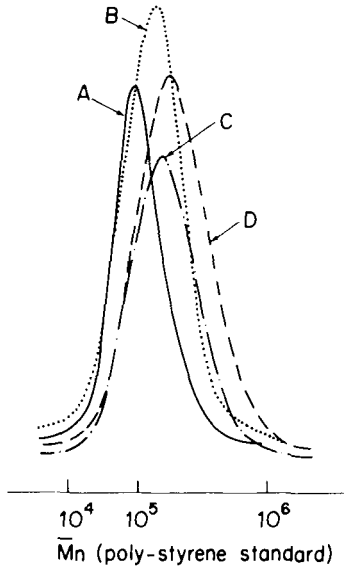


FIGURE 12. Gel permeation chromatogram of poly-BCQs with three additional monomer additions. Initiator butyllithium; polymerization temperature, 0 °C; solvent, toluene; concentration of the monomer, 8.13 mM; volume of the monomer solution at each addition, 7 ml. (A) The initial polymerization at [BCQ]/[BuLi] = 21(——). Molecular weight ($\bar{M}n$) of the polymer = 9.1×10^4 and the index of $\bar{M}w/\bar{M}n = 1.59$. (B) After the first additional monomer addition (. . . .). $\bar{M}n$ of the polymer = 14.0×10^4 and $\bar{M}w/\bar{M}n = 1.76$. (C) After the second addition (— · —). $\bar{M}n$ of the polymer = 18.0×10^4 and $\bar{M}w/\bar{M}n = 1.79$. (D) After the third addition (— — —). $\bar{M}n$ of the polymer = 20.0×10^4 and $\bar{M}w/\bar{M}n = 1.83$

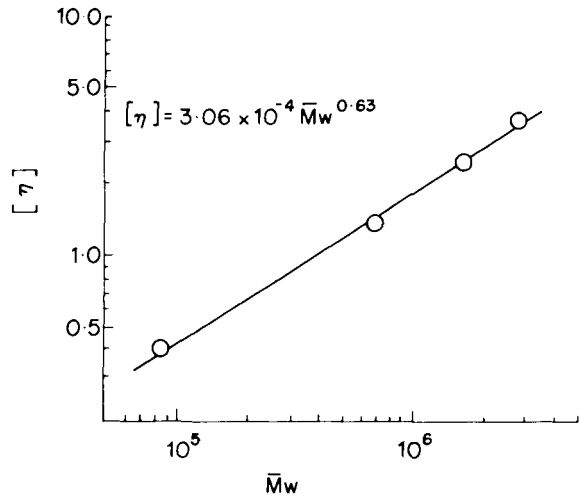
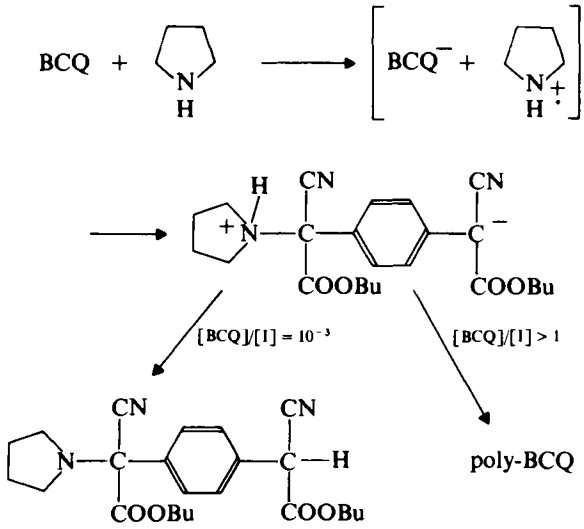


FIGURE 13. Relationship of solution viscosity[a] vs. molecular weight[b] for poly-BCQ. [a] Limiting viscosity number, using Ubbelohde viscometer in tetrahydrofuran, at 25 °C. [b] Light scattering measurement

concentration of the zwitterions will be sufficiently high and an intermolecular proton transfer from a pyrrolidinium moiety to the anionic moiety will give the 1:1 adduct before reaction with another BCQ monomer. In the case of triethylamine, a similar formation of a



zwitterion also takes place, but since the quaternary ammonium ion has no hydrogen for the proton transfer reaction, the zwitterion is able to add the BCQ monomer in preference to termination reactions to give a polymer with a molecular weight of ca. 10^4. Moreover, an efficient electron transfer reaction of triethylamine to BCQ (the first step of an initiation reaction) was assumed to be important only at relatively high concentration of triethylamine molecules, due to very low initiator efficiency and the slow polymerization rate at the low initiator concentration.

The Mark–Houwink equation for poly-BCQ in tetrahydrofuran has been obtained. The polymer obtained with butyllithium was fractionated by means of fractional gel permeation chromatography to give four fractions for which the limiting viscosity number and the weight-average molecular weight were obtained from solution viscosity and light scattering measurements, respectively. The results are shown in Figure 13, where the α-index was found to be 0.63, indicating that this polymer chain is fairly flexible in solution even though it was expected to be stiff due to the presence of phenylene and tetra-substituted ethylene groups in the backbone chain.

The solubility of poly-ACQ (poly-BCQ, poly-MCQ and poly-ECQ) is summarized in Table 6. The glass transition temperature (Tg) for poly-BCQ, poly-MCQ and poly-ECQ

TABLE 6. Solubility of poly-ACQ

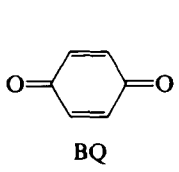
Poly-ACQ	Soluble	Swell	Insoluble
Poly-BCQ Poly-ECQ	(Benzene, acetone, THF $CHCl_3$, DMSO, DMF)		(MeOH, hexane isopropyl ether (IPE))
Poly-MCQ	conc. H_2SO_4	DMSO, DMF	(Benzene, acetone, THF, $CHCl_3$, MeOH, hexane, IPE)

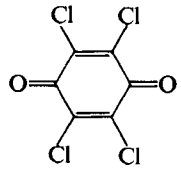
was measured by differential scanning calorimetry. The results are summarized in Table 7, together with data[82] for poly(alkyl methacrylate), poly(alkyl α-cyanoacrylate), poly(*p*-alkylstyrene), and poly-QM for comparison. Tgs for poly-ACQs at 108°C are independent of the alkoxy group, whereas Tgs for polymers of vinyl compounds such as poly(alkyl methacrylate), poly(alkyl α-cyanoacrylate), and poly (*p*-alkyl-styrene) vary significantly, depending upon the alkyl group. The difference in Tg dependence on substituent was thought to be attributable to the difference in the backbone chain structure. Poly-ACQs exhibit higher Tg by ca. 30°C than poly-QM. The difference was considered to arise from the fact that poly-ACQs carry many highly polar substituents, such as cyano and alkoxycarbonyl groups.

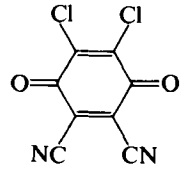
VII. POLYMERIZATION BEHAVIOR OF QUINODIMETHANES AS ACCEPTOR MONOMERS

A. Introduction

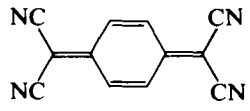
p-Benzoquinone(BQ) which displays electron-accepting properties is a well-known inhibitor[83,84] and retarder[85] in free radical polymerization; it undergoes copolymerization with styrene despite its very low susceptibility to copolymerization[85,86]. *p*-Chloranil (PCA), which is a much stronger electron acceptor than BQ, undergoes alternating copolymerization with styrene in the presence of free radical initiators[87,88]. 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone (DDQ), an even stronger electron acceptor than PCA, is also

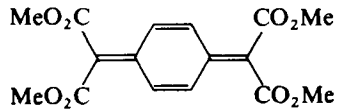

BQ


PCA


DDQ

alternatingly copolymerized with styrene even in the absence of a free radical initiator[89,90]. The relative reactivity of these benzoquinones as acceptor monomers toward the polymer radical with a terminal styrene unit is closely related to their electron-accepting character[90,91].


TCNQ


TMCQ

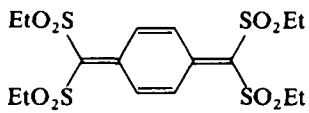
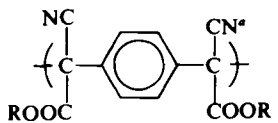
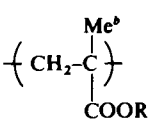
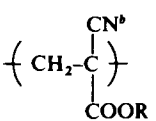
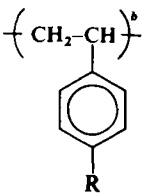
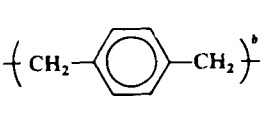
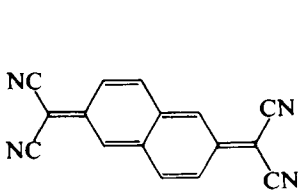

TESQ

TABLE 7. Glass transition temperature (Tg) of the poly-ACQ, poly-alkyl methacrylates, poly-(alkyl α-cyanoacrylates), poly (*p*-alkyl styrenes) and poly-*p*-xylylene

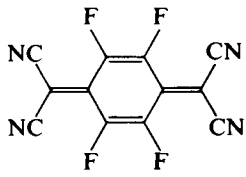
R					
-H				100	
-Me	108	105	170	93	
-Et	108	65	175	<78	~80
-Bu	108	20	(140)	6	

[a] Obtained by DSC.
[b] Ref. 82.

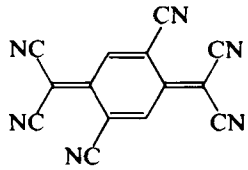
Chemists at Du Pont described the preparation of a series of new compounds with electron-accepting properties such as 7,7,8,8-tetracyanoquinodimethane (TCNQ)[92], 7,7,8,8-tetrakis(methoxycarbonyl)quinodimethane (TMCQ)[92], 7,7,8,8-tetrakis(ethylsulfonyl)quinodimethane (TESQ)[93] and 11,11,12,12-tetracyanonaphtho-2,6-quinodimethane(TNAP)[94] in the early 1960s.



TNAP



$TCNQF_4$

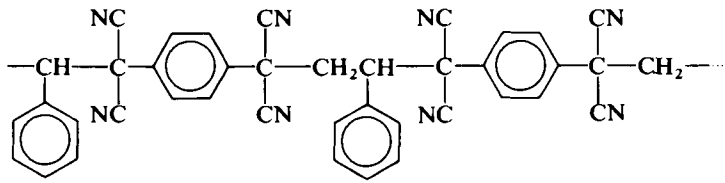


$TCNQ(CN)_2$

In addition, 2,3,5,6-tetrafluoro-7,7,8,8-tetracyanoquinodimethane ($TCNQF_4$)[95] and 2,5,7,7,8,8-hexacyanoquinodimethane ($TCNQ(CN)_2$)[95], which display stronger electron-accepting properties than TCNQ, were prepared in 1975[95]. These compounds have been extensively studied due to their powerful electron-accepting character, in connection with their charge transfer complexes with high electric conductivity referred to as organic metal[96]. Whereas TCNQ was reported to initiate a cationic polymerization of alkyl vinyl ethers[97,98], polymerization of these quinodimethanes as acceptor monomers had not been studied in detail until the spontaneous alternating copolymerization of TCNQ with styrene was reported in 1978[73].

B. TCNQ–Styrene System

When TCNQ is mixed with a styrene solution in acetonitrile, a dark red color attributed to the formation of a charge transfer complex between TCNQ and styrene develops instantaneously. On standing at room temperature for a day, TCNQ dissolves slowly in acetonitrile and reacts with styrene at the interface of the TCNQ crystals, thereby producing a gelatinous shell of swollen pink-colored copolymer[73]. The copolymer is insoluble in conventional organic solvents such as benzene and chloroform, and it swells in aprotic polar solvents such as *N*,*N*-dimethylformamide and dimethyl sulfoxide at room temperature and eventually dissolves on prolonged heating at higher temperatures (e.g. 80 °C). Elemental analysis and NMR data reveal that the copolymer is a truely alternating copolymer. Its ^{1}H-NMR spectrum contains only two kinds of peaks; an aromatic peak of δ7.0–7.5 ppm and a peak at δ3–3.5 ppm assigned to the methine and methylene protons of the styrene units which are much more deshielded than the corresponding protons of homopolystyrene whose peaks generally appear between δ1.0 and 3.0 ppm[99]. This deshielding is presumed to arise primarily from the powerful electron-withdrawing effect of the neighboring dicyanomethylene groups when the styrene unit directly links two TCNQ units on both its sides.



C. Systems of Styrene with $TCNQF_4$, TNAP and $TCNQ(CN)_2$

$TCNQF_4$ displays considerably stronger electron-accepting properties[100] and is better soluble in organic solvents than TCNQ and is therefore conveniently used for kinetic studies. The electron-accepting character of TNAP is intermediate between that of TCNQ and $TCNQF_4$, and $TCNQ(CN)_2$ displays the strongest electron-accepting properties[100]. The addition of styrene to a solution of TCNQ, TNAP, or $TCNQF_4$ in acetonitrile causes a deepening of the color of the respective acceptor solution, due to the formation of the colored charge transfer complexes. TCNQ–styrene (St), TNAP–St and $TCNQF_4$–St systems absorb light in the range of 450–580 nm[73], 530–639 nm[101] and 500–750 nm[102] respectively. The charge transfer transition absorption of the $TCNQ(CN)_2$–St system cannot be measured because the absorbance of the mixture decreases so rapidly that it disappears completely within a minute, probably due to a very rapid polymerization[101]. $TCNQF_4$, TNAP and $TCNQ(CN)_2$ undergo alternating copolymerization with styrene without any initiator, similarly to TCNQ[101,102]. Kinetic studies of the spontaneous alternating copolymerization of $TCNQF_4$–St system revealed that the copolymerization follows the three-halves order with respect to each of $TCNQF_4$ and styrene[102]. The copolymerizations of the TCNQ–St[102] and TNAP–St[101] systems were found to obey the same kinetics. On the other hand, the copolymerization of the $TCNQ(CN)_2$–St system follows first-order kinetics with respect to both $TCNQ(CN)_2$ and styrene[101]. A three-halves order kinetics has previously been found for the spontaneous alternating copolymerizations of the systems *p*-dioxene–maleic anhydride and 1,2-dimethoxyethylene–maleic anhydride[103] and a similar multi-step copolymerization reaction scheme[103] was suggested in those cases: (*a*) The donor and the acceptor monomers form a charge transfer complex and an intramolecular first-order reaction of the complex gives the propagating radical species, (*b*) the radical species adds to the complex to give an alternating copolymer, and (*c*) termination takes place between the propagating polymer radicals which are assumed to be in stationary state (Scheme 5). The first-order kinetics observed in the copolymerization of the $TCNQ(CN)_2$–St system was also found for the TCNQ–methyl methacrylate (MMA) system as mentioned below. The rate constants, overall activation energies and the half-life times (for the acceptor monomer under a given monomer concentration) of the TCNQ–St, TNAP–St, $TCNQF_4$–St and $TCNQ(CN)_2$–St systems, are compiled in Table 8. These systems have similar overall activation energies of copolymerization. The $TCNQ(CN)_2$–St systefn copolymerizes about 1000 times as rapidly as the TCNQ–St system. The rates of copolymerizations are closely related to the electron-accepting ability of the acceptor monomer as measured by its electron affinity (EA) (see Tables 8 and 9).

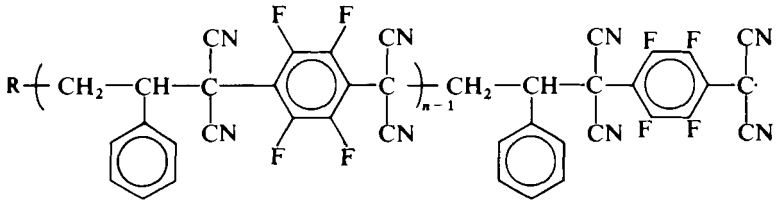
When acceptor monomers with a low positive e value of the Alfrey–Price Q–e scheme such as methyl methacrylate (MMA) ($e = 0.4$)[79], methyl acrylate (MA) ($e = 0.6$)[79] and acrylonitrile (AN) ($e = 1.2$)[79] are used as comonomers in the copolymerization with $TCNQF_4$, it has been found[102] that MMA is alternatingly and spontaneously copolymerized, MA undergoes alternating copolymerization only by means of a radical initiator, and AN is not susceptible to copolymerization. It is noteworthy that MMA and MA with positive e value undergo alternating copolymerization as donor monomers instead of acceptor monomers with $TCNQF_4$ which is a very strong electron-acceptor monomer. This alternating tendency in the $TCNQF_4$–MMA and $TCNQF_4$–MA systems cannot be explained in terms of the Alfrey–Price Q–e scheme because all monomers of these systems have positive e values and repulsive forces instead of attractive forces would be expected. It has therefore been proposed that the large difference in the polar character between $TCNQF_4$ and the alternatingly copolymerizable comonomers, which causes a charge transfer interaction, is one of the primary factors responsible for their alternating tendency. In addition, TCNQ, which is a weaker acceptor monomer than $TCNQF_4$, also

(*a*) $TCNQF_4 + St \underset{}{\overset{K_{CT}}{\rightleftharpoons}} CT\ Complex \overset{k_i}{\rightarrow} 2\ R$

$$\text{Rate of initiation: } = \frac{d[R\cdot]}{dt} = 2k_i K_{CT}[TCNQF_4][St]$$

when $K_{CT} \ll 1$

(*b*) $P\cdot_{n-1} + n\text{CT Complex} \overset{k_p}{\rightarrow}$



propagating polymer radical $[P_n\cdot]$

$$\text{Rate of polymerization: } \frac{-d[TCNQF_4]}{dt} = \frac{-d[St]}{dt} = k_p K_{CT}[P_n\cdot][TCNQF_4][St]$$

(*c*) $2\ P_n\cdot \overset{k_t}{\rightarrow}$ dead Polymer

$$\text{Rate of termination: } -\frac{d[P_n\cdot]}{dt} = 2k_t[P_n\cdot]^2$$

At stationary state of propagating polymeric radical

$$R_i = R_t$$

$$2k_i K_{CT}[TCNQF_4][St] = 2k_t[P_n\cdot]^2$$

$$[P_n\cdot] = \sqrt{\frac{k_i K_{CT}}{k_t}[TCNQF_4][St]}$$

then

$$R_p = k_p \sqrt{\frac{k_i}{k_t}} K_{CT}^{3/2}[TCNQF_4]^{3/2}[St]^{3/2}$$

SCHEME 5

TABLE 8. Rate constants (k_p), overall activation energies (E_a), and half-life times ($T_{1/2}$) of the copolymerization of the TCNQ–St, TNAP-St, $TCNQF_4$–St, and $TCNQ(CN)_2$–St systems

Systems	Kinetic order in the complex	$10^3 k_p/l^{1/2}$ $mol^{-1/2} s^{-1}$	At T °C	E_a (kcal mol^{-1})	$T_{1/2}$ at 34.5 C (min)
TCNQ–St	1.5	2.75	34.5	17.3	1000[a]
TNAP-St	1.5	21.4	34.5	16.3	151
$TCNQF_4$–St	1.5	52.9	34.5	16.6	4.0
$TCNQ(CN)_2$–St	1.0	1.05	10	16.7	1.2

[a] Calculated from the rate constant.

TABLE 9. Modes of polymerization in acetonitrile

Vinyloxy compound (e value)[77]		TCNO(CN)$_2$	TCNQF$_4$[102]	DDQ[90]	TNAP[101]	TCNQ[105]	TESQ[106]	TMCQ[106]
	Electron affinity (eV)		3.22[78]	3.00[78]		2.88[78]		
	Reduction potential(V)	0.65[100]	0.53[100]	0.51[107]	0.21[94] 0.20[100]	0.17[100] −0.2[117]	0.092[108]	−0.83[117]
VAc (−0.22)		Adduct	Alternating copolymer	Alternating copolymer	Adduct	Alternating copolymer	Adduct	Alternating copolymer
PhVE (−1.21)		Adduct	Alternating copolymer	Alternating copolymer	Adduct	Alternating copolymer	Adduct	Alternating copolymer
CEVE (−1.41)		Homopolymer	Homopolymer	Homopolymer	Homopolymer	Alternating copolymer	Homopolymer	Alternating copolymer
n-BVE (−1.20)		Homopolymer	Homopolymer	Homopolymer	Homopolymer	Homopolymer	Homopolymer	Alternating copolymer
i-BVE (−1.77)		Homopolymer	Homopolymer	Homopolymer	Homopolymer	Homopolymer	Homopolymer	Alternating copolymer

copolymerizes alternatingly and spontaneously with MMA whereas MA is not copolymerizable with TCNQ[104]. The rate of spontaneous alternating copolymerization between TCNQ and MMA is about one thousandth as slow as that between $TCNQF_4$ and MMA[104]. Moreover, the slow rate of the copolymerization obeys first-order kinetics with respect to the TCNQ monomer concentration[104].

D. Modes of Polymerization of Vinyloxy Monomers with Electron-accepting Quinodimethanes

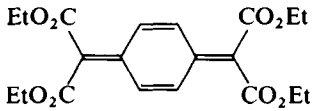
As vinyloxy monomers *n*-butyl vinyl ether (*n*-BVE), isobutyl vinyl ether (*i*-BVE), 2-chloroethyl vinyl ether (CEVE), phenyl vinyl ether (PhVE), and vinyl acetate (VAc) have been used. The electron-donating character of these compounds may be arranged in the above order by means of Taft and Hammett substituent constants of the vinyloxy and vinyl groups. Stille and coworkers[97, 98] reported that TCNQ initiates the cationic homopolymerization of alkyl vinyl ethers in acetonitrile in line with its powerful electron-accepting character which causes an electron transfer. In the polymerization of TCNQ with each of the five monomers in acetonitrile, it has been found[105] that *n*-BVE and *i*-BVE homopolymerize whereas CEVE, PhVE and VAc copolymerize in an alternating fashion with TCNQ. The two modes of polymerization are consistently correlated with the electron-donating character of the vinyloxy monomers[105]. Moreover, when other electron-accepting quinodimethane derivatives such as $TCNQ(CN)_2$[101], $TCNQF_4$[102], DDQ[90], TNAP[101], TESQ[106] and TMCQ[74] are used, the modes of polymerization indicated in Table 9 are observed. These results, except for the case of TESQ, suggest that the modes of polymerization are also correlated with the electron-accepting character of these monomers. It is concluded, therefore, that the difference in polar character between the donor and acceptor monomers is responsible for an electron transfer reaction and strongly affects the determination of the mode of polymerization.

Furthermore, it has been found[109] that the mode of polymerization of TCNQ with CEVE depends upon the solvent used. An alternating copolymer is obtained in acetonitrile, whereas in ethylene carbonate a homopolymer of CEVE results. Low molecular weight products composed of TCNQ and CEVE units are obtained when dimethyl sulfoxide (Me_2SO) and *N*-methylformamide are employed as solvents. This solvent effects on the mode of polymerization may be ascribed to the polarity and basicity of the solvent. The dielectric constants of acetonitrile, Me_2SO, ethylene carbonate and *N*-methylformamide are 37.5, 46.68, 89.6, and 182.4, respectively[110]. The frequency shifts, $\Delta\nu_{OH}$, of phenol with acetonitrile, ethylene carbonate and Me_2SO are 155, 159 and 350 cm^{-1}, respectively[111]. Frequency shifts, $\Delta\nu_{OH}$, of *p*-fluorophenol with *N*-methylformamide and Me_2SO are 271 and 367 cm^{-1}, respectively[112]. It is therefore obvious that the basicity of these solvents increases in the following order: acetonitrile $\leqslant$ ethylene carbonate $<$ N-methylformamide $<$ Me_2SO. From the difference in the dielectric constants the following order of reactivity of the electron transfer reaction between TCNQ and CEVE may be deduced: *N*-methylformamide $>$ ethylene carbonate $>$ Me_2SO $>$ acetonitrile. Since *N*-methylformamide is more basic than ethylene carbonate, the cationic end of the radical cation species formed by the electron transfer reaction can be more tightly solvated in it by solvent molecules, probably leading to a deactivation of the cationic end[113]. Another free radical end may add monomer molecules to give low molecular weight products composed of both monomer units. Likewise, the formation of low molecular weight products in Me_2SO may also be attributed to its high basicity. The drastic difference in the mode of polymerization between acetonitrile and ethylene carbonate conceivably arises primarily from the difference in polarity of these solvents. The more polar ethylene carbonate permits the electron transfer reaction between TCNQ and CEVE to occur, while the less polar acetonitrile does not. Because both solvents have a low basicity of similar magnitude,

the cationic polymer end is only weakly solvated and does not inhibit the cationic polymerization.

E. Amphoteric Behavior of TMCQ and TECQ in Alternating Copolymerization

7,7,8,8-Tetrakis(methoxycarbonyl)- and tetrakis(ethoxycarbonyl)-quinodimethane, TMCQ[72, 74] and TECQ[75], are quinodimethane derivatives with an electron-withdrawing functional group similar to that of TCNQ. A study of the charge transfer absorption bands between TMCQ or TECQ and conventional donor compounds revealed that TMCQ and TECQ display electron-accepting properties which are much weaker than those of TCNQ[75]. TECQ has been found to exhibit only a slightly weaker electron-accepting nature than TMCQ. Moreover, it has been found that TMCQ[74] and TECQ[75] behave as electron donors when they meet with TCNQ which has very strong electron-accepting properties. A comparison of the absorption bands reveals that TECQ[74] displays only a slightly more electron-donating character toward TCNQ than TMCQ. Consequently, it is



TECQ

concluded[75] that TMCQ and TECQ exhibit an amphoteric polar character in the formation of charge transfer complexes. Their amphoteric polar nature may be explained consistently in terms of a π-electron density scheme. Styrene has the highest π-electron density followed by TECQ which has only a slightly higher density than TMCQ, and TCNQ clearly has the lowest density. The sufficiently large difference in the π-electron density therefore gives rise to the formation of charge transfer complexes between styrene and TECQ or TMCQ as well as between TECQ or TMCQ and TCNQ.

TMCQ and TECQ copolymerize alternatingly and spontaneously as acceptor monomers with conventional electron-donating comonomers such as styrene, *i*-BVE, *n*-BVE, CEVE, PhVE and VAc. TMCQ and TECQ are also copolymerized alternatingly and spontaneously as donor monomers with the acceptor monomer TCNQ. This amphoteric behavior in alternating copolymerization was found first in the terpolymerization[74] of styrene, TMCQ and TCNQ, where the terpolymers obtained contain 50 mol % of TCNQ units regardless of the monomer feed ratio. This indicates that TMCQ and styrene copolymerize as donor monomers with TCNQ, contrary to the expectation that TMCQ would copolymerize as an acceptor monomer. The compositional relationships of the terpolymerization of styrene, TMCQ and TCNQ, as well as of styrene, TECQ and TCNQ are shown in Figures 14 and 15, respectively, where open and closed circles refer to the monomer feed and the terpolymer composition, respectively. The terpolymerization composition relationships can be illustrated by the composition diagrams of the binary copolymerization between TMCQ and styrene and between TECQ and styrene (St) (Figure 16), because the content of the TCNQ unit is always constant (50 mol %) in any run. According to the mechanism involving the complex formation[114] in the alternating copolymerization, the apparent monomer reactivity ratios of the complexes are calculated as follows: $r_1(K_1/K_2)$ (TMCQ–TCNQ complex) $= 7 \pm 3$ and $r_2(K_2/K_1)$ (St–TCNQ complex) $= 0.7 \pm 0.3$ for the St–TMCQ–TCNQ system and $r_1(K_1/K_2)$ (TECQ–TCNQ complex) $= 15 \pm 10$ and $r_2(K_2/K_1)$ (St–TCNQ complex) $= 0.5 \pm 0.3$ for the St–TECQ–TCNQ system. The relative reactivities of the TMCQ–TCNQ and

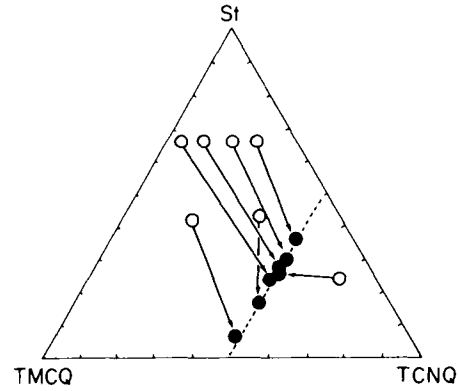


FIGURE 14. Triangular diagram of the composition of the terpolymer of TCNQ, TMCQ and styrene (St): (○), feed composition; (●) terpolymer composition. Arrows denote change in the composition from the feed to the terpolymer obtained

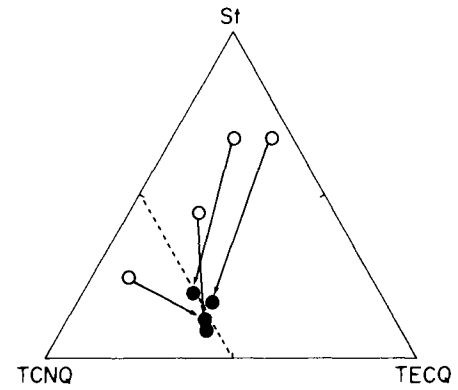


FIGURE 15. Triangular diagram of the composition of the terpolymer of TECQ, TCNQ and styrene (St): (○), feed composition; (●), terpolymer composition. Arrows denote change in the composition from the feed to the terpolymer obtained

TECQ–TCNQ complexes toward the polymer radical with a terminal St–TCNQ complex unit are as follows: St–TCNQ complex (1) < TMCQ–TCNQ complex (1.4) < TECQ–TCNQ complex (2.0). Thus, the TECQ–TCNQ complex is more reactive than the TMCQ–TCNQ complex. The reactivity of these complexes coincides with the electron-donating efficiency of the donor with respect to TCNQ, TECQ being a better electron donor than TMCQ.

The terpolymerization of TECQ–TMCQ–St[75] using monomer feed mol ratios of TECQ/TMCQ/St = 14.2/14.9/70.9 and 11.2/36.4/52.4 at 60°C gave the terpolymers (conversion of 11.5 and 7.6%) with the mol ratios TECQ/TMCQ/St = 22.6/27.4/50.0 and 10.2/39.8/50.0, respectively. From the difference of the ratios of the TECQ to TMCQ content in monomer feed (TECQ/TMCQ = 0.49/0.51 and 0.24/0.76) and in the terpolymers (TECQ/TMCQ = 0.45/0.55 and 0.20/0.80, respectively) it may be assumed that

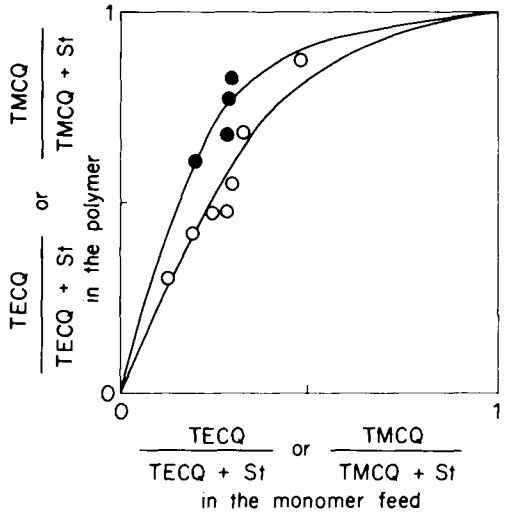


FIGURE 16. Diagram of the composition of the terpolymerizations of TECQ, TCNQ and styrene (St), and of TMCQ, TCNQ and St as binary copolymerizations between TECQ and St and between TMCQ and St, respectively. The lines are calculated using $r_1(K_1/K_2) = 15 \pm 10$ and $r_2(K_2/K_1) = 0.5 \pm 0.3$ for the terpolymerization of the TECQ–TCNQ–St system (●) and $r_1(K_1/K_2) = 7 \pm 3$ and $r_2(K_2/K_1) = 0.7 \pm 0.3$ for the terpolymerization of the TMCQ–TCNQ–St system (○)

TMCQ is somewhat more reactive than TECQ in the alternating copolymerization with styrene, i.e. the TMCQ–St complex is more reactive than the TECQ–St complex. Consequently, the reactivity order of the acceptor monomers TMCQ and TECQ in their alternating copolymerization with styrene is in good agreement with their electron-accepting character in their charge transfer complex formation with styrene. However, it is difficult to ascribe the small difference between TMCQ and TECQ to an inductive substituent effect reflected in the Hammett constant[115] and to a steric substituent effect reflected in the Taft steric parameter[116] between methyl and ethyl groups since differences are very small.

When TMCQ is heated above 175 °C or exposed to light, it polymerizes even though the product appears dimeric or trimeric[92]. Recently, Hall and Bently[117] reported that TMCQ polymerizes with free radical and anionic initiators to give homopolymer with a melting point of about 300 °C and an intrinsic solution viscosity of 0.91 dl g^{-1} (as a poly-carboxonium salt). Thus, TMCQ readily undergoes homopolymerization. However, TECQ cannot be homopolymerized by means of azobisisobutyronitrile (AIBN), *n*-butyllithium and boron trifluoride etherate[75]. Only when TECQ is kept in the crystalline state at room temperature for a month, a white powder insoluble in benzene with molecular weight of 2600 ($\bar{D}P = 6.6$), is formed in poor yield[75]. Therefore, it is obvious that TECQ exhibits only a very slight tendency to homopolymerize, in contrast to TMCQ. This difference in homopolymerizability cannot be attributed to a steric effect due to the very small difference in the Taft steric parameters between methyl ($E_s = 0.00$) and ethyl ($E_s = -0.07$)[116]. Presumably, the specific structure of the tetrakis(alkoxy-carbonyl)quinodimethane may amplify significantly the small difference between methyl and ethyl groups, and leads to the different amphoteric character of the monomers observed in the charge transfer complexation and in the alternating copolymerization and the difference in the homopolymerizability of TMCQ and TECQ.

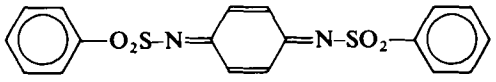
F. Polymerization Behavior of TESQ

Since the ethylsulfonyl group ($\sigma_p = 0.68$) exhibits the same electron-withdrawing power as cyano group ($\sigma_p = 0.66$) judged by the Hammett substituent constant[115], TESQ was expected to display similar polymerization behavior as an acceptor monomer to TCNQ. However, it has been found[106] that in the charge transfer transition TESQ (EA = 1.17 eV) exhibits a much lower electron affinity than TCNQ (EA = 2.84 eV)[78]. TESQ and styrene have been subjected to spontaneous alternating copolymerization in nitromethane, but when *p*-dioxane or dichloromethane is used instead of nitromethane, an alternating copolymer is not obtained, and the content of the styrene unit is higher than 50 mol%. From this it may be assumed that a cationic polymerization of styrene takes place simultaneously. This solvent effect cannot be explained in terms of its polarity and basicity[104]. Indeed, 1-phenylethanol and TESQ may readily undergo dehydration and polymerization to polystyrene, suggesting that TESQ and its hydrogenation product may initiate simultaneously both cationic polymerization of styrene and the alternating copolymerization of styrene with TESQ. Moreover, when the TESQ fraction in monomer feed is above 40 mol%, no copolymer but only the 1:1 adduct in high yield is obtained, in contrast to the copolymerization of TCNQ and styrene.

TESQ initiates the cationic oligomerization of *i*-BVE, *n*-BVE, CEVE and PhVE, but a reaction of TESQ with VAc has not been observed. Consequently, TESQ is considered to be more acidic (as proton acid) than TCNQ from the observed modes of polymerization of a series of those vinyloxy monomers whereas TESQ exhibits lower electron affinity than TCNQ. Concerning these differences between TESQ and TCNQ, it should be taken into account that in the π conjugation between the substituents and the quinodimethane part, the 3p orbital of sulfur participates for the ethylsulfonyl group, and the 2p orbital of carbon for the cyano group. Price and Oae[118] suggested that the 2p–3p π bond is less stable than the 2p–2p π bond. According to the theory of hard and soft acids and bases it may be assumed that TESQ is a much harder acid than TCNQ.

G. Polymerization Behavior of QBS

Quinone diimine, prepared as a colorless crystalline compound by Willstätter and Mayer[119], is expected to show an intermediate behavior between *p*-benzoquinone and quinodimethane from the relationship of Coppinger and Bauer[15] between the stability of hetero *p*-benzoquinones and the electronegativity of their exocyclic atoms, carbon (2.50), nitrogen (3.07) and oxygen (3.50)[120]. Unsubstituted *p*-quinone diimine is very susceptible to light and acid, especially in solution, and may undergo reactions such as hydrolysis and polymerization[121]. Adams and Nagarkatti[121] reported that *p*-quinone diimines carrying electron-withdrawing substituents such as acyl, alkylsulfonyl and arylsulfonyl groups at exocyclic nitrogen atoms become less susceptible to hydrolysis.



QBS

The electron-accepting character of *p*-quinone bis(benzenesulfonimide) (QBS) was examined. The charge transfer transition between QBS and hexamethylbenzene (HMB) appears in benzene at room temperature at 495 nm as shown in Figure 17[122]. The electron affinity (EA) of QBS could be estimated as 2.17 eV on the basis of the value of 2.48 eV[78] for the EA of *p*-chloranil (PCA) and the charge transfer transition at 510 nm between PCA

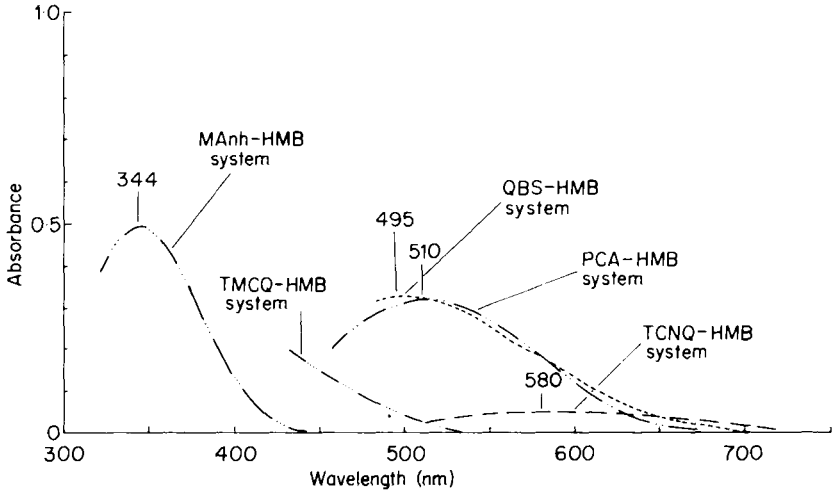


FIGURE 17. UV–VIS difference spectra between HMB and various acceptor compounds in benzene at room temperature. Concentrations of solutions employed are [TCNQ] = 1.69×10^{-4} mol l^{-1} and [HMB] = 0.102 mol l^{-1} for the TCNQ–HMB system, [PCA] = 1.06×10^{-2} mol l^{-1} and [HMB] = 1.0×10^{-2} mol l^{-1} for the PCA–HMB system, [QBS] = 1.0×10 mol l^{-1} and [HMB] = 0.1 mol l^{-1} for the QBS–HMB system, [TMCQ] = 7.11×10^{-3} mol l^{-1} and [HMB] = 9.95×10^{-2} mol l^{-1} for the TMCQ–HMB system, and [MAnh] = 1.05×10^{-2} mol l^{-1} and [HMB] = 6.10×10^{-2} mol l^{-1} for the MAnh–HMB system, respectively

and HMB, as shown in Figure 17. It was concluded, therefore, that QBS is intermediate in electron-accepting character between PCA and maleic anhydride (MAnh) (EA = 1.33 eV)[78]. Electron-accepting character was compared among TCNQ, PCA, QBS and MAnh by means of their charge transfer transition maxima with HMB, appearing at 580, 510, 495 and 344 nm, respectively, as shown additionally in Figure 17. The maximum for the TMCQ–HMB system was not observed because it overlaps seriously with the absorption of TMCQ alone. However, it certainly exists in the wavelength range below 450 nm, implying that TMCQ is a weaker electron acceptor than QBS. Comparison between TMCQ and MAnh could not be carried out by this charge transfer transition method. Consequently, the following order of the electron-accepting character of the acceptor compounds was found: TCNQ > PCA > QBS > TMCQ, MAnh.

The copolymerization of QBS with styrene and acenaphthylene were attempted at 60 °C in benzene without initiator for 168 h and 23.2 h, respectively[122]. In both cases no polymeric material could be obtained, and only the starting materials were recovered quantitatively. When a free radical initiator such as azobisisobutyronitrile (AIBN) was added, copolymers were obtained[122]. Figure 18 shows the composition diagrams of the homogeneous copolymerizations of QBS with styrene and acenaphthylene. The copolymers obtained as a white powder and their elemental analysis showed almost fixed amounts of carbon, hydrogen and nitrogen regardless of monomer feed ratio. The analysis is in good agreement with the calculated values for the copolymers composed of equimolar amounts of each component monomer. The molecular weight of the copolymers obtained for the QBS–styrene and QBS–acenaphthylene systems were measured by vapor pressure osmometry in chloroform to be about 7000 and 4000–7000, respectively, corresponding to degrees of polymerization of about 15 and 8–13, respectively, based upon an alternating

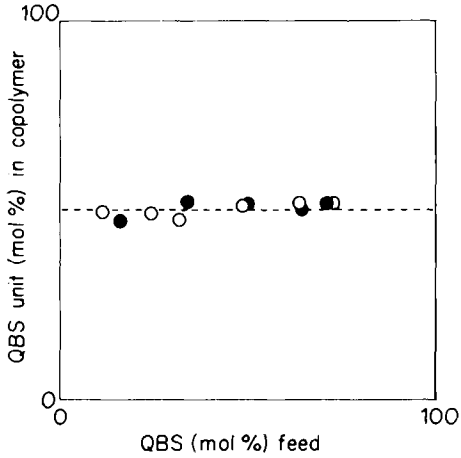


FIGURE 18. Composition diagram of the copolymerizations of QBS with styrene (St) (O) and with acenaphthylene (●)

structure of donor and acceptor units[122]. These molecular weights are very low, in contrast to those of the alternating copolymers of styrene with TCNQ ($[\eta] = 0.407$ dl g^{-1} in *N,N*-dimethylformamide–0.1 wt % LiCl at 30 °C)[73], TMCQ ($\eta_{sp}/C = 0.1$–0.4 dl g^{-1} in benzene at 30 °C)[74] and PCA ($\eta_{sp}/C = 0.19$ dl g^{-1} in benzene, molecular weight 15 900)[88]. In the IR spectra, the QBS monomer shows absorption at 1550 cm^{-1} due to the stretching vibration of the imide group but the QBS–styrene copolymer does not. In the ^{1}H-NMR spectrum of this copolymer, the methine and methylene protons appear in the δ5.2 and δ4.0 regions, respectively, being much more deshielded than the corresponding hydrogens of homopolystyrene, which generally appear in the δ1–2 ppm region[99]. Presumably, the deshielding arises from the powerful electron withdrawal by the neighboring benzenesulfonamide group when the styrene monomer unit is sandwiched between QBS monomer units in the copolymer. In addition, these methine and methylene protons in the copolymer appear as very broad signals, presumably due both to the influence of the quadrupole moment of the neighboring nitrogen nuclei and to the decrease in the flexibility of the main chain. It can be concluded therefore that QBS can copolymerize (co-oligomerize) in an alternating fashion with styrene and acenaphthylene when a free radical initiator is used and QBS reacts at exocyclic nitrogen sites[122].

The copolymerization between QBS and vinyl monomers with small positive *e* values such as methyl methacrylate (MMA), methyl acrylate (MA) and acrylonitrile (AN) were attempted with AIBN in benzene at 60 °C for 48 h. In no case was polymeric material obtained, and unreacted QBS was recovered almost quantitatively, similarly to the reactions of PCA with those monomers[88]. Since QBS has a much lower electron-accepting character than $TCNQF_4$ and TCNQ, the gap in π-electron density between QBS and MMA was considered to be too small to enable formation of a charge transfer complex between them and consequent further alternating copolymerization.

The copolymerizations of QBS with *n*-BVE, *i*-BVE, CEVE, PhVE and VAc gave the reaction products as white powders except in the case of VAc, in which no reaction took place and the starting materials were recovered quantitatively[122]. It is conceivable that the gap in π-electron density between VAc, which is the weakest donor monomer among the five vinyloxy monomers[105], and QBS, the weak acceptor monomer, is not sufficient to enable charge transfer complex formation and alternating copolymerization. It is evident

from the composition data of the copolymers obtained that the copolymers are composed of equimolar amounts of QBS and donor comonomers, indicating the alternating copolymer structures. It can be pointed out that QBS, the weak acceptor monomer, cannot initiate the cationic polymerization of the vinyloxy compounds in benzene similarly to TECQ[75], TMCQ[74] and MAnh, whereas the stronger acceptor monomers, TCNQ and $TCNQF_4$, can initiate the cationic polymerization of a strong donor monomer such as *n*-BVE and *i*-BVE[102,105]. The results correspond well to the low electron-accepting character of QBS.

Terpolymerizations of the QBS–MAnh–styrene (St), QBS–PCA–St, QBS–TMCQ–St and QBS–TCNQ–St systems were carried out at 60 °C for a quantitative comparison in the polymerizability of the five acceptor monomers. The terpolymers of all systems were obtained as white powders and were always composed of about 50 mol% of the styrene monomer unit regardless of the monomer feed ratio, and thus the sum of the QBS and other acceptor monomer (MAnh, PCA, TMCQ, or TCNQ) unit was about 50 mol%. Consequently, the terpolymerization composition relationships of the QBS–MAnh–St, QBS–PCA–St, QBS–TMCQ–St and QBS–TCNQ–St systems can be illustrated by their composition diagrams of binary copolymerizations between QBS and MAnh, between QBS and PCA, between QBS and TMCQ, and between QBS and TCNQ, shown in Figures 19–22, respectively. According to the complex mechanism treatment[114] the modified monomer reactivity ratios of the complexes were calculated to be $r_1(K_1/K_2) = 30 \pm 20$ and $r_2(K_2/K_1) = 0.1 \pm 0.1$ for the QBS–MAnh–St system (C_1 is QBS–St complex and C_2 is MAnh–St complex), $r_1(K_1/K_2) = 15 \pm 10$ and $r_2(K_2/K_1) = 0.2 \pm 0.2$ for the QBS–PCA–St system (C_1 is QBS–St complex and C_2 is PCA–St complex), $r_1(K_1/K_2) = 1.18 \pm 0.1$ and $r_2(K_2/K_1) = 0.15 \pm 0.05$ for the QBS–TMCQ–St system (C_1 is QBS–St complex and C_2 is TMCQ–St complex), and $r_1(K_1/K_2) = 0.01 \pm 0.01$ and $r_2(K_2/K_1) = 45 \pm 10$ for the QBS–TCNQ–St system (C_1 is QBS–St complex and C_2 is TCNQ–St complex), respectively. K_1 and K_2 refer to equilibrium constants for formation

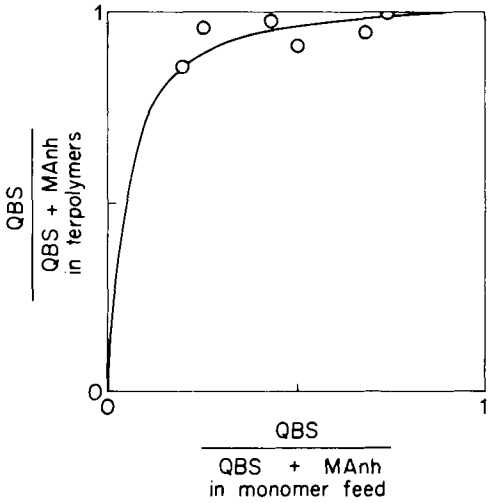


FIGURE 19. Composition diagram of the terpolymerization of QBS, MAnh and St as binary copolymerization between QBS and MAnh. The line is calculated by using $r_1(K_1/K_2)$ (QBS–St complex) = 30 and $r_2(K_2/K_1)$ (MAnh–St complex) = 0.1

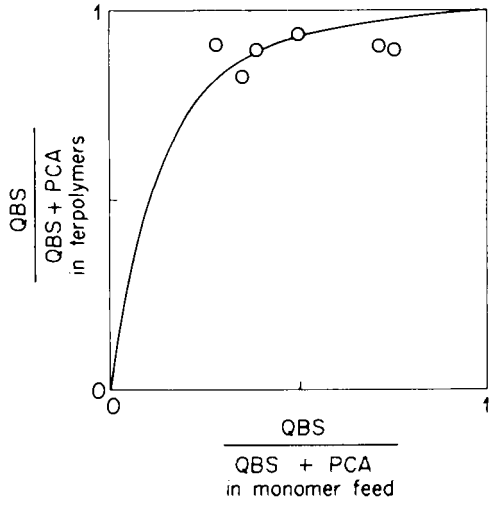


FIGURE 20. Composition diagram of the terpolymerization of QBS, PCA and St as binary copolymerization between QBS and PCA. The line is calculated by using $r_1(K_1/K_2)$ (QBS–St complex) = 15 and $r_2(K_2/K_1)$ (PCA–St complex) = 0.2

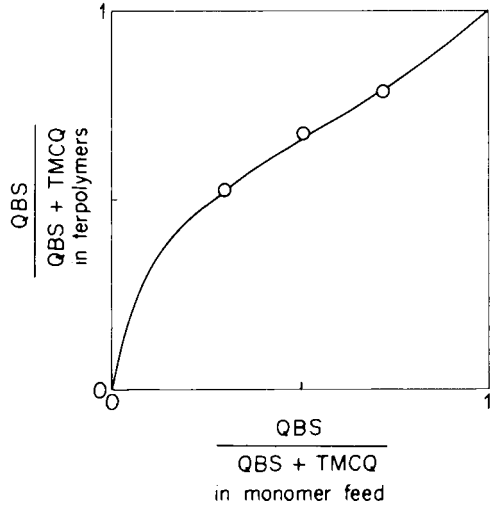


FIGURE 21. Composition diagram of the terpolymerization of QBS, TMCQ and St as binary copolymerization between QBS and TMCQ. The line is calculated by using $r_1(K_1/K_2)$ (QBS–St complex) = 1.18 and $r_2(K_2/K_1)$ (TMCQ–St complex) = 0.15

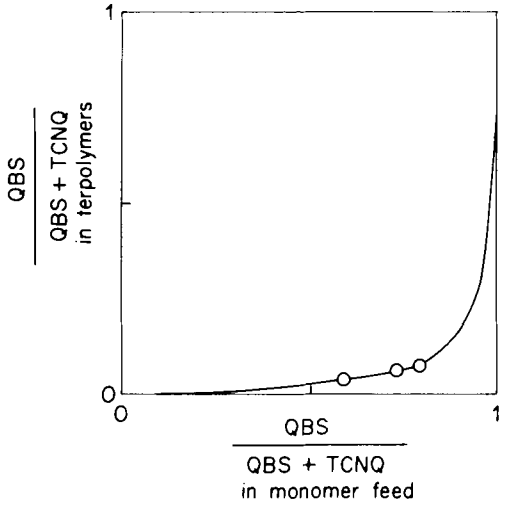
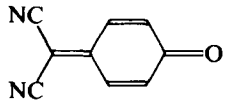


FIGURE 22. Composition diagram of the terpolymerization of QBS, TCNQ and St as binary copolymerization between QBS and TCNQ. The line is calculated by using $r_1(K_1/K_2)$ (QBS–St complex) = 0.01 and $r_2(K_2/K_1)$ TCNQ–St complex) = 45

of complex 1 (C_1) and complex 2 (C_2), respectively. The reciprocals of the modified monomer reactivity ratios were used as a measure of the relative reactivity of the complexes toward the polymer radical with a given terminal complex unit. The relative reactivity order of the MAnh–St, PCA–St, TMCQ–St and TCNQ–St complexes toward the polymer radical with the QBS–St complex unit was obtained as MAnh–St complex (1/30) < PCA–St complex (1/5) < TMCQ–St complex (1/1.18) < QBS–St complex (1) < TCNQ–St complex (1/0.01). Previously, it was pointed out[101,102] from the alternating copolymerizations of those electron-accepting quinodimethane derivatives with styrene that reactivity of their styrene complexes is related intimately to the electron-accepting character of the quinodimethanes. EA values of MAnh, QBS, PCA and TCNQ were reported to be 1.33, 2.17, 2.48 and 2.88 eV, respectively[78]. Although the EA value of TMCQ has not yet been reported, it is likely from the charge transfer complexation profile as shown in Figure 17 that TMCQ is a weaker electron acceptor than QBS. Thus, the order of electron-accepting character for the acceptor monomers is assumed to be MAnh, TMCQ < QBS < PCA < TCNQ and is in good agreement with the reactivity order of their styrene complexes except for PCA. The PCA–St complex is regarded as much less reactive than expected from the electron-accepting character of PCA. Coppinger and Bauer[15] pointed out on the basis of experimental data on the π–π electron transition of Hückel molecular orbital calculation that the stability of hetero *p*-benzoquinone compounds is related well to the energy difference between the quinonoid ground state and the benzenoid transition state. Increase in electronegativity of the exocyclic atom results in a decrease in the highest occupied bonding energy level and an increase in the lowest unoccupied antibonding level, leading to an increase in energy difference between ground and transition states and a large stability of the compound. Consequently, the exocyclic atom of hetero *p*-benzoquinones affects not only the stability of their compounds, that is, the reactivity, but also their electron-accepting character. In the case of the PCA–St system, it may be presumed that the exocyclic electronegative oxygen atom of PCA affects its



7,7-Dicyanoquinonemethide

stability more effectively than its electron-accepting character. Furthermore, 7,7-dicyanoquinonemethide[123] was found to be alternatingly copolymerizable with styrene[124].

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CHAPTER **19**

Isotopically labelled quinones

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I. SYNTHESES OF LABELLED QUINONES AND RELATED COMPOUNDS

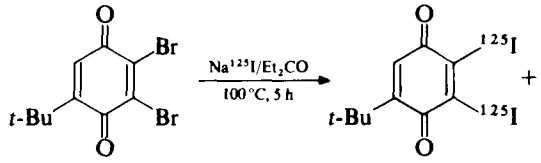
Numerous isotopically labelled quinonoid compounds have been obtained in the course of isotopic biochemical studies reviewed in Section III. In the present section the recently elaborated synthetic procedures used for the preparation of labelled quinones or related compounds of practical importance are briefly described.

A. Syntheses of Labelled Benzoquinones and Related Compounds

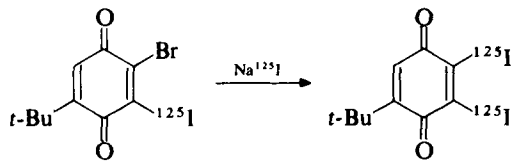
1. Syntheses of ^{125}I- and ^{123}I-labelled quinones

a. Synthesis of 2,3-^{125}*diiodo*-5-t-*butyl*-1,4-*benzoquinone*

The ^{125}I-labelled benzoquinone **I**, a powerful inhibitor of photosynthetic electron transfer, was prepared with 49 % overall radiochemical yield with specific radioactivity of



(1)

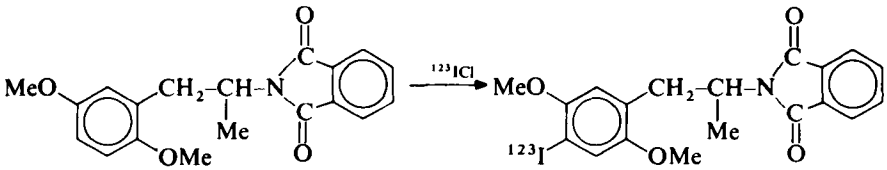


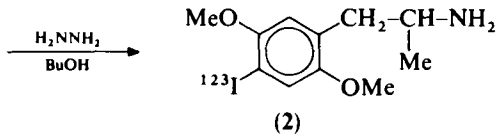
(I)

49 mCi mmol^{-1} based on Na^{125}I using the exchange reaction (1) between 2,3-dibromo-5-*t*-butyl-1,4-benzoquinone and Na^{125}I[1].

b. Synthesis of ^{123}I-labelled 4-iodo-2,5-dimethoxyphenylisopropylamine (**2**)

Labelled with short half-life iodine-123 ($t_{1/2}$ = 13 h) the title compound which has clinical potential for the imaging of normal brain tissue and in the study of mental disorder, has been prepared according to a rapid synthetic scheme (equation 2)[2]. It comprises the protection of the amine against oxidation with a phthalimido group to give **3** followed by a direct iodination of the ring of **3** with iodine monochloride. The amide (**4**) was quickly hydrolysed with hydrazine in butanol without isolation. Compound **2** was obtained as its hydrochloride with 10% radioiodine incorporation efficiency.



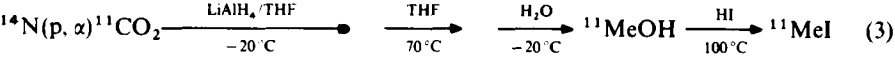


(2)

2. *Syntheses of ^{11}C-, ^{14}C- and ^{13}C-labelled quinones and related compounds*

a. Synthesis of ^{11}C-labelled coenzyme Q_{10}.

Coenzyme ^{3}H-Q_{10} and ^{14}C-Q_{10} function as one component of the electron transfer sequence in mitochondrial membrane, act as an antioxidant toward the superoxidative reaction *in vivo* and are used as a therapeutic agent for myocardial ischaemia. The coenzyme has been also labelled with short-lived carbon-11 ($t_{1/2}$ = 20.34 min), by *O*-methylation of 3-demethyl Co-Q_{10} (**5**) with ^{11}MeI, synthesized in furan from $^{11}CO_2$ by the automated cyclotron synthesis within approximately 25 min (equation 3). The specific

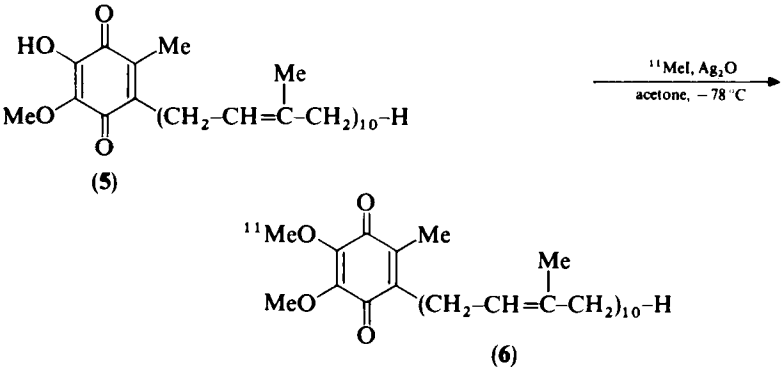


(3)

radioactivity of the ^{11}C-coenzyme-Q_{10} (**6**), obtained within 35–50 min according to equation 4, was 4–5 mCi μmol^{-1}, radiochemical purity of 95%. Good radiochemical yields (6–16% based on trapping ^{11}MeI) were achieved by using Ag_2O as a base. In the presence of NaOH and other bases a chromene derivative was mainly obtained[3].

b. 4-Nitrocatechol-[UL-^{14}C] (**7**).

Uniformly ring-labelled compound (**7**) with specific radioactivity of 1.25 mCi mg^{-1} or 1.76 mCi mmol^{-1}, with purity higher than 99%, was synthesized in 49% yield by



(4)

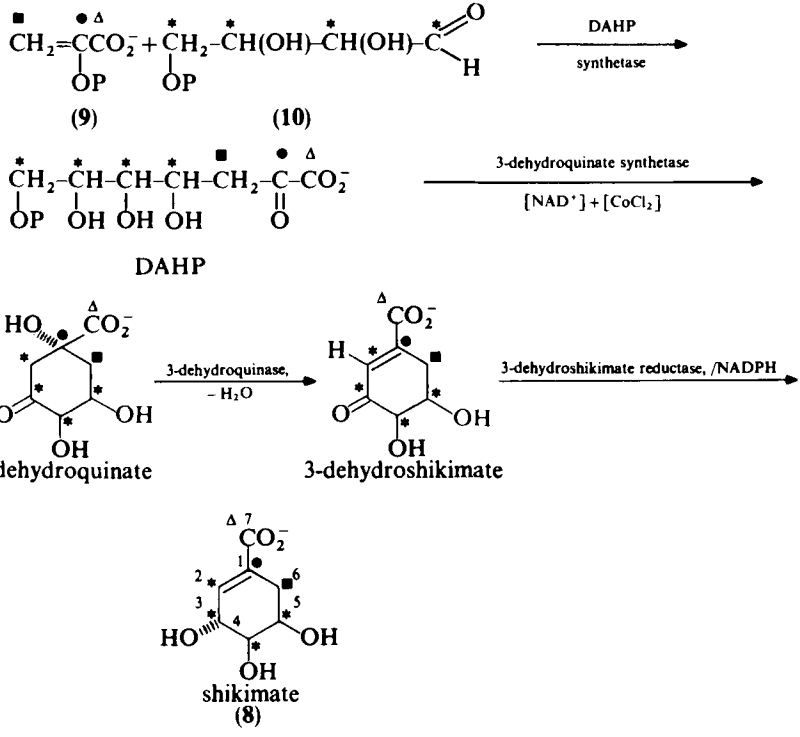
irradiation of 4-nitrophenol-[UL-^{14}C] (0.57 mmol, 1.0 mCi) in aqueous solution of hydrogen peroxide for 1 hour, at 45–50 °C[4].

$$4\text{-}NO_2C_6H_3(OH)_2$$

(7)

c. Preparation of specifically ^{14}C- and ^{3}H-labelled shikimic acids

Tritium([2-T]) and carbon-14 ([1-^{14}C], [6-^{14}C], [7-^{14}C], [2,3,4,5-^{14}C])-labelled D-shikimates (**8**), which are used as precursors in biosynthetic investigations of numerous



(5)

quinonoid compounds are usually synthesized according to Scharf and Zenk[5] as exemplified in equation 5. The precursor [^{14}C] phosphoenolpyruvate (**9**) is synthesized from pyruvate-1,2 or 3-^{14}C (ca. 25 mCi mmol^{-1}) and ATP using pyruvate synthase (equation 6). The yield of purified **9** was 78–85 % of the labelled pyruvate. The precursor

$$\overset{*}{C}H_3\text{–}\overset{*}{C}O\text{–}COO^- + ATP + H_2O \xrightleftharpoons{30\,^\circ C,\ 15\ min} \overset{*}{C}H_2{=}\overset{*}{C}(OPO_3H_2)\text{–}COO^- + AMP + \text{phosphate} \quad (6)$$

(**9**)

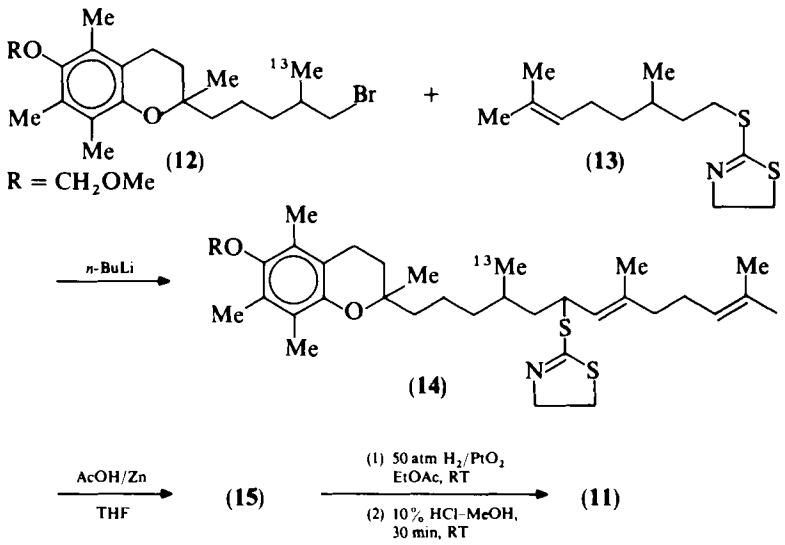
erythrose-4-phosphate [1,2,3,4-^{14}C] and 4-T (**10**) was prepared from glucose-[U-^{14}C] or glucose-[6-T] by enzymatic phosphorylation to labelled glucose-6-phosphate and subsequent treatment with lead tetraacetate. Condensation of **9**-[^{14}C] with unlabelled **10** or of labelled **10** with unlabelled **9** to yield shikimic acids labelled with ^{14}C or T has been achieved in the presence of cell-free extract of the *E. coli* mutant 83-24 which lacks shikimate kinase. An 86 % maximal conversion of **9**-[1-^{14}C] to shikimate carboxyl-[^{14}C] was reached by incubating the reactants for 2.5 hours at 37 °C.

d. Synthesis of ^{13}*C-labelled vitamin E*

To elucidate the interactions[6] between vitamin E and lipids in biomembrane by measurement of ^{13}C-relaxation time on vitamin E in biomembrane, [4′a-^{13}C] all-rac-α-tocopherol (**11**) was synthesized by coupling a solution of 2-([4-methyl-^{13}C]-5-bromo-4-methylpent-1-yl)-6-methoxymethoxy-2,5,7,8-tetramethylchroman (**12**) in a mixture of THF and HMPA with 3,7-dimethyl-1-(thiazolin-2-yl)thio-2,6-octadiene (**13**) in THF in the presence of *n*-butyllithium in hexane (equation 7). The total yield of the labelled α-tocopherol based on [^{13}C]methyl iodide was 59 %[6].

e. Synthesis of [7α-^{14}*C*]*-methoxycephalosporin, antibacterial agent, CS*-1170

The quinonoidal compound **16** has been utilized in the synthesis of the ^{14}C-labelled 7-methoxy Schiff base (**17**) in 49 % yield based on ^{14}MeOH, and of the key intermediate (**18**)



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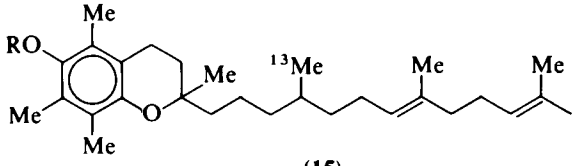

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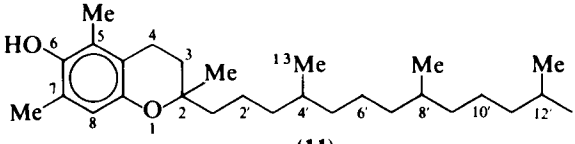

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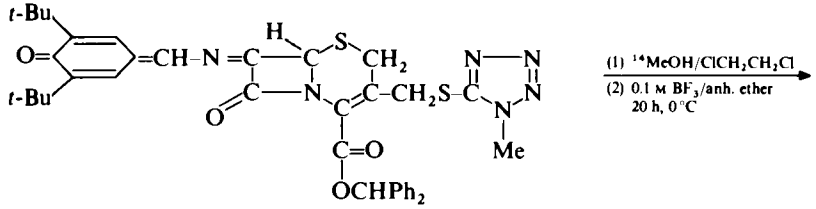

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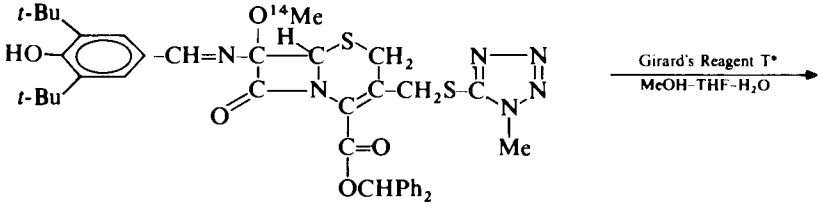

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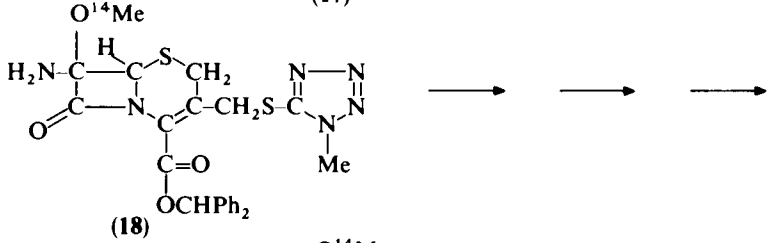

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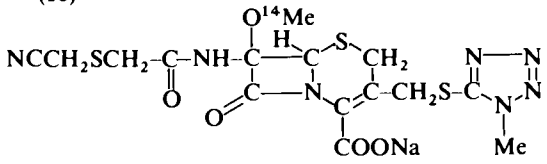


(8)

CS-1170 (19)

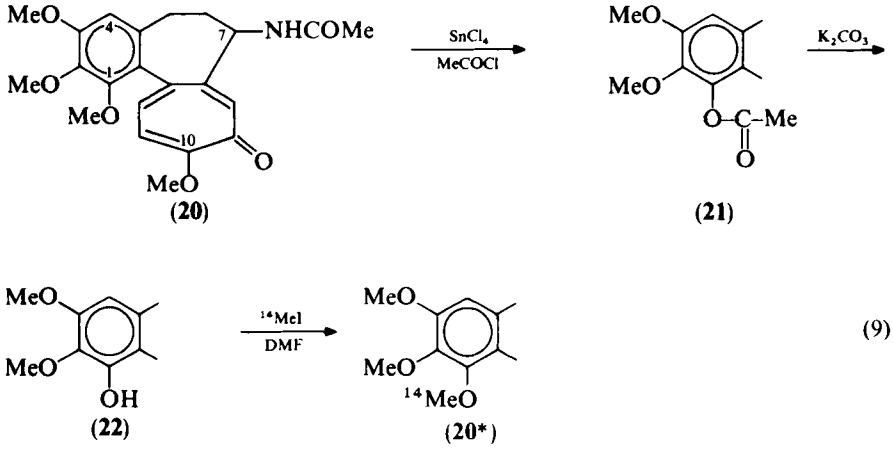
$[Me_3\overset{+}{N}CH_2CONHNH_2]Cl^-$

*Girard's Reagent T (2-hydrazino-*N*,*N*,*N*-trimethyl-2-oxoethanaminium chloride)

in the synthesis of the new semisynthetic cephamycin derivative CS-1170 (**19**), containing labelled 7α-methoxy-^{14}C group[7] (equation 8). The specific activity of the diluted CS-1170 drug was 6.25 mCi mmol^{-1} and the radiochemical purity was 96.7%.

f. Synthesis of 1-*methoxy* [^{14}C] *colchicine*

Colchicine (**20**), a poisonous alkaloid, was used for many centuries in treating rheumatism and gout. It was labelled with a non-metabolizable 1-methoxy ^{14}C group by selective demethylation of **20** and condensing 1-demethylcolchicine (**22**) with ^{14}MeI. The specific radioactivity of the purified product (**20***), measured by mass spectrometry, was 57 mCi mmol^{-1} with a radiochemical purity of 99%[8]. Metabolic studies[9, 10] have shown that in the course of biotransformations '*in vivo*' colchicine is transformed to products demethylated at the 2 and the 3 positions and partly at the 10 position. Consequently in order to study the metabolism of **20** in rats the reaction scheme of equation 9 has been chosen for the synthesis of labelled alkaloid.



(9)

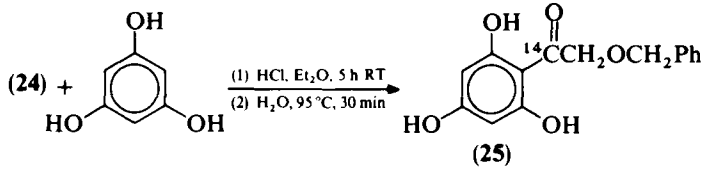
g. Synthesis of quercetin-[4-^{14}C]

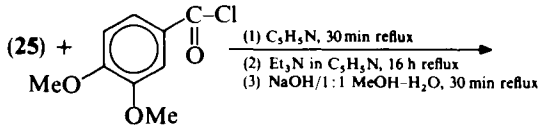
Radiolabelled quercetin-4-^{14}C (**23**) has been synthesized[11] in order to study its physiological mode of action upon insect larvae (growth inhibition) and its mutagenicity and to clarify the question if the ingestion of flavonoids is a source of human cancer. Since all the hydrogens of the quercetin nucleus are potentially exchangeable[12] the ^{14}C was incorporated into the flavone skeleton. The synthesis starts with benzyloxyacetonitrile-^{14}C (**24**), which is prepared from benzyl chloromethyl ether and H^{14}CN (equation 10)

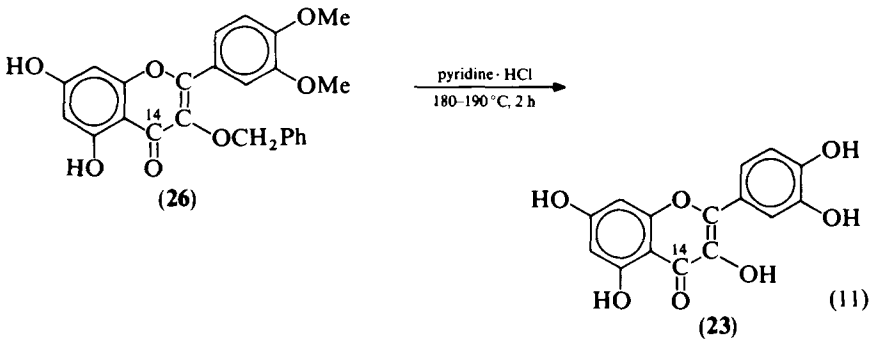
$$K^{14}CN + PhCH_2OCH_2Cl \xrightarrow[\text{benzene}]{\text{18-crown}} PhCH_2OCH_2{}^{14}CN \quad (10)$$

(**24**)

utilizing phase transfer with 18-crown-6 ether. Condensation of **24** with phluoroglucinol gave the ketone (**25**). Esterification of **25** with veratroyl chloride, subsequent rearrangement with triethylamine and base hydrolysis of the intermediate flavone ester yielded **26**. Simultaneous debenzylation and demethylation affected at high temperature using pyridine hydrochloride provided quercetin-4-^{14}C in 75% yield and specific activity of 2.07 mCi mmol^{-1} (equation 11).

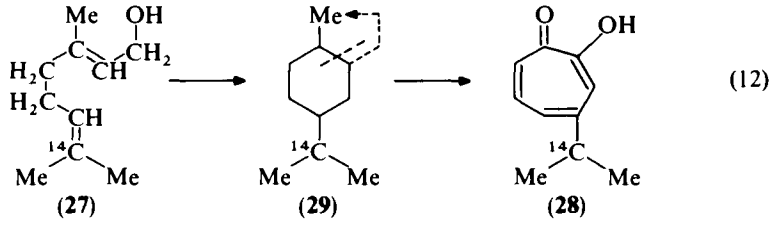






h. Synthesis of geraniol-7-^{14}C

Labelled geraniol (**27**) has been synthesized in five steps from acetone-2-^{14}C in 46% yield, 99% purity and 0.26 mCi mmol^{-1} specific radioactivity. It was used to test the proposed mechanism of biotransformation of β-thujaplicin (**28**) in the *Thuja plicata* tree involving ring enlargement of the cyclohexano-terpene (**29**) which is derived from geraniol (**27**)[13] (equation 12).

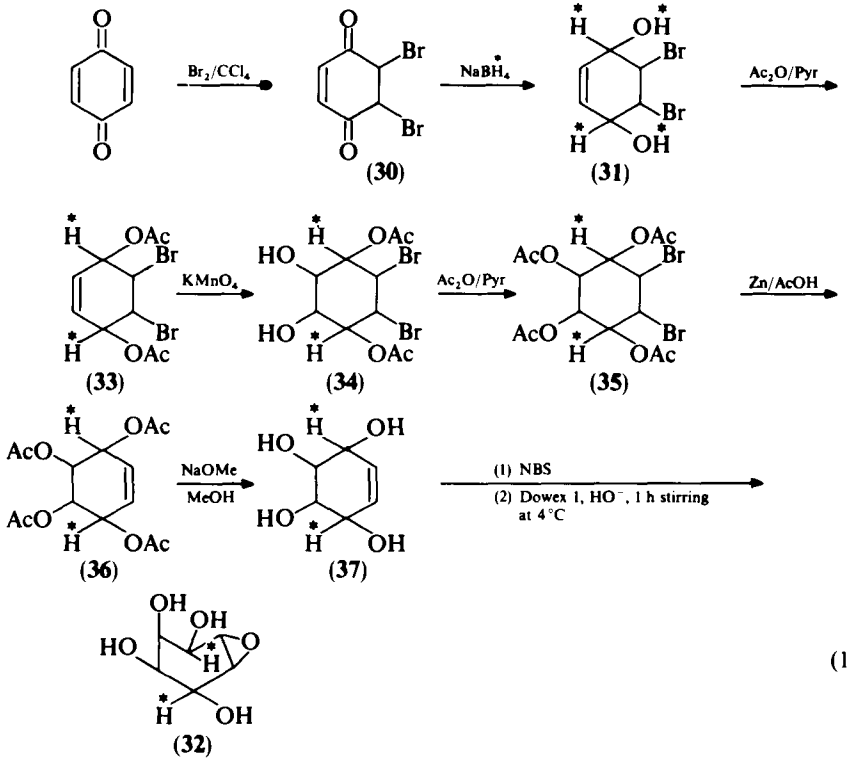


3. Synthesis of tritium- and deuterium-labelled quinones and their derivatives

a. Synthesis of [^3H]conduritol C cis-epoxide

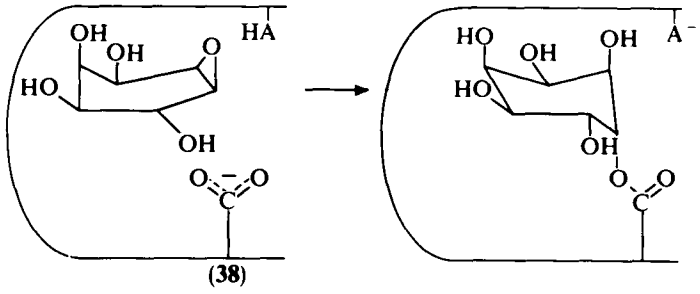
A considerable kinetic tritium isotope effect was found[14] in the course of the reduction of 5,6-dibromo-2-cyclohexene-1,4-dione (**30**) with tritiated [^3H] $NaBH_4$. The product,

5,6-dibromo-2-cyclohexene-1,4-diol (**31**), had a 2.74×10^{10} cpm mmol^{-1} specific activity and served as the precursor to [^{3}H]conduritol C *cis*-epoxide (**32**), the enzyme inhibitor for β-galactosidase from *E. coli* (equation 13). A satisfactory yield of the dibromodiol (**31**) is



(13)

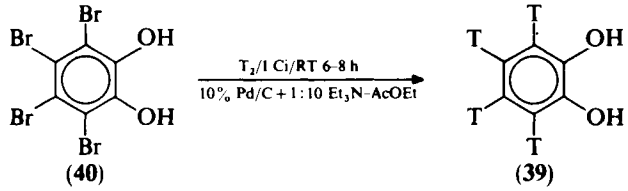
obtained when equimolar or higher amounts of the tritiated reductant is used. The reaction has to be carried out in the two-phase ether/water system in order to avoid aromatization to bromohydroquinone. Reacting equimolar amounts of **30** and [^{3}H]$NaBH_4$ and using excess of *p*-acetamidobenzaldehyde to trap the unreacted hydride gave a diol with specific radioactivity of 0.45 times that of the original borohydride whereas the specific activity of the unreacted hydride was 2.5 times higher. Thus, the specific activity



of the reduction product has to be determined experimentally during the synthesis by a liquid scintillation counting technique. By using tritium-labelled **32** it has been shown that the inhibition reaction of β-galactosidase with **32** is due to formation of an ester bond between **32** and a carboxylate group at the active site of **38**[14].

b. Synthesis of tritium-labelled catechol

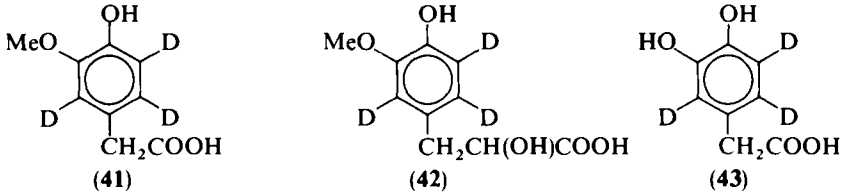
1,2-Dihydroxybenzene (catechol) is the most abundant phenol in cigarette smoke condensate[15]. It shows biological activity, including carcinogenic activity with benzo[*a*]pyrene. Labelled [U-^{3}H] catechol was synthesized in a one-step catalytic reduction of 1 mmol of tetrabromocatechol in a low pressure hydrogenation apparatus with 1 Ci of tritium gas, followed after 30 minutes by addition of hydrogen gas[15] (equation 14). Purification gave 68 % of catechol [U-^{3}H] (**39**), with 2.5 mCi mmol^{-1} specific activity.



(14)

c. 2,5,6-Trideuteriohomovanillic acid, 2,5,6-trideuteriovanillactic acid and 2,5,6-trideuterio-3,4-dihydroxyphenylacetic acid synthesis

HVA-d_3 (**41**), VLA-d_3 (**42**) and DOPAC-d_3 (**43**) were synthesized from the corresponding unlabelled analogues by dissolving each of them in 9 % DCl/D_2O and heating for 6 h at 80 °C in a sealed tube. A quantitative replacement of the exchangeable 2,5,6-hydrogens was achieved under these conditions as judged by mass fragmentography and gas chromatography[16]. These compounds were used for the preparation of internal standards for quantitative mass-fragmentographic analysis of biological materials.

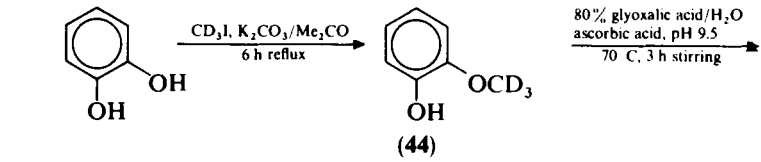


d. Synthesis of methyl-labelled catechol

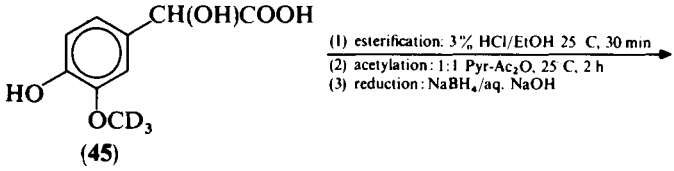
Monomethylated catechols, i.e. 2-methoxy-d_3-phenol (**44**), 4-hydroxy-3-methoxy-d_3-mandelic acid (**45**), 4-hydroxy-3-methoxy-d_3-phenylacetic acid (**46**) and 4-hydroxy-3-methoxy-d_3-phenylethylene glycol (**47**), were prepared according to the general method of equation 15 (and 15a)[17].

e. Isotopic synthesis by nuclear deuterium exchange in methoxybenzenes

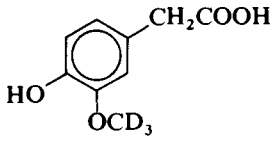
The 6,8-d_2-catechin/epicatechin 5,7,3′,4′-tetramethyl ether (**48**) was obtained when methylated procyanidin, isolated from *Vitis vinifera*, was cleaved with 0.05 N DCl/D_2O, 20% MeCOOD/D_2O or D_2O/dioxan mixtures. The molecular ion of **48** in the mass spectrum showed the presence of two deuterium atoms and the ions derived from the A



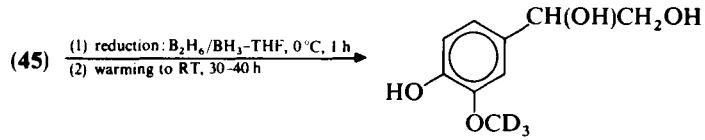
(44)



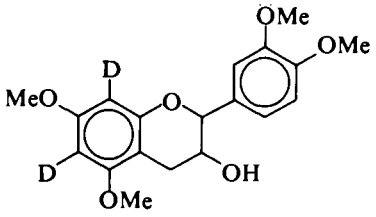
(45)



(46, 54% yield) (15)



(47, 21% yield from 45) (15a)



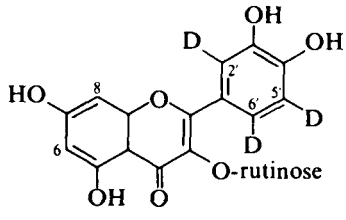
(48)

ring of **48** have *m/e* values higher by two units[18] than those from the unlabelled compound. This result prompted an NMR investigation of the deuterium exchange between the ring hydrogens of methoxybenzenes or the C(6) and C(8) hydrogens of methylated flavonoids with 3:1 D_2O/dioxan mixtures at 95 °C in Pyrex ampoules. After 16 hours of heating the following % exchange were found: methoxybenzene, 0%; 1,2-dimethoxybenzene, 0%; 1,3-dimethoxybenzene, 36.2%; 1,2,3-trimethoxybenzene, 21.5%; 1,2,4-trimethoxybenzene, 16.1%; 1,3,5-trimethoxybenzene, 100%; catechin 5,7,3′,4′-tetramethyl ether, 100%; 5,7,3′,4′-tetramethoxyflavan, 100%; dihydroquercetin 5,7,3′,4′-tetramethyl ether, 0%; 5,7,3′,4′-tetramethoxy-2,3-*trans*-flavan-3,4-*cis*-diol, 0%. These data are considered to be consistent with an electrophilic aromatic substitution mechanism involving two consecutive slow proton transfers steps, each involving addition of a proton to give an intermediate

phenonium ion followed by proton abstraction to yield the exchanged methoxybenzene. In the absence of an acidic catalyst, the exchange is assisted by the Pyrex glass surface. No exchange was found in soda glass NMR tubes.

f. Synthesis of deuterium-labelled rutin

Rutin, a flavonyl glycoside, used in the treatment of capillary bleeding, has been selectively[19] labelled with deuterium in the stable 2',5',6'-positions of the catechol ring to give **49** by a two-step hydrogen–deuterium exchange mechanism under mild alkaline



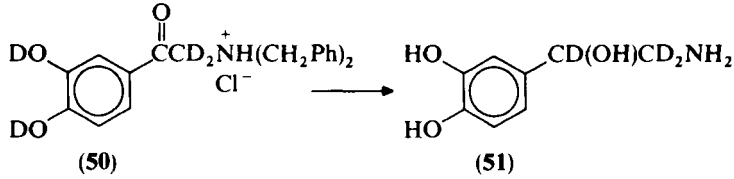
(49)

conditions[19]. In the first step rutin-2',5',6',6,8-d_5 was obtained by heating a mixture of sodium hydroxide and rutin in D_2O at 95 °C during 8 hours under nitrogen. In the second step the labile deuterium atoms in the 6,8 positions of the resorcinol ring were replaced with hydrogen by stirring the solution of sodium hydroxide and rutin-2',5',6',6,8-d_5 in water for 1 h at 25 °C, acidification with 10% acetic acid and repetition of the procedure. No loss of deuterium at any position was observed when the rutin-2',5',6'-d_3, which is useful for the metabolic study in man, was heated at 60 °C for 2 hours in methanol or water.

*g. Synthesis of deuterium and oxygen-*18 *labelled norepinephrine*

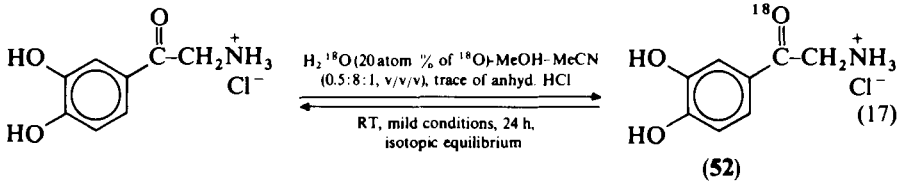
2-Dibenzylamino-1-(3,4-dihydroxyphenyl)ethanone-2,2-d_2 hydrochloride (**50**) was obtained[20] by D/H exchange of the protons α to the keto moiety of 2-dibenzylamino-1-(3,4-dihydroxyphenyl)ethanone-2,2-H_2 (at 80 °C for 4 days) with DCl/D_2O-dioxane. The post-exchange solution was lyophilized to dryness, the fresh solvent added and the exchange reaction repeated for an additional 7 days. Mass spectral analysis showed 87.5 atom % d_2, 11.8 atom % d_1 and 0.7 atom % d_0.

4-(2-Amino-1-hydroxyethyl-1,2,2-d_3)benzene-1,2-diol, NEd_3 (**51**), was synthesized by reduction the deuteriated precursor (**50**) with $D_2/Pd/C$ for 4 hours (equation 16). The



(50) **(51)** (16)

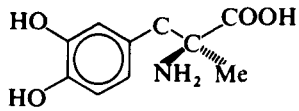
labile deuterium atoms in the free base of norepinephrine (neurotransmitter) were washed out by back exchange with aqueous ammonia solution. The protecting benzyl groups are removed in the course of reduction. 2-Amino-1-(3,4-dihydroxyphenyl)ethanone-^{18}O hydrochloride (**52**), useful for *in vivo* biochemical studies due to an 'unmeasurable' isotope effect, was prepared according to equation 17.



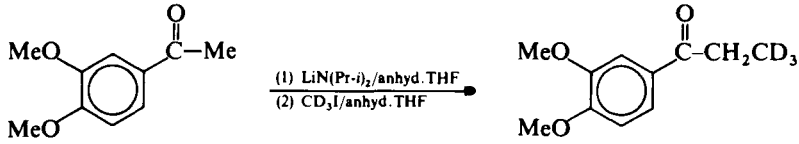
(17)

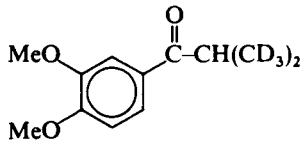
h. Synthesis of deuterium-enriched erythro-α-*methylnorepinephrine and norepinephrine*

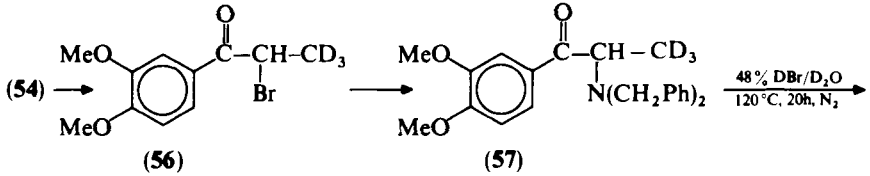
In the course of biomedical studies of (*S*)-α-methyldopa (**53**), the antihypertensive agent[21], *erythro*-α-methylnorepinephrine (**59**), enriched with six or seven deuterium atoms, has been needed as a mass spectrometric stable internal standard and it was synthesized according to equation 18. 1-(3,4-Dimethoxyphenyl)-1-propanone-3,3,3-d_3

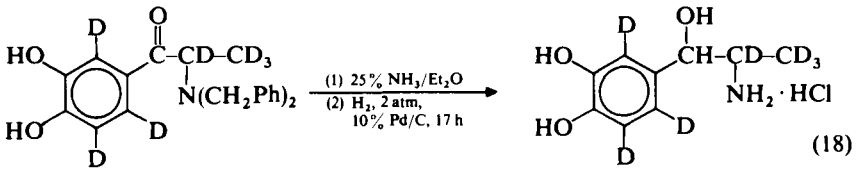


(**53**)



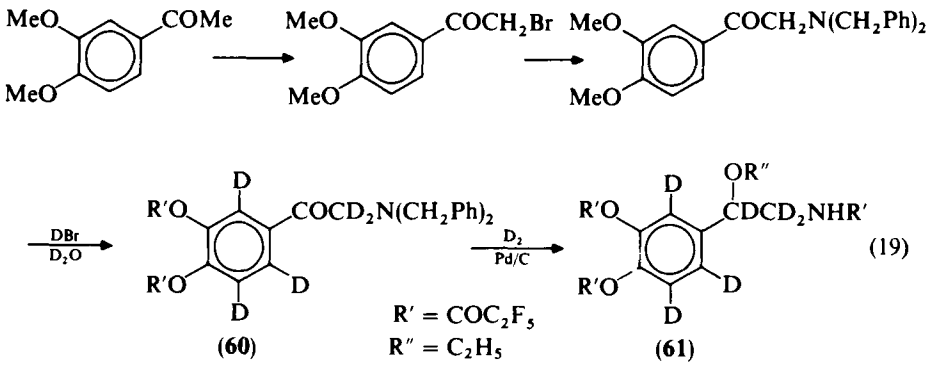






(18)

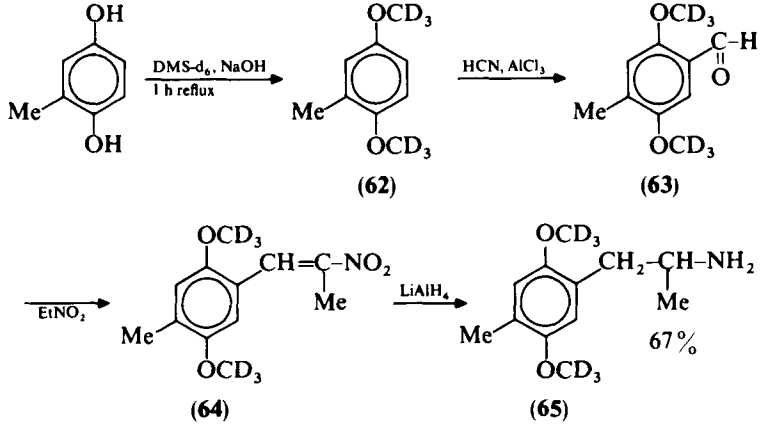
(**54**) was obtained by trideuteriomethylation of the lithio derivative of 3,4-dimethoxyacetophenone. Bromination of the propanone-d_3 with phenyltrimethylammonium tribromide in tetrahydrofuran yielded 2-bromo-1-(3,4-dimethoxyphenyl)-1-propanone-3,3,3-d_3 (**56**), which when treated with dibenzylamine gave 2-dibenzylamino-1-(3,4-dimethoxyphenyl)-1-propanone-3,3,3-d_3 (**57**). In the course of the cleavage of methyl ether groups with deuterium bromide three to four additional deuterium atoms were introduced in the resulting 2-dibenzylamino-1-(3,4-dihydroxyphenyl-2,5,6-d_2,d_3)-1-propanone-3,3,3-d_3 (**58**). Catalytic hydrogenation of **58** gave the desired *erythro*-2-amino-1-(3,4-dihydroxyphenyl-2,5,6-d_2,d_3)-1-propanol-2,3,3,3-d_4 hydrochloride (**59**) enriched with seven deuterium atoms. In a similar reaction sequence deuteriochloride (**60**) and 2-amino-d_2-1-(3,4-dihydroxy-d_2-phenyl-2,5,6-d_2,d_3)-1-ethanol-1,2,2,0-d_4 deuteriochloride were prepared as the *tris*-perfluoropropionyl derivatives (**61**) (equation 19)[21].



(19)

i. Synthesis of deuteriated methylhydroquinone derivatives and DOM-d_6

In the course of synthesis of deuterium-labelled internal standards for quantitative determination of organic compounds, especially drugs, pesticides and food additives in complex mixtures at low levels, by selected ion monitoring[22] several deuterium-labelled derivatives of methylhydroquinone have been obtained[22]. These include: 2,5-di(methoxy-d_3) toluene (**62**), from reaction of methylhydroquinone with dimethyl-d_6 sulphate (DMS-d_6) under nitrogen; 2,5-di(methoxy-d_3)-4-methylbenzaldehyde (**63**), by treating an ice-



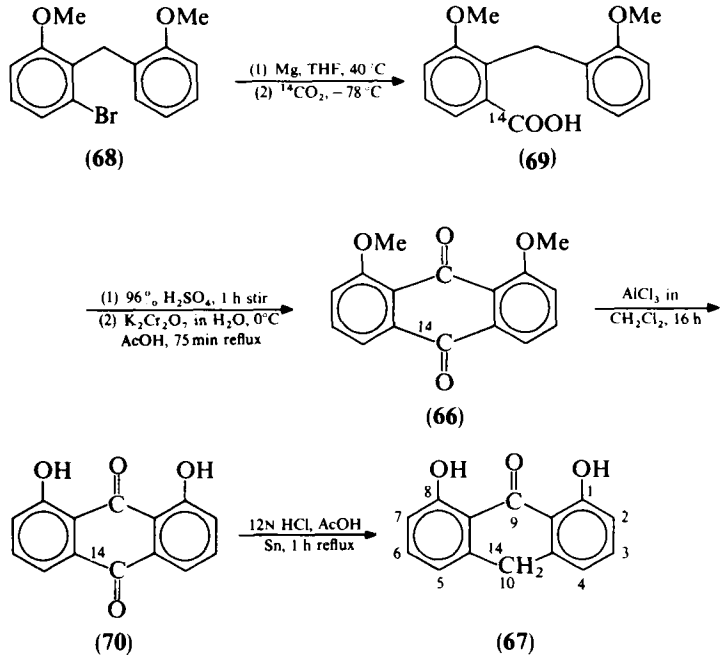
(20)

cooled solution of **62** in benzene with dry hydrogen cyanide, followed by addition of aluminium chloride and gaseous hydrogen chloride; 2-nitro-1-[2,5-di(methoxy-d_3)-4-methylphenyl]-1-propene (**64**), by reacting a solution of **63** in glacial acetic acid with nitroethane and ammonium acetate; 2,5-di(methoxy-d_3)-4-methylamphetamine (DOM-6) (**65**), by addition of ether solution of nitropropene (**64**) to solution of lithium aluminium hydride in anhydrous ether and subsequent careful addition of water and 30% Rochelle salt solution (equation 20). The free base (**65**) obtained was converted to the hydrochloride with hydrogen chloride–ether complex. The product had the following isotopic composition: d_6, 96.1%; d_5, 3.1%; d_4, 0.6%; d_1 and $d_0 < 0.1\%$.

B. Synthesis of ^{14}C-, ^{35}S- and ^{3}H-labelled Complex Anthraquinones and Labelled Drugs

1. *Synthesis of* [^{14}C]*anthralin*

The chemically stable 1,8-dimethoxy-[10-^{14}C]anthraquinone (**66**) was found[23] to be a suitable precursor of the unstable 1,8-dihydroxy-[10-^{14}C]-9-anthrone, anthralin (**67**), extensively used in the topical treatment of psoriasis. Quinone **66** can be stored indefinitely at low temperatures as such and converted efficiently to **67** when required (equation 21).



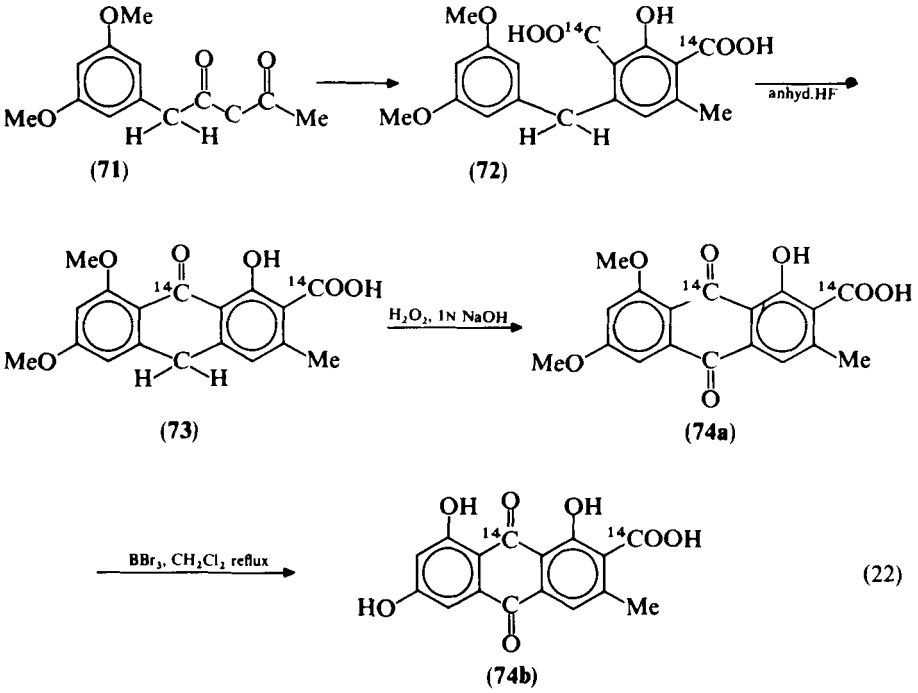
(21)

Isotopic carbon-14 was introduced to the anthraquinone **66** by carboxylation of the Grignard reagent derived from 3-bromo-2-(2-methoxybenzyl)anisole (**68**), using inexpensive $^{14}CO_2$. Cyclization/oxidation of the resultant 3-methoxy-2-(2-methoxybenzyl)(carbonyl-^{14}C)benzoic acid (**69**) gave the labelled **66**, which is easily transformed in 80% yield to **67** by demethylation with aluminium chloride in dichloromethane to form 1,8-dihydroxy-[10-^{14}C]anthraquinone (**70**), followed by reduction with powdered tin and

hydrochloric acid. The final product (**67**) was obtained with specific activity of 57 mCi mmol^{-1}. The bromo compound (**68**) was obtained from inactive 3-methoxy-2-(2-methoxybenzyl)benzoic acid by a Curtius/Sandmeyer reaction sequence[23].

2. *Synthesis of endocrocin and endocrocin-9-one*

Endocrocin-9-one (**73**) and endocrocin (**74b**) are important intermediates in the biosynthesis of emodin and related anthraquinones. They have been prepared[24] by treatment of the dicarboxylic acid (**72**), ^{14}C-labelled at both carboxyl groups, with polyphosphoric acid or anhydrous HF, oxidation of the resulting **73** with H_2O_2 in 1 N NaOH and *O*-demethylation of the formed endocrocin 6,8-dimethyl ether (**74a**) with BBr_3 in refluxing CH_2Cl_2 followed by chromatography. The ^{14}C-labelled Mühlemann's dicarboxylic acid (**72**) has been synthesized by condensation of the diketone (**71**) with dimethyl[1,5-$^{14}C_2$]acetonedicarboxylate (equation 22).



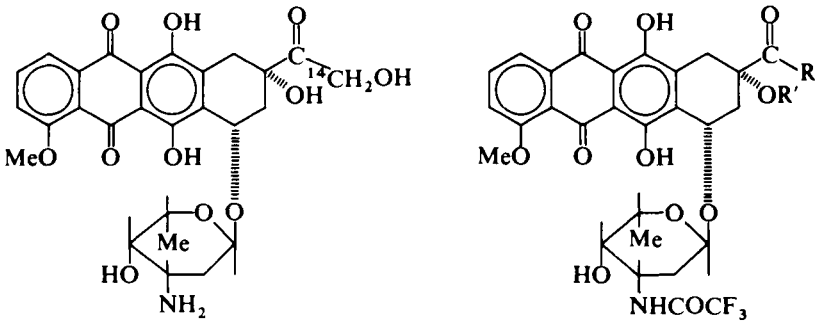
(22)

3. *Synthesis of [14-^{14}C]adriamycin and daunorubicin*

a. [14-^{14}C]*Adriamycin·HCl* (**75**)

This important anticancer antibiotic has been prepared from unlabelled adriamycin using ^{14}C-diazald as the source of the label, followed by reaction scheme of equation 23[25] which does not require protection of the phenolic hydroxyl groups. *N*-TFA-adriamycin (**76**), in tetrahydrofuran reacted with aqueous periodic acid at room temperature to give the carboxylic acid (**77**) in 82% yield. Stirring a suspension of the isolated unpurified key intermediate (77) in chloroform with triethylamine and isobutyl chloroformate in the cold

afforded the unstable mixed anhydride (**78**). Addition of **78** to etheral solution of ^{14}C-diazomethane afforded, after workup, the diazoketone (**79**) in 25% yield. The methyl ester (**80**) was the major 20% by-product in this step. The intermediate **79** was converted with excess of hydrogen bromide in 95% yield to bromoketone (**81**). Treatment of **81** in THF with aqueous potassium carbonate yielded *N*-trifluoroacetyl-adriamycin[14-^{14}C] (**76**[x]). Protection of the 14-hydroxyl group of *N*-TFA-adriamycin in 56% yield was achieved with *p*-anisyldiphenylchloromethane in pyridine[26]. [14-^{14}C]Adriamycin (**75**) was obtained from **82** by removal of the *N*-TFA group with sodium hydroxide solution and successive removal of the *p*-anisyldiphenylmethyl group by 80% acetic acid. The formed **75** was converted to its hydrochloride with methanolic HCl in 45% yield. The resulting red [14-^{14}C]-(**75**) was identical in all respects with adriamycin · HCl.



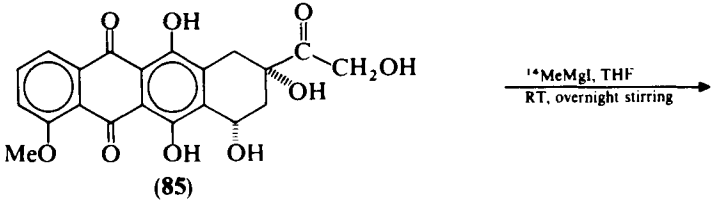
(**75**)

(**76**) R = CH_2OH, R′ = H
(**77**) R = OH, R′ = H
(**78**) R = CO_2Bu-*i*, R′ = CO_2Bu-*i*
(**79**) R = $^{14}CHN_2$, R′ = CO_2Bu-*i*
(**80**) R = OMe, R′ = CO_2Bu-*i*
(**81**) R = $^{14}CH_2Br$, R′ = CO_2Bu-*i*
(**82**) R = $^{14}CH_2OCPh_2C_6H_4OMe$-*p*, R′ = H

(**76**) → (**77**) → (**78**) → (**79**) → (**81**) → (**76**[x]) → (**82**) → (**75**) (23)

b. Synthesis of daunorubicin-[14-^{14}C] *and adriamycin-*[14-^{14}C]

The clinically useful antineoplastic agents, anthracycline antibiotics adriamycin (**75**) and daunorubicin (**83**), were also labelled with ^{14}C at the C(14) position by using the reaction scheme of equation 24[27]. Treatment of adriamycinone (**85**) in THF with 15 : 1 molar excess of $^{14}CH_3MgI$ and periodate oxidative cleavage of the glycol (**86**) affords daunomycinone [14-^{14}C] (**87**). Condensation of **87** with the protected 1-chlorodaunosamine (**91**), prepared from *N*-trifluoroacetyl-1,4-di-*O*-*p*-nitrobenzoyldaunosamine with HCl, followed by deacylation of the resulting α-glycoside with aqueous sodium hydroxide and addition of HCl, afforded daunorubicin-[14-^{14}C] · HCl (**83**), with 6.9 mCi mmol^{-1} activity. Bromination of daunomycinone-[14-^{14}C] (**87**) and hydrolysis gave **88** and adriamycinone-[14-^{14}C] (**89**), respectively. The 14-OH group of **89** was protected by coupling with *p*-anisylchlorodiphenylmethane to give 14-*O* (*p*-anisyldiphenylmethyl)-adriamycinone [14-^{14}C] (**90**). The latter was condensed with **91** to produce the α-glycoside. Basic deacetylation gave crude 14-*O*(*p*-anisyldiphenylmethyl) adriamycin [14-^{14}C] (**84**). Deprotection of **84** with 80% acetic acid afforded adriamycin-[14-^{14}C] which with HCl gave adriamycin · HCl (**75**), in 40% yield (specific activity 6.5 mCi mmol^{-1}).



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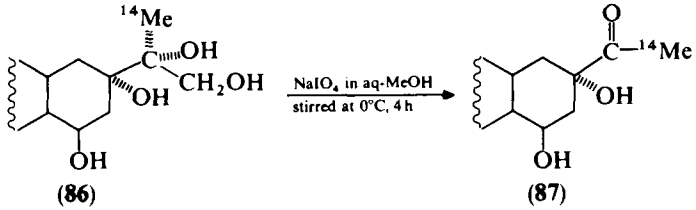
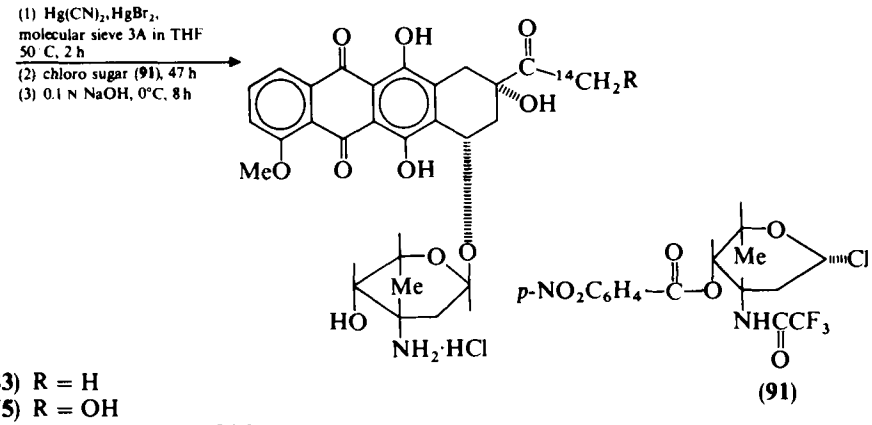
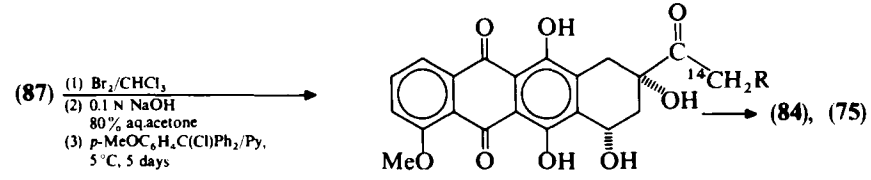


(86) (87)



(91)

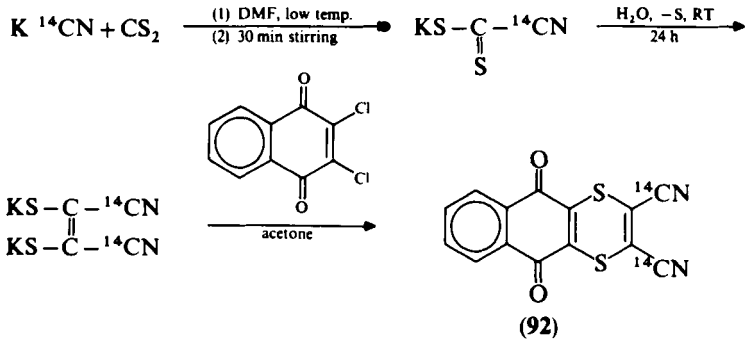
(83) R = H
(75) R = OH
(84) R = $OCPh_2C_6H_4OMe$-*p*



(88) R = Br (24)
(89) R = OH
(90) R = $OCPh_2C_6H_4OMe$-*p*

4. *Synthesis of ^{14}C- or ^{35}S-labelled 2,3-dicyano-1,4-dithia-9,10-anthraquinone*

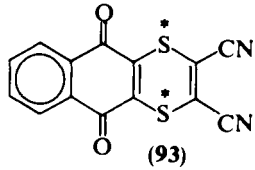
The ^{14}C- and ^{35}S-labelled title compounds **92**, **93** and **94** which exhibit pesticidal and fungicidal properties and are used in the protection of agricultural and fruit production, have been prepared on a milligram scale in closed all-glass apparatus useful for the



(25)

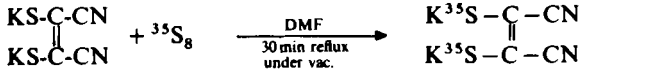
(92)

production of labelled compounds[28] with high specific radioactivity. Dithianones having 88 Ci of ^{14}C mol^{-1} and 44 Ci of ^{35}S mol^{-1} were obtained on a microscale according to reaction scheme 25. Dithianon-^{35}S (**93**), was also prepared according to equation 25. The



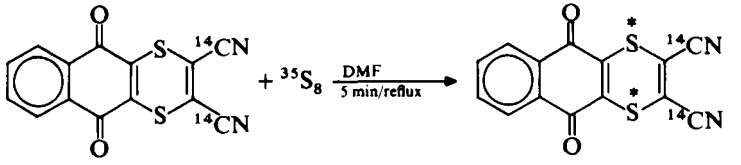
(93)

required ^{35}S-labelled dipotassium 1,2-dicyanoethenedithiolate was obtained by the exchange with elemental sulphur under reduced pressure (equation 26). Dithianon (**93**)



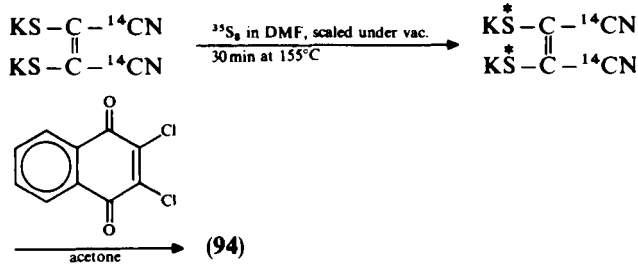
(26)

was also synthesized by a direct rapid exchange of the pure dithianon with elemental sulphur-^{35}S in dimethylformamide. A dithianon doubly labelled with both ^{14}C and ^{35}S (**94**) was prepared similarly by the direct exchange of dithianon-^{14}C with ^{35}S (equation 27), as well as according to equation 28. The use of the exchange scheme (27) for simultaneous labelling with ^{14}C and ^{35}S is recommended since the potassium 1,2-dicyanoethenedi-



(27)

(94)

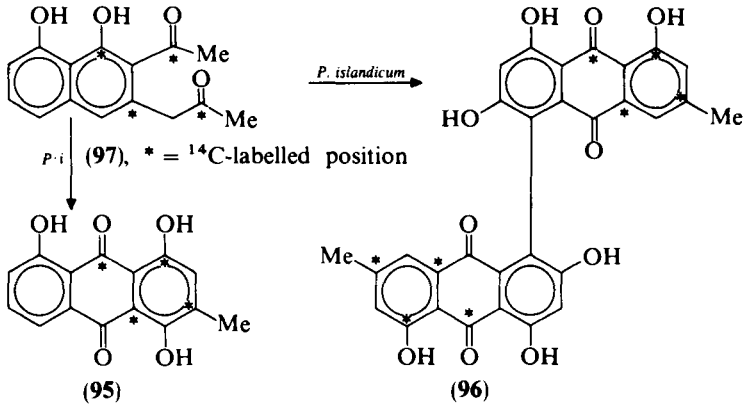


(28)

thiolate undergoes a rapid thermal decomposition, and the final radiochemical and chemical yields of the labelled substance obtained according to scheme 28 are rather low (radiochem. yield 16.3%, chem. yield 13.2%, radiochem. purity 97.2%). The lower specific activity of ^{35}S can be improved by the use of higher activities of elemental ^{35}S in the exchange scheme (27).

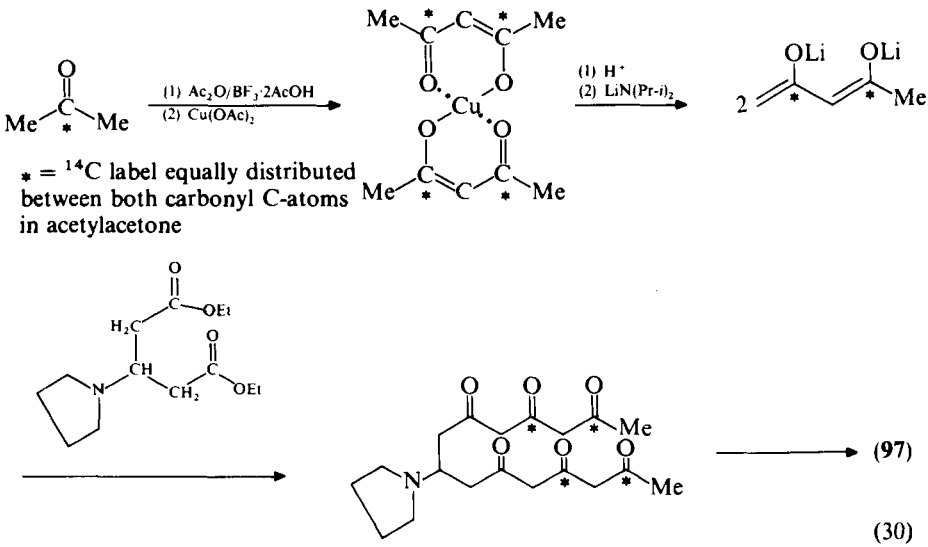
5. *Synthesis of ^{14}C- and ^{3}H-labelled islandicin, skyrin, emodin, emodinanthrone, secalon acid and moniliformin*

The ^{14}C-labelled islandicin (**95**) and skyrin (**96**) were obtained in significant yield[29] by feeding the synthetically ^{14}C-labelled diketonaphthol (**97**) to the surface cultures of the mould fungus *Penicillium islandicum* (equation 29). The chemical synthesis of the ^{14}C



(29)

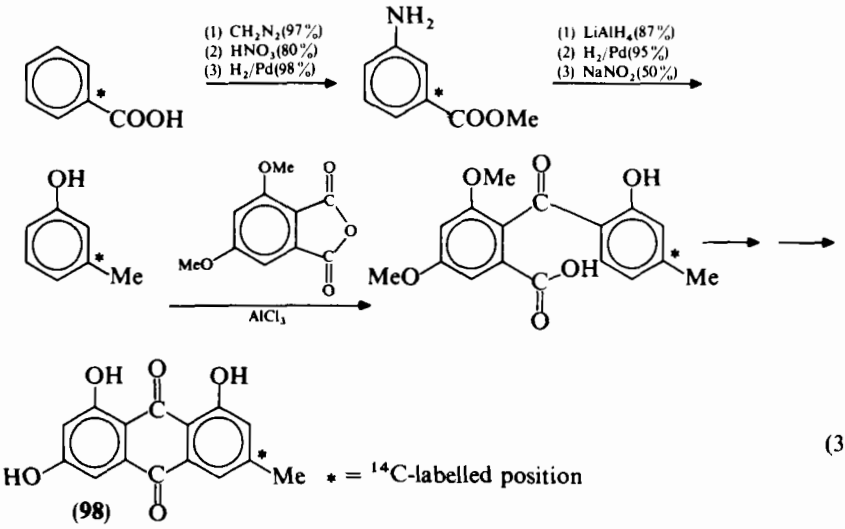
intermediate (**97**) was carried out following reaction scheme 30[30–32]. The diethyl 3-pyrrolidinoglutarate was obtained in 82% yield by reacting pyrrolidine with diethyl



(30)

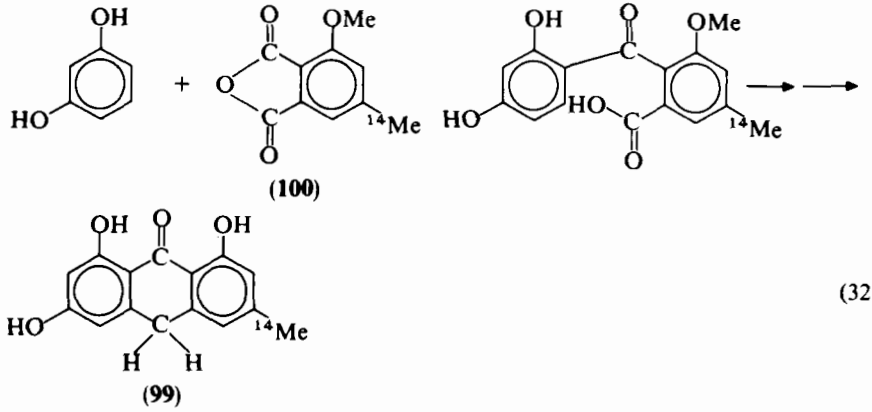
glutaconate. By these labelling experiments the participation of the bicyclic intermediate (**97**) in the general polyketide route of anthraquinone biosynthesis by microorganism has been established.

In the course of biochemical studies of the ergochrome synthesis by 8-day-old *Penicillium oxalicum* (ATCC 10476) the 3-^{14}C-labelled emodin (**98**) and the intermediate [11-^{14}C]emodinanthrone were obtained by chemical methods. **98** was synthesized with a rather low (8 %) yield by the Friedel–Crafts reaction of the anhydride of 3,5-dimethoxyphthalic acid with [3-^{14}C]-*m*-cresol. The latter was obtained in a six-step synthesis from [1-^{14}C]benzoic acid with 31 % overall yield (equation 31). **99** was obtained in a 45 % yield



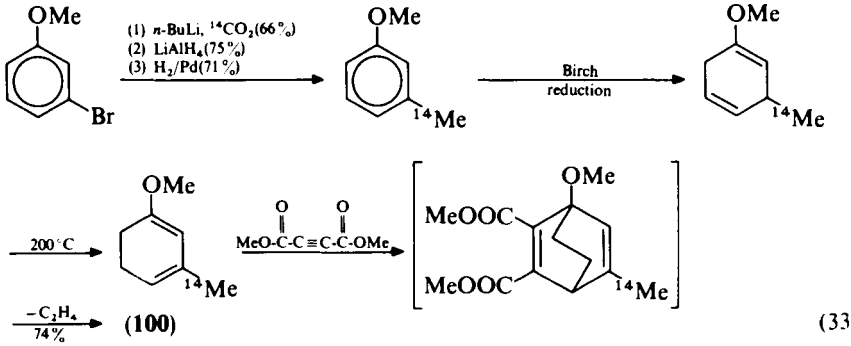
(31)

by condensing the 3-methoxy-5-(methyl-^{14}C)-phthalic anhydride (**100**), with 1,3-dihydroxybenzene (equation 32). The labelled anhydride (**100**) was synthesized according



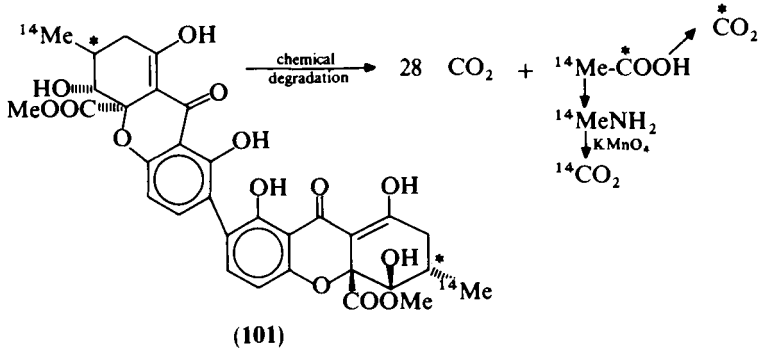
(32)

to reaction scheme 33. When a mixture of both ^{14}C-labelled compounds **98** and **99** was added to *Penicillium oxalicum* growing medium it was incorporated effectively into the



(33)

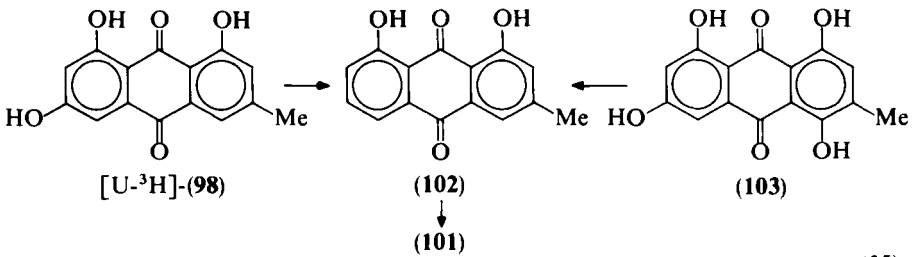
^{14}C-labelled acid (**101**). ^{14}C- and tritium-labelled acid (**101**) was also obtained by growing the *Penicillium oxalicum* culture (ATCC-10476) in the presence of biosynthetically



(**101**)

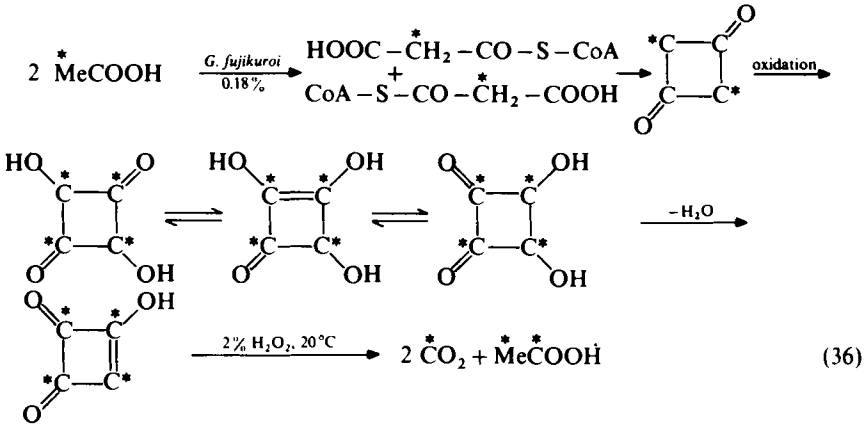
(34)

uniformly labelled [U-^{3}H]emodin and one of the [U-^{14}C]anthraquinones: [U-^{14}C]emodin, [U-^{14}C]chrysophanol (**102**), [U-^{14}C]islandicin or [U-^{14}C]catenarin (**103**).



(35)

The radioactivities of the product (**101**), isolated and purified up to a constant specific radioactivity, were measured and the ratio ^{3}H/^{14}C was established by using a scintillation counter. The cumulative data concerning the incorporation of radioactive anthraquinones into **101** by *P. oxalicum* indicate that chrysophanol (**102**) incorporated into **101** 3.6 times better than emodin (**98**) and 11.8 more effectively than islandicin (**95**). The conclusion was also made that emodin and islandicin are incorporated into **101** through the intermediate



(104) (36)

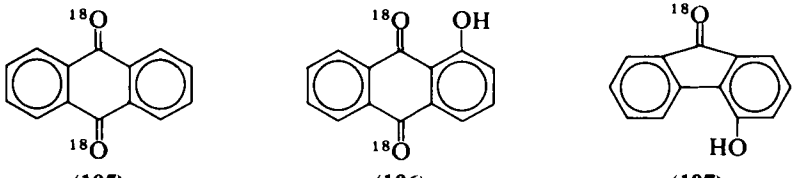
chrysophanol (**102**)[33, 34]. In Franck's review[35] on the synthesis, structure and applications of mycotoxine derivatives, the biosynthesis of [U-^{14}C]moniliformins (**104**), from [1-^{14}C]- and [2-^{14}C]acetate by *Gibberella fujikuroi* has been outlined (equation 36). All carbon atoms in **104** had the same specific radioactivity[35, 36].

II. ISOTOPIC CHEMICAL STUDIES WITH QUINONES

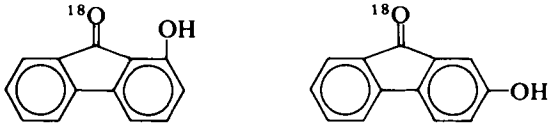
A. Mass Spectrometric Gas Phase and Liquid Phase Reactions with ^{18}O- and ^{2}H-labelled Quinones

1. *Gas phase reactions with positively charged [^{18}O]anthraquinone, [^{18}O]hydroxyanthraquinone and [^{18}O]hydroxyfluorenones*

[9,10-bis-^{18}O]Anthraquinone (**105**) (obtained by concentrated HCl-catalysed exchange of parent anthraquinone with $H_2{}^{18}O$) and [9,10-bis-^{18}O]-1-hydroxyanthraquinone (**106**), [9-^{18}O]-4-hydroxy-9-fluorenone (**107**), [9-^{18}O]-1-hydroxy-9-fluorenone (**108**) and [9-^{18}O]-2-hydroxy-9-fluorenone (**109**), prepared by a similar method and containing 40%, 8%, 60%, 55% and 60% of ^{18}O respectively were used for investigation of the gas phase reactions of positively charged ions[37]. Mass spectrometric studies of the gas phase



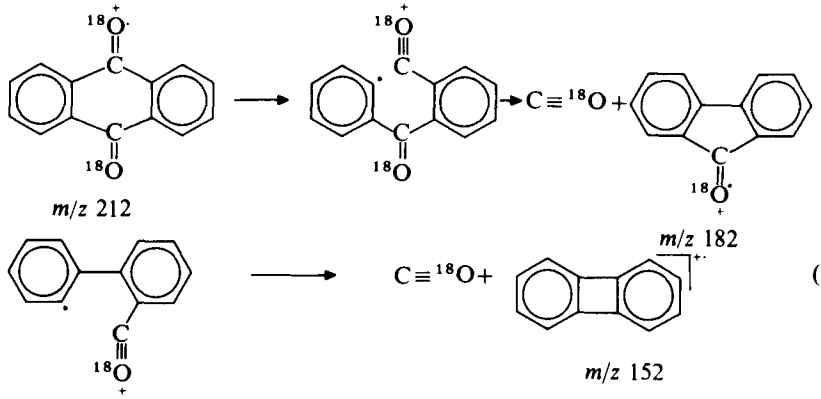
(**105**) (**106**) (**107**)



(**108**) (**109**)

decomposition of the positive ions derived from **105** confirmed the suggestion that the principal reaction of positively charged quinones in the gas phase is the loss of neutral carbon monoxide from the molecular ion. This is followed by ejection of the second carbon monoxide molecule from the resulting $[M-CO]^{+\cdot}$ ion (equation 37). A more detailed schematic representation of this consecutive loss of two carbon monoxide molecules from the molecular ion of labelled anthraquinone is given in equation 38. By

$$[M]^{+\cdot} \rightarrow [M-CO]^{+\cdot} \rightarrow [M-CO-CO]^{+\cdot} \tag{37}$$

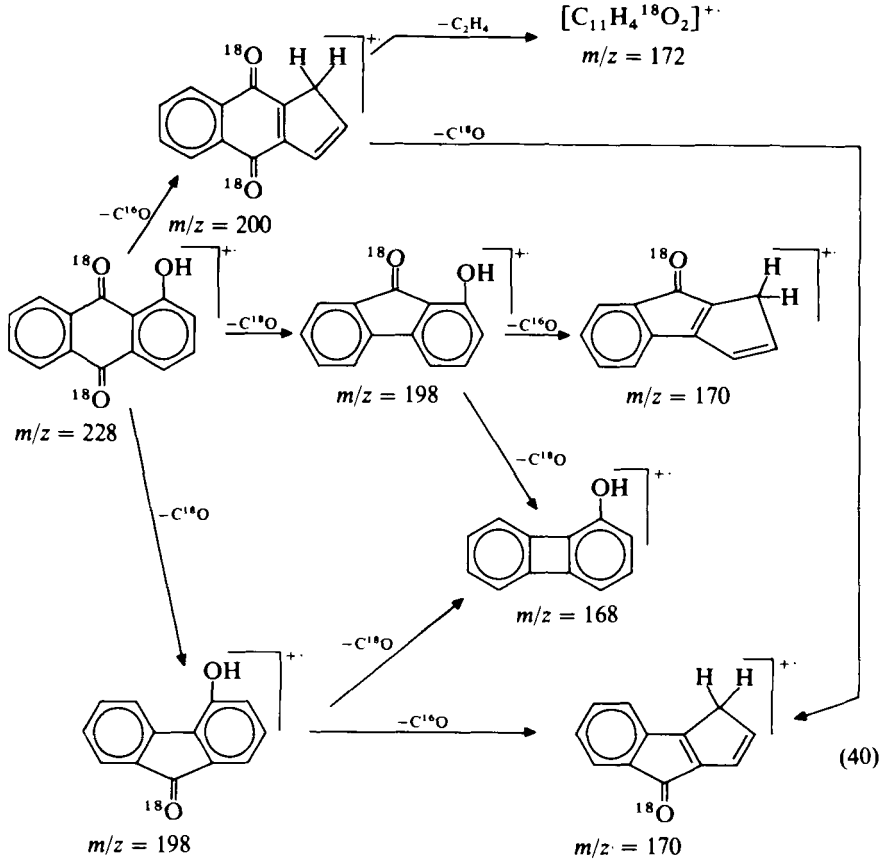


(38)

using [9,10-di-^{18}O]-1-hydroxy-9,10-anthraquinone (**106**) it was possible to distinguish between the loss of carbon monoxide from the two different functional groups of the molecular ion of 1-hydroxyanthraquinone whose schematic decomposing is given in equation 39.

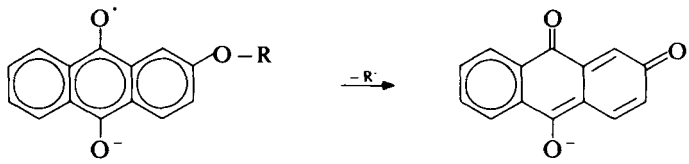
$$M^{+\cdot} \rightarrow [M-CO]^{+\cdot} \rightarrow [M-CO-CO]^{+\cdot} \rightarrow [M-CO-CO-CO]^{+\cdot} \tag{39}$$

It also enabled the estimation of the relative probability of the different decomposition channels shown in equation 40. Thus it has been shown that the *m/z* 228 ion loses $C^{18}O$ and $C^{16}O$ in an approximate ratio of 4 : 1. Consequently the loss of carbon monoxide from the carbonyl position is preferred over its loss from the hydroxyl position. Moreover the loss of the *m/z* 28 fragment is entirely due to $C^{16}O$ loss and not to C_2H_4 loss. It has also been found that the peaks corresponding to reactions $(228^+ \rightarrow 170^+)/(228^+ \rightarrow 168^+)$ are observed in a ratio of 1 : 1.6. This implies that the consecutive loss of two $C^{18}O$ molecules, i.e. the formation of the hydroxybiphenylene structure, is favoured over the loss of carbon monoxide from the hydroxyl position in the second step. The simultaneous loss of *m/z* $56[C^{16}O + C_2H_4]$ from the molecular ion appeared to be a minor process. The *m/z* 200 ions generate the 172^+ and 170^+ ions in a 1 : 5 ratio. In the case of the *m/z* 198 ions the decomposition route depends largely upon the isomer studied. The [9-^{18}O]-1-hydroxy-9-fluorenone ion loses virtually only $C^{16}O$ from the hydroxyl group position, while [9-^{18}O]-4-hydroxy-9-fluorenone prefers to lose $C^{18}O$ from the central ring, as judged by the $C^{18}O/C^{16}O$ ratio of ca. 10 : 1, and probably to form hydroxybiphenylene. In the case of molecular ion of [9-^{18}O]-2-hydroxy-9-fluorenone, $C^{18}O$ and $C^{16}O$ isotopic molecules are lost in a ratio of 2 : 3. It has also been found that the ratio of 4-hydroxyfluorenone to 1-hydroxyfluorenone is 2 : 1 when ^{18}O-enriched 1-hydroxyanthraquinone loses $C^{18}O$ in the ion source of the mass spectrometer. This means that the carbonyl group adjacent to the hydroxyl group is lost preferentially, probably because among the hydroxyfluorenones **107** has a greater stability than **108**.



2. *Negative-ion mass spectrometric studies with labelled quinones*

Isotopically labelled substituted naphthoquinones and anthraquinones have been used in negative-ion mass spectrometry[38–42], especially of esters of the type R^1–COO–R^2, where R^1 or R^2 is a quinone residue. The basic fragmentation of ethers of the type **110** proceeds by a loss of an alkyl radical with formation of the resonance-stabilized form (**111**) (equation 41). Electron impact studies with 1-d_3-methoxyanthraquinone and the

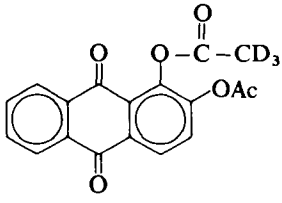


(41)

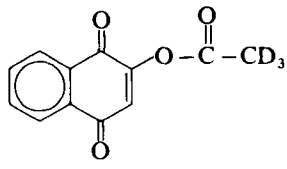
(**110**) (**111**) m/z = 223

observed elimination of the CD_3O· group established that the 'M – RO·' process is the minor fragmentation path in the mass spectrometry of complex ethers[39]. By using

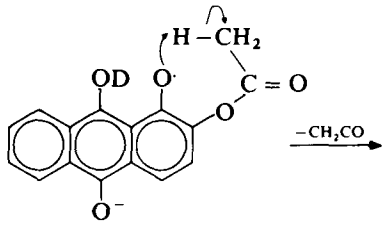
deuterium-labelled anthraquinone esters (**112**), prepared from alizarin-2-acetate and [$^2H_6$]acetic anhydride, and naphthoquinone ester (**113**) obtained by treatment of 2-hydroxynaphthoquinone with [$^2H_6$]acetic anhydride it has been demonstrated[38] that **113**



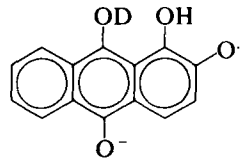
(**112**)



(**113**)



(**114**)



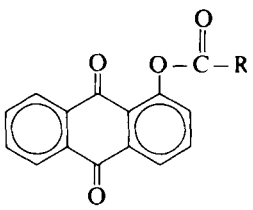
(**115**)

(42)

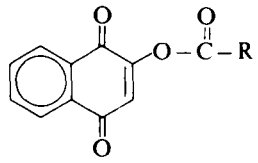
specifically eliminates ketene CD_2CO, while **112** undergoes two fragmentation pathways, M–CD_2CO–CH_2CO and M–CD_2CO–MeCO$^{\cdot}$. Elimination of ketene from the 1-position of **112** produces **114** which decomposes by loss of a second ketene molecule to form **115** (equation 42). Thus it has been shown that the presence of an adjacent phenoxide radical or anion to the acetoxy group is sufficient prerequisite for elimination of ketene in the acetoxyanthraquinone system.

a. *Deuterium isotope effect study of the mechanism of negative-ion reactions in the gas phase*

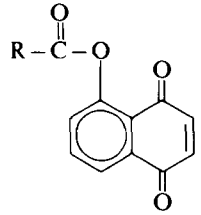
Expecting that hydrogen loss or transfer takes place in the rate-determining step of the unimolecular elimination of ketene from negatively charged quinone acetate molecular ions, deuterium-labelled anthraquinone 1-acetate and 1-propionate and deuterium-labelled analogous 2- and 8-substituted 1,4-naphthoquinones have been prepared from the corresponding phenols with anhydrides. The negative-ion mass spectra of the esters were investigated and the deuterium isotope effects were determined for the quinone derivatives **116**–**133**[43]. The estimated ratios of the unimolecular rate constants for hydrogen atom transfer (i.e. formation of M–CHDCO) and for deuterium transfer (i.e. formation of M–CH_2CO) for quinones singly labelled with deuterium at the tertiary or secondary carbon are listed in Table 1. (Data corresponding to MeCO$^{\cdot}$ and to $CD_3CO^{\cdot}$ analogues were probably utilized in the course of evaluations of these isotope effects.) The data shown in Table 1 indicate that the hydrogen transfer is taking place in the rate-determining step of the reaction. The k_H/k_D values are relatively low and imply rather the unsymmetrical 'product-like' transition state characteristic for endothermic radical reactions. The tunnelling contributions are therefore ignored. The authors ascribed the slightly lower k_H/k_D values for 2-acetoxy-1,4-naphthoquinone (**121**) than for 8-acetoxy-1,4-naphthoquinone (**125**) to stabilization by delocalization of the radical centre at position 1 in compounds **121** and **123**, with a consequent effective stabilization of both



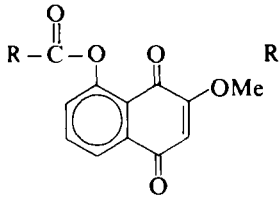
(**116**) R = Me
(**117**) R = CH_2D
(**118**) R = Et
(**119**) R = CHDMe



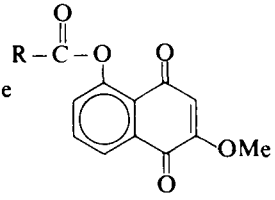
(**120**) R = Me
(**121**) R = CH_2D
(**122**) R = Et
(**123**) R = CHDMe



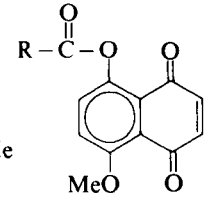
(**124**) R = Me
(**125**) R = CH_2D
(**126**) R = Et
(**127**) R = CHDMe



(**128**) R = Me
(**129**) R = CH_2D



(**130**) R = Me
(**131**) R = CH_2D



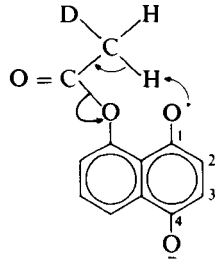
(**132**) R = Me
(**133**) R = CH_2D

TABLE 1. Kinetic isotope effect in the gas phase elimination of CH_2=C=O or MeCH=C=O from 1-acetates and 1-propionates of substituted quinones.

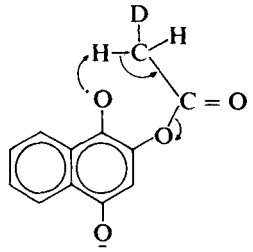
	$k_{H\ transfer}/k_{D\ transfer}$	
Compound	Ion source	First field free region
117	1.7	1.8
119	1.8	1.9
125	2.3	2.45
127	2.35	2.5
121	1.45	1.5
123	1.4	1.55
129	1.45	1.5
131	2.1	2.25
133	1.55	1.65

reactant and product with respect to the transition state, thus increasing asymmetry of the transition state. In contrast the acyloxy group of **125** and **127** does not stabilize the radical centre and the isotope effect is higher (cf. structures **134** and **135**).

The proposal that these rearrangements are endothermic radical reactions with 'unsymmetrical product-like' transition state was corroborated by studying the methoxy derivatives. The 2-methoxy group of **129** and the 5-methoxy group in **133** decreased the isotope effect by stabilizing the radical centre in reactant and product while the 3-methoxy



(134)

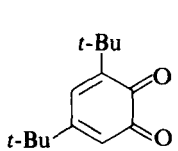


(135)

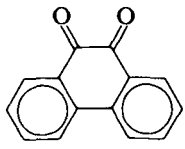
group of **131** which stabilizes only the radical centre at position 4 did not lower the isotope effect. It is also suggested that in rearrangements in which $k_H/k_D > 2.1$ the possibility that the rate-determining step involves a proton transfer cannot be completely excluded. (One can distinguish between a reactant-like and a product-like hydrogen transfer in the ketene elimination reactions studying the ^{13}C and ^{14}C kinetic isotope effects in the course of the carbon–hydrogen bond rupture.)

3. Mechanism of C–C bond cleavage of cyclic 1,2-diketones with alkaline hydrogen [^{18}O]peroxide

Oxygen-18 labelling was also applied[44] to investigate the mechanism of the carbon–carbon bond cleavage of cyclic 1,2-diketones with alkaline hydrogen peroxide. ^{18}O tracer study of the reaction of 3,5-di-*t*-butyl-1,2-benzoquinone (**136**) and 9,10-phenanthrenequinone (**137**) indicated that the carbon–carbon cleavage reaction proceeds



(136)



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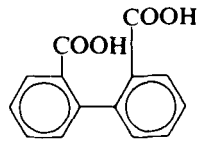

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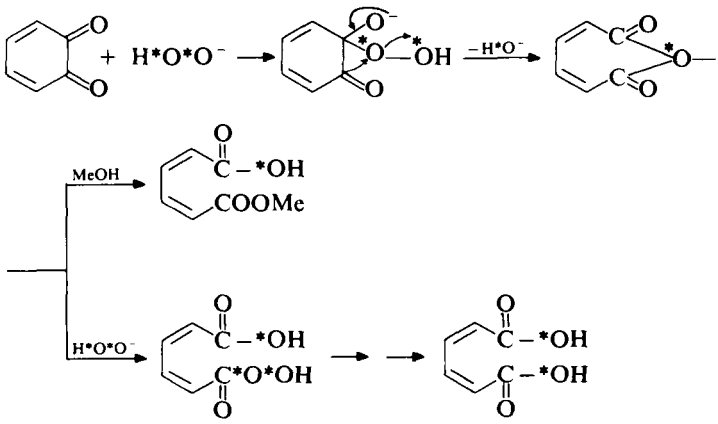
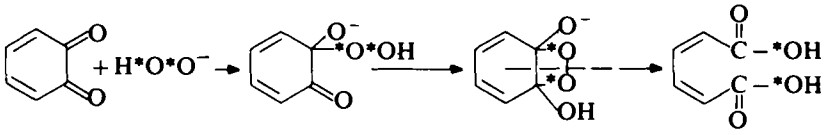


(43)

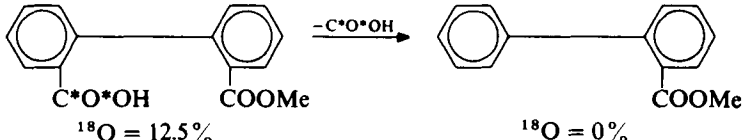
* = ^{18}O label

via an acyclic Baeyer–Villiger type mechanism (equation 43). Mass spectral determination of the $^{18}O\%$ excess in the molecular fragments of the oxidation products eliminates the rather attractive cyclic dioxetane mechanism in the oxidation with $H_2^*O_2$ (equation 44), as



(44)

well as a mechanism involving an intermediate peroxide. Thus in the reaction of phenanthrenequinone with $H_2^*O_2$/NaOH in 1 : 1 THF/MeOH the diphenic acid (**138**) and its monoester (**139**) are obtained, each in about 34% and 25% isolated yields respectively. One oxygen atom in the monomethyl diphenate (**139**) should be derived from $H_2^*O_2$ since mass spectral cleavage of the acid group of **139** results in loss of the excess ^{18}O (equation 45), while cleavage of the COOMe group yields [^{18}O]carboxyl labelled acid[44]. These



(45)

(**139**)

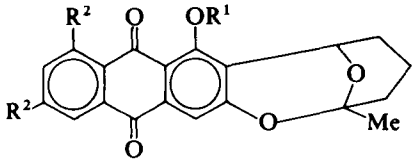
experimental observations are interpreted as strongly supporting the acyclic type mechanism of equation 43. However, it needs further theoretical and isotope effect investigation.

B. Spectroscopic, Radiation and Chemical Investigations of Labelled Quinones

1. Spectroscopic studies of labelled quinones

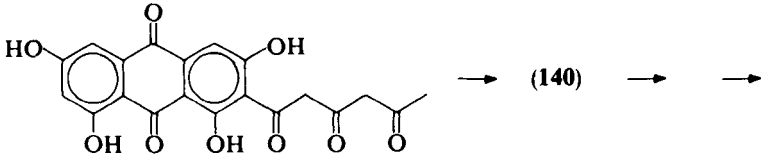
a. ^{13}C Nuclear magnetic resonance studies with quinones

Carbon-13 nuclear magnetic resonance spectra of hydroxymethoxyanthraquinones, acetoxymethoxyanthraquinones and naturally occurring anthraquinone analogues were measured for isotopically enriched compounds in deuteriated $CDCl_3$ and $(CD_3)_2SO$ solvents[45]. The structures of averufin (**140**), tri-*O*-methylaverufin (**141**) and tri-*O*-acetylaverufin (**142**) have been elucidated by using labelled averufin obtained from the

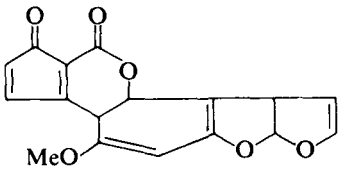


(**140**) $R^1 = H$, $R^2 = OH$
(**141**) $R^2 = OMe$; $R^1 = Me$
(**142**) $R^2 = OCOMe$; $R^1 = COMe$

$^{13}C(1)$-enriched acetate[46,47] by *Aspergillus versicolor*. The precursor–product relationship between the acetate and averufin has been demonstrated by using [^{13}C]acetate[48a]. Compound **143** was proposed as the precursor of averufin, which in turn has been suggested to be the intermediate in the biosynthetic production of aflatoxin (**144**) B_1, a potent hepatocarcinogen, by *Aspergillus flavus* (equation (46)[48b,49]. Deuteriation effects

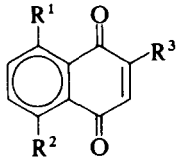


(143) → (140) → →



(144) (46)

were used to determine the ^{13}C chemical shift[50,51] δ_C for 1,4-naphthoquinone (**145**), vitamin K_3(**146**), juglone (**147**), naphthazarin (**148**) and their methyl ethers and acetates **149** and **150**[51].



(**145**) $R^1 = R^2 = R^3 = H$
(**146**) $R^1 = R^2 = H$, $R^3 = Me$
(**147**) $R^1 = OH$, $R^2 = R^3 = H$
(**148**) $R^1 = R^2 = OH$, $R^3 = H$
(**149**) $R^1 = OMe$, $R^2 = OH$, $R^3 = H$
(**150**) $R^1 = OAc$, $R^2 = OH$, $R^3 = H$

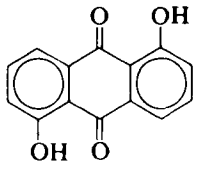
b. EPR study of hydroxyanthrasemiquinones

Deuterium-labelling experiments had to be carried out in the course of determinations of the hydroxyl proton coupling constants of six α-hydroxylated, two β-hydroxylated and three α,β-dihydroxylated anthrasemiquinones by EPR[52]. The semiquinones studied were prepared by reduction of quinones with sodium dithionite in alkaline solvent (pH ca. 12) composed of D_2O, EtOD and NaOD. Any hydroxyl proton doublet was then replaced by a 1 : 1 : 1 triplet and the splitting was reduced to about one-sixth of the proton splitting. The deuterium triplet splitting often becomes smaller than the experimental line width, leading to a considerable simplification of the spectrum. This has been found for instance in the EPR spectra of 1,2,5,8-tetrahydroxyanthrasemiquinone taken in deuteriated solvents.

Biological semiquinone anions and neutral semiquinone anions and neutral semiquinone radicals generated by irradiation with a 250 Hg/Xe lamp in quartz ESR tubes and immobilized in a solvent matrix frozen in liquid nitrogen were reviewed by Hales and Case[53].

c. Fluorescence studies with 1,5-dihydroxyanthraquinone

The effect of deuteration on the absorbance and fluorescence spectra of 1,5-dihydroxyanthraquinone (**151**) has also been investigated. Deuterium substitution of the

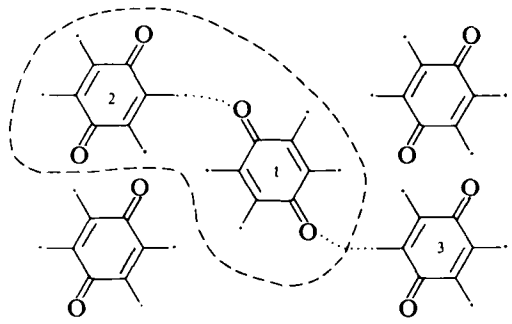


(151)

hydroxy protons almost[54] totally eliminates the structure in the room temperature absorbance, and it also regularizes the room temperature fluorescence profile. The deuterium replacement has a very minor effect on the S_1–S_2 oscillator strength but it shifts the transition by 3–4 nm (ca. 150 cm^{-1}) to the blue. At wavelengths shorter than 375 nm the absorbance spectra of non-deuteriated and deuteriated **151** are virtually indistinguishable since the π–π^* transitions of the anthraquinone framework have only little charge-transfer character. Deuterium substitution increases the fluorescence quantum yield by nearly four-fold and diminishes the short wavelength component of the emission. Changes at $\lambda > 575$ nm are comparatively minor. The marked fluorescence intensity increase in the 560–575 nm region is interpreted as the symptom of the O–H stretching vibration activity in this wavelength region (ω_{OH} = ca. 3000 cm^{-1} in the IR spectrum, $\omega_{O\text{-}D} = 2300\,cm^{-1}$)[55]. The intensity of the low-temperature short wavelength fluorescence (SWF) is greatly reduced when the hydroxy protons are deuteriated (the beginning—the 'origin'—of the very weak bands is shifted 86 ± 3 cm^{-1} to the blue from its normal isotopic species counterparts). The long wavelength fluorescence (LWS) commencing around 560 nm is much stronger, devoid of any sharp structure and is qualitatively the same at room temperature as at 10 K and intrinsically broader vibronically than SWF. Also in hexane solvent a very substantial effect of isotopic substitution on the LWF/SWF intensity ratio (vibronic intensity distribution) was found, while the changes of the fundamentals are small and within 10 cm^{-1} of the 339, 377 and 400 cm^{-1} values. The intensity ratio of SWF to LWF always drops drastically when the hydroxy protons are isotopically replaced. The frequencies of a number of fundamentals identified in the fluorescence and excitation spectra of **151** are not particularly sensitive to deuterium substitution of the hydroxy protons because of their mostly skeletal character. However, the decoupling of modes is not complete since some significant intensity effects are caused by deuteriation. The observations listed above have been interpreted as indicating that in the photoexcited state a single proton transfer is taking place with very small potential energy barrier creating a 1,10-quinone stable form in the S_1 state. A similar excited-state proton transfer (ESPT) was found for other α-hydroxyanthraquinones in contrast to quinizarin, 1,2,4-trihydroxyanthraquinone, 1,2,5,8- and 1,4,5,8-tetrahydroxyanthraquinones where the 1,4-substitution pattern, which stabilizes the system against excited-state proton transfer, is operating.

d. Isotope effect study of the optical absorption–emission by p*-benzoquinone*

Deuterium-labelled *p*-benzoquinones BQ-d[56], BQ-2,6-d_2, BQ-d_4 and d_3-Metoluquinone were used to investigate spectroscopically the lowest $n\pi^*$ triplet state of BQ-h_4 at 1.8 K. Vibrational analysis of the 537, 537 nm absorptions of all the isotopically substituted *p*-benzoquinones and vibrational analysis of the phosphorescence spectrum of BQ-h_4 in a BQ-d_4 crystal permitted the location at $18\,609 \pm 1\ cm^{-1}$ of the unobserved origin of the B_{1g} ($n\pi^*$) triplet state of BQ-h_4 monomer as a guest in the BQ-d_4 crystal. The electronic origin of the emitting state is directly observed in the asymmetrically substituted isotopic quinones. The origin of the phosphorescence spectrum of BQ-2,6-d_2 as a guest (1 mol %) in BQ-d_4 at 1.8 K was found to be at $18\,627\ cm^{-1}$. It has been shown that isotope effects observed in the singlet–triplet absorption in isotopic mixed crystals of BQ-h_4 in BQ-d_4 at 1.8 K are due to hydrogen (deuterium) bonding effects that shift the mainly centred on oxygen electronic excitation of BQ-h_4. It was also concluded that the observed isotope effect on the vibronic structure in the phosphorescence spectra of the *p*-benzoquinones is at least partly due to an isotope-dependent excited state geometry[56]. Absorption studies of the BQ-h_4 in BQ-d_4 isotopic mixed crystals revealed the existence of the so-called 'cluster state' absorption caused by formation of 'translationally inequivalent dimer' (**152**), which does not have inversion symmetry. Molecule No. 1 in this 'dimer' absorbs $4.0\ cm^{-1}$ to lower energy than molecule no. 2. In the trimer, formed by the BQ molecules numbered 1, 2 and 3, the inversion symmetry is preserved.



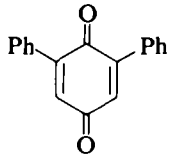
(152)

No. 1 and no. 2 (encircled with dashed lines) BQ-h_4 molecules form the translationally inequivalent dimer in the BQ-d_4 host crystal. Dotted lines indicate the hydrogen bonds responsible for the cluster formation.

The splitting observed in the absorption spectra of pure BQ-d and BQ-2,6-d_2 crystals at 1.8 K was ascribed to the existence of 'chemical disordering', implying that the excitation energy of a particular molecule depends upon the positions of isotopic hydrogens of the neighbouring molecules. (The observed deuterium isotope effects are partly due to change in short range static forces upon deuteriation.) The EPR spectrum of BQ-h_4 in BQ-d_4 host crystal was also taken and the large isotope effect on the ZFS parameters of the lowest triplet state of BQ-h_4 found was interpreted as an intramolecular phenomenon caused by isotope-dependent spin-orbit coupling effects.

e. Deuterium isotope effects on the quenching of the triplet state with substituted phenols

In the course of the detailed kinetic studies of the mechanism of the quenching of the triplet state of 2,6-diphenyl-*p*-benzoquinone (**153**) and anthanthrone (**154**)[57a] by sub-



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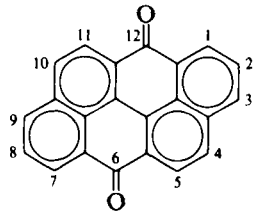


(154)

stituted phenols the effect of deuteriation of the OH group of phenols (obtained by exchange with D_2O or MeOD), on the rate constants of the quenching of the triplet state of **154** with phenols in benzene was also examined[57b]. The deuterium isotope effect, $k_T(H)/k_T(D)$, expressed as a ratio of rate constants of quenching of the ketone triplet state with undeuterated and with deuterated phenolic group depends to a large extent on the nature and the position of the substituent in the aromatic ring. For example, for quenching of anthanthrone triplet state with 2,6-di-*t*-butyl-4-methylphenol $k_T(H)/k_T(D) = 1.5$. For quenching of **154** with *p*-$PhC_6H_4OH(D)$ and with 2,4-$(NO_2)_2C_6H_3OH(D)$ no deuterium isotope effect is observed. In the quenching reaction with 3-nitro- and 2,6-di-*t*-butyl-4-nitrophenol $k_T(H)/k_T(D)$ equals 2.0 ± 0.1 but $k_T(H)/k_T(D) = 9.5$ in the quenching reaction of anthanthrone triplet state with 2,3-$Cl_2C_6H_3OH(D)$ in benzene. These isotope effects were interpreted as indicating that in quenching reactions in which $k_T(H)/k_T(D) = 1.0$, formation of a hydrogen bonded complex is the rate-limiting step while in the pair of isotopic reactions characterized by $k_T(H)/k_T(D) = 9.5$ the homolytic one-step hydrogen transfer in the hydrogen bonded complex is rate limiting. Introduction of a nitro group into the phenolic ring diminishes the deuterium isotope effect partly due to some steric hindrances in the formation of the hydrogen bonded complex. In the case of quenching of the triplet state of **154** with very acidic nitro-substituted phenols, the deuterium isotope effect is very small or it nearly disappears since it is determined by the hydrogen/proton equilibrium isotope effect in the reversible transfer expressed by equation 47:

$$s\left(\rangle C{=}O \ldots PhOH\right) \rightleftharpoons s\left(\rangle C{-}OH^{+} \ldots PhO^{-}\right) \begin{cases} \rangle \dot{C}{-}OH + PhO^{\cdot} \\ \rangle C{=}O + PhOH \end{cases} \quad (47)$$

The authors of this work[57b] also suggested the general conclusion that the deuterium isotope effect on the quenching rate constant of triplet states of quinones with phenols increases on increasing the acidity of the substituted phenols and then diminishes at further increase of the acidity of hydrogen donor, $XC_6H_4OH(D)$. The dependence of the polarization ratio '*P*' on the rate constant k_q of the triplet chemical reaction with hydrogen donor SH, appears in equation 48, where T_1 (triplet) is the spin-lattice relaxation time of the triplet and P_0 is the polarization ratio at infinite concentration of the hydrogen donor $[SH]_\infty$.

$$P = P_0\{k_q[SH]T_{1(\text{triplet})}/(1 + k_q[SH]\,T_{1(\text{triplet})})\} \quad (48)$$

A preliminary experiment concerning the photolysis of 1,4-naphthoquinone in isopropanol and ($^2H_8$) isopropanol, supports the dominant role of the phototriplet mechanism of the chemically induced dynamic electron polarization[58a]. The polarization ratios measured at $-20°C$ for the same hyperfine line of the seminaphthoquinone radical were: 0.39 in MeCH(OH)Me and 0.15 in $CD_3CD(OD)CD_3$. In a separate series of experiments using 2,6-di-*t*-butylphenol-OH and 2,6-di-*t*-butylphenol-OD as donors the

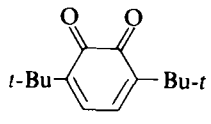
polarization ratios of the phenoxy radical were measured in the presence of 2-methylbenzoquinone. Since the same hyperfine line of the identical phenoxy radical was monitored, the same methylbenzoquinone triplet was involved, the concentrations were also kept the same, the variation of the polarization ratio could be attributed to the kinetic isotope effect. The estimated experimental k_H/k_D value for this system is 1.6 ± 0.1[58a].

2. *Photochemical and free radical studies of labelled quinones*

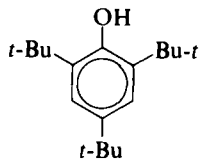
Magnetic isotope effects in the radical pairs and diradical pathways of photolysis and thermolysis of organic compounds have been reviewed recently by Turro and Kraeutler[58b].

a. Deuterium isotope effect on a radical pairs disappearance

In the photochemical reduction of the frozen solutions of 3,6-di-*t*-butyl-1,2-benzoquinone (**155**) and 2,4,6-tri-*t*-butylphenol (**156**) in vaseline and in methylcyclohexane two types of radical pairs are formed. They have different distances between unpaired electrons[59], which are 5.15 ± 0.02 Å and 6.25 ± 0.02 Å, respectively. The rates of disappearance of the radical pairs formed by photolysis of frozen glassy solutions of **155** with deuteriated and non-deuteriated **156** have been measured and activation energies, E,



(**155**)



(**156**)

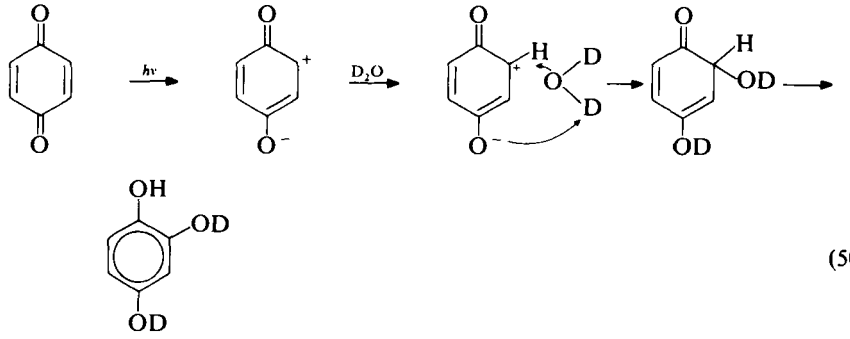
for the radical pair loss were estimated for the deuteriated and non-deuteriated compounds. The constants E_1, E_2 (in kcal mol^{-1}) and k_0 (in s^{-1}) in equation 49 relate the relative concentrations

$$n_T(t)/n_0 = \frac{E_2}{E_2 - E_1} - \frac{RT}{E_2 - E_1} \ln(k_0) - \frac{RT}{E_2 - E_1} \ln(t) \qquad (49)$$

of the radical pairs, $n_T(t)/n_0$, with the logarithm of time, ln (t), and the temperature 'T': $E_1 = 6.7 \pm 1$; $E_2 = 10 \pm 1$; $\lg(k_0) = 8 \pm 2$ were for non-deuteriated phenol, and $E_1 = 11 \pm 1$; $E_2 = 17 \pm 1$; $\lg(k_0) = 13 \pm 2$ for the deuteriated phenol. In the case of non-deuteriated phenol **156**, $\Delta E/\Delta R = 16.5 \pm 6$ kcal mol^{-1} Å^{-1}, where ΔR is the increase of the distance between the hydrogen atom traps (i.e. the unpaired electrons).

b. Deuterium isotope effect on the photochemical reactions of quinones with water

In the photolysis of an aqueous solution of *p*-benzoquinone, besides the isolated stable product hydroquinone, the transient formation of benzene-1,2,4-triol and 2-hydroxy-1,4-benzoquinone was noticed[60,61]. The photolysis rate of *p*-benzoquinone in D_2O was slightly smaller than in H_2O[60] giving a solvent isotope effect k_{H_2O}/k_{D_2O} of 1.15. This value indicates that direct abstraction of hydrogen from water is not the rate-determining step of the photolysis in water and suggests that an electrophilic attack of the excited *p*-benzoquinone on water is the slow process. Addition of *p*-nitroso-*N*,*N*-dimethylaniline (NDA), an effective hydroxyl radical scavenger, to the aqueous solution of *p*-benzoquinone did not change the absorption peak of the quinone. No direct photolysis of NDA occurred under the conditions of the irradiation. Consequently the radical



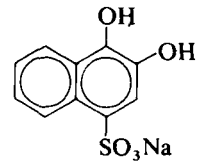
(50)

mechanism for the primary process of the photochemical reaction of *p*-benzoquinone in water has been rejected and equation 50, involving a polar intermediate, has been proposed instead[60]. However, this suggestion should be corroborated by comparative kinetic studies of the photolysis of *p*-benzoquinone-d_4 in D_2O.

c. Photoreduction of sodium 1,2-naphthoquinone-4-sulphonate in $H_2O(D_2O)$ solutions

A one-electron transfer from hydroxide ion to photoexcited sodium 1,2-naphthoquinone-4-sulphonate, NQ (**157**), was investigated by irradiating **157** in aerobic H_2O and D_2O[62]. Sodium 1,2-dihydroxynaphthalene-4-sulphonate, NQH_2 (**158**), having a

(**157**)



(**158**)

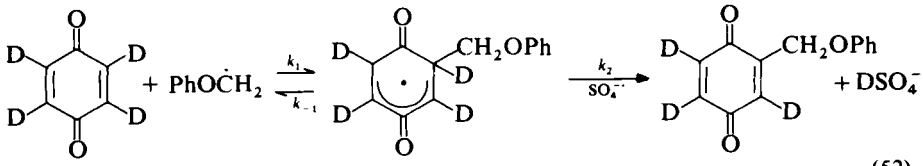
blue fluorescence emission maximum at 470 nm, was produced with 50% yield. The quantum yield at 365 nm of 0.118 ± 0.007 in the aerobic conditions was constant in the 5.0–6.8 pH region. Under nitrogen atmosphere the efficiency of the photoreaction of **157** was ca. 2.2-fold higher than in air. These facts indicate that the photoreaction of **157** in water proceeds via the triplet state. The quantum yield for the disappearance of **157** was reduced by a factor of ca. 2.5 on addition of moderate amounts of hydroquinone as a hydroxyl radical scavenger. The solvent isotope effect, k_{H_2O}/k_{D_2O}, on the initial rate of **158** formation is 1.8, indicating that the reaction involves protonation of the radical anion. On the basis of the above data the multi-step photoreduction scheme of **157** in water (equation 51) has been proposed, where $NQH^{\cdot}$ is the semiquinone radical of NQ.

$$
\begin{aligned}
NQ + h\nu &\rightarrow NQ^{*1} \\
NQ^{*1} &\rightarrow NQ^{*3} \\
NQ^{*3} + OH^- &\rightarrow NQ^{-\cdot} + {}^{\cdot}OH \\
NQ^{-\cdot} + H^+ &\rightarrow NQH^{\cdot} \\
2NQH^{\cdot} &\rightarrow NQH_2 + NQ \\
NQ + {}^{\cdot}OH &\rightarrow NQ(OH^{\cdot})
\end{aligned}
\qquad (51)
$$

The pH independence and the deuterium isotope effect indicate that the electron transfer to photoexcited NQ is fast while the protonation of $NQ^{-\cdot}$ is a relatively slow process and is partly rate determining.

d. Deuterium isotope effect on the homolytic alkylation of benzoquinone

A kinetic isotope effect, $k_H/k_D = 1.9 \pm 0.1$, was found for the competitive phenoxymethylation of 1 : 1 benzoquinone-h_4 and benzoquinone-d_4 in water at 65 °C. The result was ascribed to the reversibility of the first step in reaction scheme 52 where the k_1, k_{-1} and



(52)

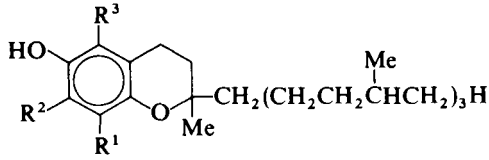
k_2 are of comparable magnitude[63]. The phenoxymethyl radical was generated[64] by a radical route decarboxylation of phenoxyacetic acid with a silver nitrate/ammonium peroxydisulphate couple (equation 53).

$$RCOOH \xrightarrow{Ag^+/S_2O_8^{2-}} R^{\cdot} + CO_2 \qquad (53)$$

3. Deuterium isotope effect on the antioxidant activity of vitamin E and on a two-electron reduction with daunomycinone hydroquinone

a. Chain-breaking activity of vitamin E

In the course of studies of the antioxidant activity of vitamin E component (α-, β-, γ- and δ-tocopherols (**159**)) and related phenols *in vitro*[65–70] the effect of deuteriation of the



α-T: $R^1 = R^2 = R^3 = Me$
β-T: $R^1 = R^3 = Me$, $R^2 = H$
γ-T: $R^1 = R^2 = Me$, $R^3 = H$
δ-T: $R^1 = Me$, $R^2 = R^3 = H$

(**159**)

phenolic hydrogen of α- and γ-tocopherols has been investigated and compared with related deuterated phenolic chain-breaking antioxidants[66]. The estimated k_H/k_D ratios for reaction 54 of the peroxyl radical with the phenolic group are collected in Table 2.

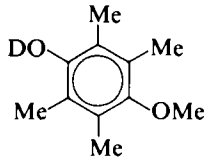
$$ROO^{\cdot} + ArOH(D) \xrightarrow[k_H/k_D]{} ROOH(D) + ArO^{\cdot} \qquad (54)$$

The deuteriation reduces the antioxidant activity of the tocopherols and related phenols such as **160** and **161** since deuteriated tocopherols react more slowly with the peroxyl radicals. The substantial kinetic deuterium isotope effects indicate that hydrogen atom abstraction in reaction **54** is the rate-controlling step. The above data imply also that the main function of vitamin E (α-tocopherol) *in vivo* is an antioxidant action. The role of the

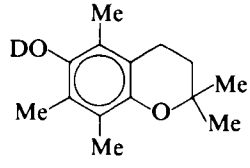
TABLE 2. Deuterium kinetic isotope effect for inhibition of autooxidation of styrene with oxygen by selected phenolic antioxidants at 30 °C[66]

Antioxidant	k_H/k_D
α-Tocopherol	4.0 ± 0.5[a]
γ-Tocopherol	9.1
2,2,5,7,8-Pentamethyl-6-hydroxychroman(**161**)	5.1 ± 0.5[a]
2,3,5,6-Tetramethyl-4-methoxyphenol (**160**)	10.6 ± 3.7[a]
2,6-Di-*t*-butyl-4-methoxyphenol	9.4
2,6-Di-*t*-butyl-4-methylphenol	6.8
1-Naphthol	4.3

[a] Average of two or more separate measurements.



(**160**)

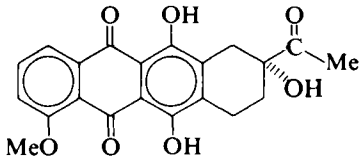


(**161**)

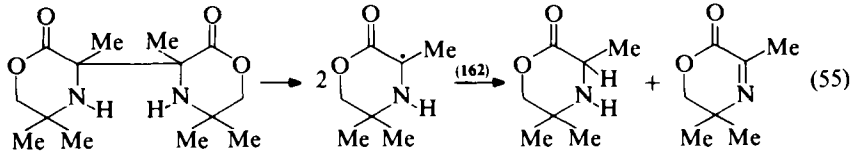
phytyl side chain attached to the hydroxychroman moiety is to increase its solubility in biomembranes and to allow its penetration into monolayers of phospholipid molecules. The chroman fused ring system maintains the *p*-type lone pair of the etheral oxygen nearly perpendicular to the aromatic plane, therefore stabilizing the phenoxyl radical ArO· (equation 54).

b. Reduction with 7-deoxydaunomycinone hydroquinone

7-Deoxydaunomycinone (**162**), a redox catalyst bound to DNA, which probably leads to cell death, is the product of a reductive glycoside cleavage of the antileukaemia drug daunomycin. This has been demonstrated by using *dl*-bi-(3,5,5-trimethyl-2-oxomorpholin-3-yl) (**163**) as the agent for reducing this drug[71]. The anaerobic solution of **163** disproportionates in the presence of **162** to **164** and **165**. The kinetics of this reaction

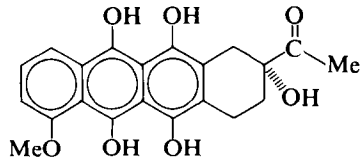


(**162**)



(55)

(**163**) (**166**) (**165**) (**164**)

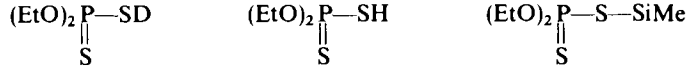


(164) + (167) $\xrightarrow[k_D \text{ in } CD_3OD]{k_H \text{ in MeOH}}$ (165) + (162) (56)

were followed spectrophotometrically in MeOH and in CD_3OD. In the absence of **162** the disproportionation either does not take place or is very slow in both solvents. For example, in CD_3OD no disproportionation of **163** after 135 h at 35 °C was observed. By monitoring the disproportionation process in the presence of **162** the reaction mechanism was established and the second order rate constants for the reduction of **164** by **167** were measured (equation 56). In MeOH at 25 °C $k_H = 2.06\ M^{-1}s^{-1}$, and in CD_3OD $k_D = 0.69\ M^{-1}s^{-1}$. The magnitude of the isotope effect, $k_H/k_D = 3.0$, indicates that the bond to hydrogen is broken in the transition state. The isotope effect of a deuteriated solvent[72, 73] on the bond homolysis of **163** and on the disproportionation of **166** to **164** and **165** in the absence of catalyst is small, being 1.10 ± 0.09 at 80 °C[72].

4. Addition of dithiophosphates to p-quinones

The mechanism of addition of the effective pesticides phosphorus dithioacids and silyl dithiophosphates to *p*-benzoquinone has been investigated[74] by using the deuteriated substrates. The deuteriated dithioacid (**168, D**) reacted with *p*-benzoquinone and with *p*-benzoquinone-d_4 about two times faster than the dithioacid (**168, H**). The k_H/k_D values

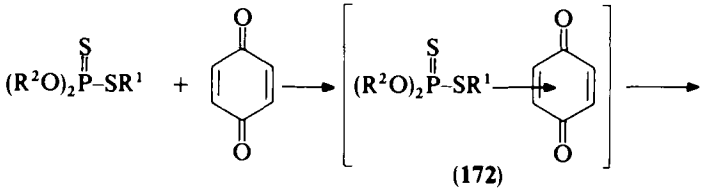


(168, D) **(168, H)** **(171)**

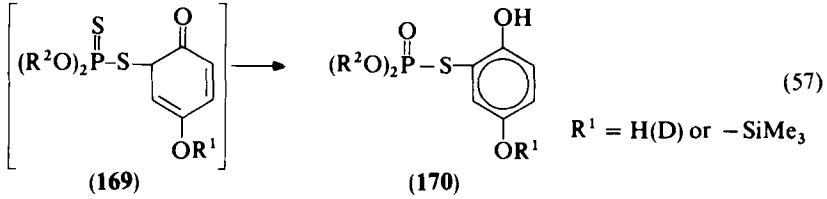
were in the range of 0.42–0.53 in *n*-heptane, benzene, 1,4-dioxane and acetonitrile. This indicates that the structure of the transition state in the process of proton migration from dithioacid to *p*-benzoquinone resembles the structure of the intermediate (**169**). The isotopic hydrogen atom is more strongly covalently bound in the transition state than in the reactant (**168**). The effect of deuteriation of the quinone on the reaction rate depends on the nature of the solvent. In heptane and benzene the deuteriated and non-deuteriated *p*-benzoquinone reacted at the same rate, implying that the ring-proton migration takes place after the rate-limiting step of the reaction. In 1,4-dioxane and in acetonitrile at 20 °C, $k_H/k_D = 2.03$ and 3.58, respectively, implying that in these non-basic solvents the conversion of the intermediate **169** to product **170** is the controlling step of the reaction. A similar behaviour was found in the reaction between *O,O*-diethyl-*S*-trimethylsilyl dithiophosphate (**171**) and *p*-benzoquinone-d_4. In heptane and benzene $k_H/k_D = 1$, and in 1,4-dioxane and in acetonitrile $k_H/k_D = 1.5$ and 2.13, respectively. These results suggest that the addition of dithiophosphates to *p*-benzoquinone takes place according to equation 57. The conversion of the n–π complex (**172**) into intermediate **169** is the rate-controlling step in weakly basic solvents. In nucleophilic solvents the dienone–phenol rearrangement in the intermediate (**169**) becomes rate limiting[74].

5. Selective reduction of anthraquinone with deuterium

Anthraquinone can be converted to 9,9,10,10-tetradeuterio-9-10-dihydroanthracene (**173**) in the presence of excess of D_2, carbon monoxide and catalytic amounts of $Co_2(CO)_8$



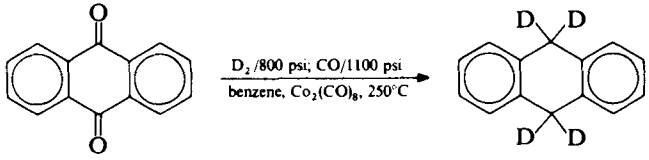
(172)



(169) (170)

(57)

$R^1 = H(D)$ or $-SiMe_3$



(173)

(58)

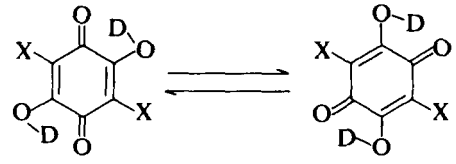
(equation 58). After 6 hours 66% of isotopic equilibrium was attained. In dioxane either D_2 or D_2O can be used as the isotopic source[75]. The selective nature of the reduction-exchange reaction can be used as a synthetic route to **173**. The specific selectivity for positions 9 and 10 in anthracene was confirmed by ^{1}H-NMR and no exchange of ring protons 1–8 was found. The product obtained from the anthraquinone reduction was used as the hydrogen source in the oxo reaction of 1-octene with CO and $Co_2(CO)_8$ and gave C_9 aldehydes randomly substituted with deuterium[75].

C. Isotope Effects in Hydrogen Transfer Reactions to Quinones

Deuterium and tritium isotope effects in hydrogen and proton transfer processes are the subject of continuous theoretical and experimental investigations. Special monographs, chapters in monographs and reviews on this topic have been published[76–90]. Several groups investigate the proton transfer processes to different organic bases[90–100]. We therefore present below only the recent isotopic results concerning hydrogen transfers (or migration) to quinones, resulting in oxidation or dehydrogenation of organic and inorganic molecules.

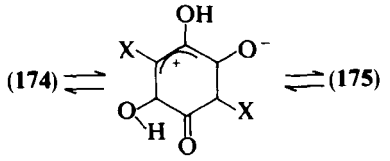
1. Deuterium migration in the 2,5-dihydroxy-1,4-benzoquinone

In the course of studies on diotropic proton migration between the *ortho* oxygen atoms in a series of 2,5-dihydroxy-1,4-benzoquinones (**174** → **175**) a kinetic deuterium isotope effect $(k_H/k_D)_{-50°C} = 1.96$, was found[101]. It was interpreted as indicating that the probability of simultaneous synchronous proton migration in the exchange reaction of equation 59 is rather low. It is also suggested that the estimated value of the kinetic isotope effect coupled with the high value of the activation enthalpy for deuterium transfer in equation 59 ($\Delta H^{\neq} = 8.3 \pm 0.2$ kcal mol^{-1}, $\Delta S^{\neq} = -8.2 \pm 0.8$ e.u., $\Delta G^{\neq}_{298}$



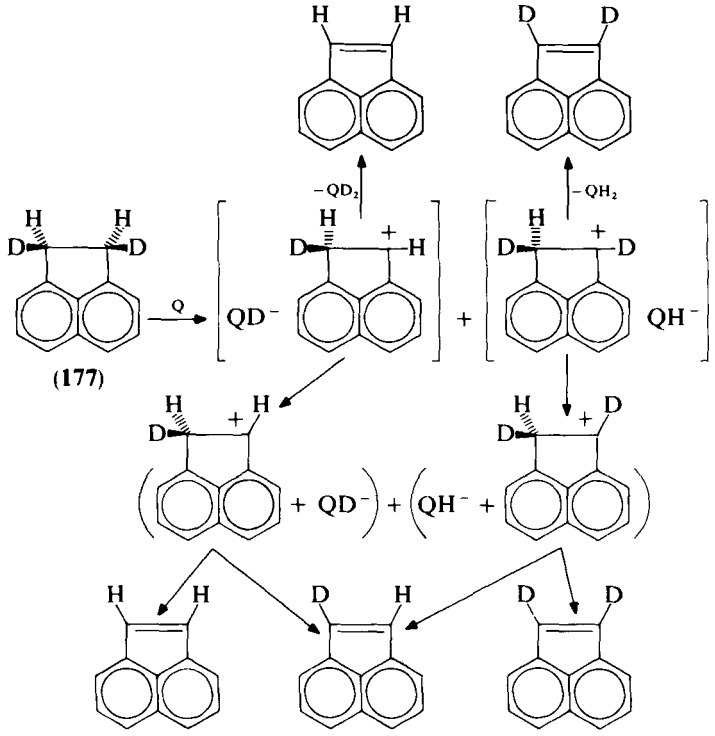
(174) X = H, Cl, OH (175) (59)

= 10.7 kcal mol^{-1}), results from the formation of energetically unfavourable zwitterionic intermediates generated in a consecutive intramolecular 1,4-hydrogen transfer processes, and formation of the structure **176** in the case of intermolecular mechanism[101]. The low k_H/k_D value may also be caused by the product-like transition state. The relative contribution of intermolecular and intramolecular mechanisms to the observed deuterium transfer process depends on the temperature of the reaction.



(174) ⇌ ⇌ (175) (59a)

(176)



(177) (60)

2. Dehydrogenation of acenaphthene by quinones

Deuterium isotope effects, k_H/k_D, of 3.49 and 4.14 have been found[102] in the dehydrogenation of a mixture of 1,1,2,2-tetradeuterioacenaphthene and acenaphthene with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) and tetrachloro-*o*-benzoquinone (TOQ). These values are considered to be inconsistent with simultaneous cleavage of both C–H bonds in the transition state, but to indicate a considerable cleavage of a single C–H bond in the transition state and to be consistent with a hydride abstraction mechanism. The stepwise carbenium ion nature of this reaction was verified by demonstrating the lack of both intermolecular deuterium scrambling in the intermediate carbenium ions and of 1,2-hydride shifts. Dehydrogenation of *cis*-1,2-dideuterioacenaphthene (177) proceeded with 77.7 % and 62.9 % *cis* elimination using DDQ and TOQ as oxidant respectively. These and other kinetic data corroborate an hypothesis involving an initial ion pair formation, which then collapses to products by *cis* elimination or dissociates into ions (equation 60).

3. Hydrogen isotope effects in the aromatization of 1,4-dihydrobenzene and 1,4-dihydronaphthalene with DDQ and chloranil

There is general agreement that the oxidation of hydroaromatic compounds with quinones proceeds either by direct hydride transfer (equation 61)

$$DH + A \overset{\text{fast}}{\rightleftharpoons} [DH \ldots A] \xrightarrow{\text{slow}} D^+ + AH^- \qquad (61)$$

or through a sequential electron and hydrogen transfer process (equation 62)

$$DH + A \overset{\text{fast}}{\rightleftharpoons} [DH \ldots A] \overset{\text{fast}}{\rightleftharpoons} [DH^{+\cdot} \ldots A^{-\cdot}] \xrightarrow{\text{slow}} D^+ + AH^- \qquad (62)$$

and that the hydrogen transfer within the charge-transfer complexes [DH ... A] is the slow step in the aromatization process. However, Hashish and Hoodless[103] did not find an isotope effect in the aromatization of partially tritiated 1,4-dihydronaphthalene, and therefore proposed a mechanism in which a rate-determining step of oxidation is associated with a slow electron transfer in the charge-transfer complex (equation 63).

$$DH + A \overset{\text{fast}}{\rightleftharpoons} [DH \ldots A] \overset{\text{slow}}{\rightleftharpoons} [DH^{+\cdot} \ldots A^{-\cdot}] \xrightarrow{\text{fast}} D^+ + AH^- \qquad (63)$$

This scheme was incompatible with the rather substantial primary isotope effect measured, for instance[104], for oxidation of 1,4-cyclohexadiene with DDQ. Hence the deuterium isotope effect for the aromatization of 1,4-dihydrobenzene-d_6 and 1,4-dihydrobenzene-d_8 with DDQ in benzene and for the aromatization of 1,4-dihydronaphthalene-d_{10} with DDQ in dichloroethane or with chloranil in 1,2-dichloroethane were reinvestigated[105]. The results collected in Table 3 clearly indicate that the oxidation of both hydroaromatic compounds involves hydrogen transfer in the rate-determining step, but the kinetic data cannot differentiate between scheme 61 and scheme 62. The deuterium isotope effects of similar magnitude, $k_H/k_D = 4.0$ and 6.9, observed in the oxidation of tropilidene-d_8 and 1,2,3-triphenyl-3-deuteriocyclopropene with DDQ in glacial acetic acid serve as models of reactions showing normal or high isotope effects where the carbon–hydrogen bond is broken in the rate-limiting step[106]. Kinetic tritium isotope effects were not observed in the aromatization of partially tritiated 1,4-dihydronaphthalene due to the low sensitivity of the method which is based on the determinations of small rate differences between partially tritiated or deuteriated molecules having several equivalent reaction sites and the unlabelled species. Assuming that the substitution of hydrogen by tritium eliminates completely one C–T reaction site in the labelled 1,4-dihydronaphthalene, the maximum

TABLE 3. Deuterium isotope effects in the aromatization of 1,4-dihydrobenzene and 1,4-dihydronaphthalene with DDQ and chloranil[104, 105]

Compound	Oxidant	Conditions	$10^2 k(M^{-1}s^{-1})$	k_H/k_D
1,4-Dihydrobenzene-h_8	DDQ	Benzene, 25°C	2.85	—
1,4-Dihydrobenzene-d_6	DDQ	Benzene, 25°C	1.67	9.8
1,4-Dihydrobenzene-d_8	DDQ	Benzene, 25°C	0.31	9.2
1,4-Dihydronaphthalene-h_{10}	DDQ	1,2-Dichloroethane, 25°C	124.5	—
1,4-Dihydronaphthalene-d_{10}	DDQ	1,2-Dichloroethane, 25°C	12.57	9.9
1,4-Dihydronaphthalene-h_{10}	Chloranil	1,2-Dichloroethane, 120°C	1.235	—
1,4-Dihydronaphthalene-d_{10}	Chloranil	1,2-Dichloroethane, 120°C	0.255	4.84
1,4-Dihydronaphthalene-d_{10}	Chloranil	1,2-Dichloroethane, 25°C		8.0

allowed ratio of aromatization rates of singly tritium-labelled 1,4-dihydronaphthalene and 1,4-dihydronaphthalene-h_{10} will be equal to ca. 1.4 (or to 1.33 neglecting the secondary tritium isotope effect). Hence at low conversion of the labelled substrate, the increase of its specific radioactivity will be very small and might escape detection.

4. Deuterium isotope effects in the dehydrogenation of alcohols by quinones

a. Oxidation of benzyl-α-d alcohol by DDQ

Kwart and George[107] have determined the isotope partitioning ratio, ipr = PhCHO/PhCDO, in the oxidation of **178** by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) (equation 64). The relative amounts of PhCHO and PhCDO in the post-reaction

$$\begin{array}{l} \text{D} \\ \text{PhCHOH} + \text{DDQ} \\ \textbf{(178)} \end{array} \begin{array}{l} \xrightarrow{k_{H'}} \text{PhCDO} + \text{DDQ}(H_2) \\ \xrightarrow{k_D} \text{PhCHO} + \text{DDQ (HD)} \end{array} \qquad (64)$$

mixture were estimated by means of the mass spectrometric technique[108] and were found to be 3.94 and temperature independent in the 343–463 K interval. The temperature dependence of the k_H/k_D ratios is usually utilized for assessing the structure of the activated complexes in hydrogen transfer processes. The 'ipr' corresponding to the $k_{H'}/k_D$ ratio can be written as the quotient of the temperature-dependent k_H/k_D and $k_H/k_{H'}$ ratios, or as a quotient of the $k_H/k_{D'}$ and $k_D/k_{D'}$ ratios derived from equations 65 and 66.

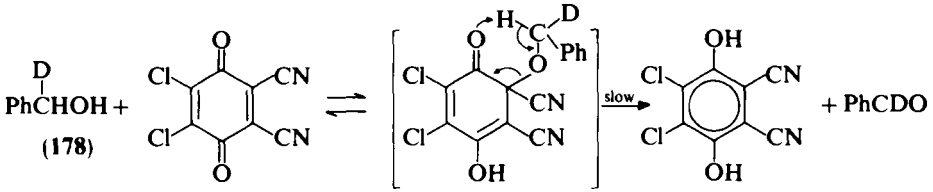
$$\text{PhCH}_2\text{OH} + \text{DDQ} \xrightarrow{2k_H} \text{PhCHO} + \text{DDQ H}_2 \qquad (65)$$

$$\text{PhCD}_2\text{OH} + \text{DDQ} \xrightarrow{2k_{D'}} \text{PhCDO} + \text{DDQ HD} \qquad (66)$$

The primary deuterium isotope effects, k_H/k_D, calculated within the harmonic one bond or symmetric transition complex approximation by using a value of $\omega_{C-H} = 2895\ cm^{-1}$ are:

Temp. (K)	343.16	363.16	383.16	403.16	423.16	443.16	463.16
k_H/k_D	5.222	4.768	4.395	4.084	3.822	3.599	3.406

Theoretical calculations of the secondary kinetic isotope effect, $(k_H/k_{H'})$, require the use of at least the four-centre transition state model. Their temperature dependence might be unlike that of the primary k_H/k_D ratio. Consequently the experimentally determined ipr is



(179) (67)

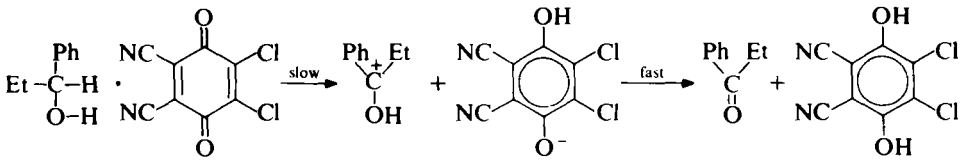
temperature independent. (The temperature dependences of the 'heavy atom' ^{13}C isotope effects in the carbon–carbon bond rupture are discussed in Ref. 109.) Kwart and George suggested that the oxidation of benzyl-α-d alcohol proceeds according to equation 67 via a bent transition state. The observed temperature independence of the $k_{H'}/k_D$ ratio was ascribed to an angular non-linear transfer of the hydrogen in the rate-determining step. A linear symmetric transition state should give a temperature-dependent deuterium isotope effect. Unfortunately the $k_H/k_{D'}$ and $2k_H/(k_{H'} + k_D)$ ratios have not been determined over 120°C temperature range studied. Hence a detailed discussion concerning the structure of the transition state in the benzyl alcohol oxidation with DDQ should be postponed until more experimental and theoretical data pertaining to this reaction are accumulated. The results obtained so far indicate only that the intramolecular hydrogen transfer taking place within adduct **179** is the rate-determining step of the process.

b. Dehydrogenation of deuteriated 1-phenyl-1-propanols

Deuterium isotope effects in the dehydrogenation of alcohols by quinones have also been investigated by Ohki *et al.*[110]. The initial oxidation rates of PhCH(OH)Et (**180**), PhCH(OD)Et, PhCD(OH)Et and PhCD(OD)Et by 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) at 60 °C give relative rates of 8.9, 9.1, 1.0 and 1, respectively. The large primary isotope effect of the α-hydrogen and the undetectable isotope effect of a deuterium atom of the OH group imply that the C_α–H bond cleavage is taking place in the rate-determining step while the rupture of the O–H bond is of secondary importance. Additional studies of solvent and substituent effects, as well as the effect of additives on the yield of the propiophenone have suggested that the hydrogen transfer proceeds via formation of a complex which precedes the rate-determining step, and that the complex and/or the transition state of the rate-determining step are solvated and considerably polarized. A free radical mechanism which is inconsistent with the large negative activation entropy was excluded. The most probable mechanism and the corresponding rate equations are given in equations 68–70,

$$\text{DDQ} + \text{A} \overset{K}{\rightleftharpoons} \text{complex} \overset{k}{\rightarrow} \text{products} \tag{68}$$

$$\text{Rate} = k_{obs}[\text{DDQ}][\text{A}] = k[\text{Complex}] = kK[\text{DDQ}][\text{A}] \tag{69}$$



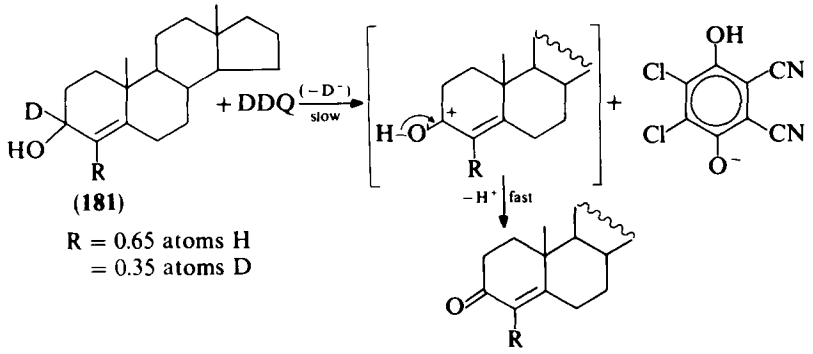
complex of equation 68. (70)

where [A] is the concentration of 1-phenyl-1-propanol, K is the equilibrium constant between the reactants and the charge-transfer complex, k is the rate constant of the rate-

limiting step and k_{obs} is the observed second order rate constant. The mechanistic scheme (equation 70) is also supported by the fairly large negative ρ value of -2.7 indicating the formation of a positively charged transition state. An electron-deficient carbon centre in the transition state has been found similarly in the oxidation of substituted benzyl alcohols and α,α-dideuteriobenzyl alcohol by chloramine-T in acid solution[111]. The suggested scheme does not rule out the possibility of solvent participation in a subsequent rapid proton transfer step.

c. Oxidation of allyl alcohols with DDQ

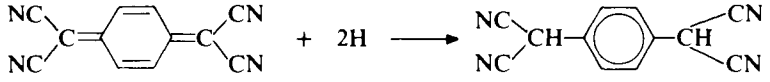
The deuterated secondary allyl alcohol, 3α-deuterio-3β-hydroxy-Δ^4 steroid, **181**, underwent oxidation with DDQ at 27°C in *t*-butyl alcohol at a five-fold slower rate than the 3α-hydrogen compound. Consequently the 3-C–H bond is cleaved in the rate-determining step, and the reaction proceeds via a slow hydride transfer followed by a rapid proton loss (equation 71)[112].



(71)

5. Deuterium isotope effect study of the dehydrogenation of alcohols with 7,7,8,8-tetracyanoquinodimethane (TCNQ)

TCNQ (**182**), which is structurally similar to quinones readily dehydrogenates benzyl-type alcohols and hydroaromatic compounds while being reduced to *p*-benzene-dimalononitrile (**183**) (equation 72). The reaction proceeds via the intermediacy of a



(72)

(182) (183)

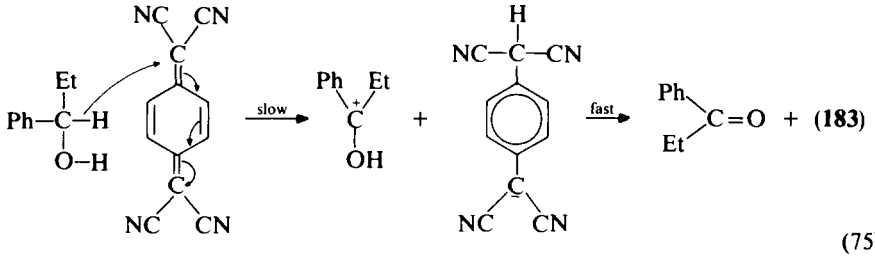
carbenium ion when 1,2-dihydrobenzenes are used as the hydrogen donors. Indeed when 1,2-dihydro-1,1-dimethylnaphthalene was used as the hydrogen donor, 1,2-dimethyl-naphthalene was obtained, i.e. the oxidation was accompanied by methyl group migration. The dehydrogenation of hydrogen donors 'HD' by TCNQ was suggested to occur via the intermediacy of a charge-transfer (CT) complex (equations 73 and 74).

$$\text{TCNQ} + \text{HD} \overset{K}{\rightleftharpoons} [\text{CT complex}] \overset{k}{\rightarrow} \text{products} \tag{73}$$

$$\text{rate} = k_{obs}\,[\text{TCNQ}]\cdot[\text{HD}] = k[\text{CT complex}] = kK[\text{TCNQ}]\cdot[\text{HD}] \tag{74}$$

The rate-determining step and the nature of the hydrogen transfer step in the

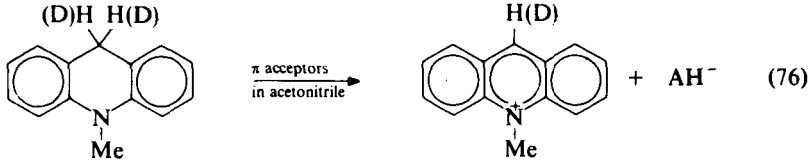
dehydrogenation by TCNQ were investigated by studying the deuterium isotope effects[113] in the dehydrogenation of isotopic 1-phenylpropanols to propiophenones. The relative reaction rates of PhCH(OH)Et, PhCH(OD)Et, PhCD(OH)Et and PhCD(OD)Et with TCNQ at 140 °C in dioxane were: 4.0, 4.0, 1.0 and 1, respectively. These data indicate that the C–H bond rupture is of primary importance in the rate-determining step whereas the cleavage of the O–H bond is of secondary importance in this hydrogen transfer thermal process. The experimental k_H/k_D value of 4.0 is close to the calculated value of 3.95 at 140 °C, neglecting tunnelling and taking $\omega_{C-H} = 2985\ cm^{-1}$ for the C–H frequency. The deuterium kinetic isotope effect combined with solvent and substituent effects on the reaction rate suggest a similar two-step ionic mechanism for the thermal dehydrogenation of alcohols by TCNQ or tetracyanoethylene (TCNE) and of 1,2-dihydronaphthalene by quinones. The dehydrogenation of 1-arylpropanols by TCNQ involves a rate-limiting hydride transfer with carbenium ion formation, followed by proton loss and ketone formation in subsequent rapid steps (equation 75)[113].



(75)

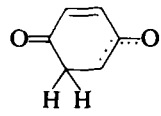
6. *Deuterium isotope effects in the oxidation of* N*-methylacridan by quinones*

Primary and secondary isotope effects in the oxidation of *N*-methylacridan (**184**) to *N*-methylacridinium ion (**185**) have been determined[114–116a] by studying spectrophotometrically the kinetics of the reaction of (**184**)-9,9-h_2, (**184**)-9,9-hd and (**184**)-9,9-d_2 with *p*-benzoquinone (BQ), TCNQ, *p*-chloranil (CA), TCNE and 2,3-dicyano-1,4-benzoquinone (DCBQ) in acetonitrile or in acetonitrile–water mixture at 25°C (equation 76). Tracer



(76)

studies have shown that in the course of the reaction hydrogen is transferred to an oxygen of the oxidants and no intermediate of type **186** is formed. The hydroquinone which was isolated from the post-reaction mixture did not contain excess of deuterium. The product



(**186**)

(**185**) formed in the oxidation of (**184**)-9,9-d_2 by BQ in 90% acetonitrile did not contain ^1H in the 9 position and no exchange of the 9-hydrogens with the solvent during the oxidation was found. However, indirect kinetic evidence and direct NMR monitoring of solutions containing isotopically labelled **184** and **185** showed scrambling of the deuterium between unreacted **184** and **185** during the oxidation which lowers the observed ipr ratio. When the BQ to **184** ratio increased from 1:1 to 1000:1 the measured ipr in 90% acetonitrile increased from 2.9 to the upper limit of 9.4. This deuterium exchange caused visible discrepancies between the ipr and p/s values (equation 78) only in the case of relatively slow oxidation with BQ in 75% and 90% acetonitrile. The oxidation rate constants for the isotopomeric *N*-methylacridans, the derived primary and secondary deuterium isotope effects, including isotope partitioning ratio 'ipr = $k_{H'}/k_D$', determined by mass spectral analysis of the isolated *N*-methylacridinium chloride, are presented in Table 4. The notations used in Table 4 are defined by equations (77 a–c) and (78).

$$\text{(184)-9,9-h}_2 \xrightarrow{2k_H} \text{(185)-h} \qquad k_{HH} = 2k_H \tag{77a}$$

$$\text{(184)-9,9-hd} \begin{cases} \xrightarrow{k_{H'}} \text{(185)-d} \\ \xrightarrow{k_D} \text{(185)-h} \end{cases} \qquad k_{HD} = (k_{H'} + k_D) \tag{77b}$$

$$\text{(184)-9,9-d}_2 \xrightarrow{2k_{D'}} \text{(185)-d} \qquad k_{DD} = 2k_{D'} \tag{77c}$$

$$p = k_H/k_D = k_{H'}/k_{D'} \qquad k_{HD}/k_{DD} = (p+s)/2$$

$$s = k_H/k_{H'} = k_D/k_{D'} \qquad \text{ipr} = k_{H'}/k_D = \frac{p}{s} = \frac{[\textbf{185-d}]}{[\textbf{185-h}]} \tag{78}$$

$$k_{HH}/k_{DD} = p \cdot s$$

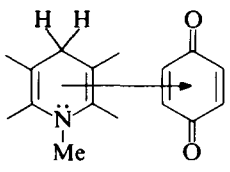
The kinetically determined p/s values are given in Table 4 for comparison. It is seen that with the slow reacting acceptor BQ it was practically impossible to suppress completely the scrambling in 90% and 100% acetonitrile even at a 1000:1 ratio of BQ to **184**. The data in the third column of Table 4 indicate that the experimental k_{HH}/k_{HD} ratios are not very sensitive to the oxidizing ability of the π acceptors. The lack of useful correlations between the k_{HH}/k_{HD} values and the redox potentials of the oxidant is probably due to the low accuracy in the determinations of the k_{HD} values. The k_{HH}/k_{DD} ratios are much more useful in that respect and are comparable with the calculated primary kinetic isotope effects given in the seventh column. They suggest a contribution of quantum mechanical tunnelling to the k_H/k_D isotope effect in the oxidation with benzoquinone but kinetic studies at other temperatures should be carried out before drawing further conclusions concerning the energetic profiles in these oxidations. The 'p' values for reaction with TCNQ and CA are quite close to the theoretical isotope effect of 6.7 at 25°C for a single carbon–hydrogen bond rupture, k_{C-H}/k_{C-D}, neglecting tunnelling. The last two values of 4.75 and 5.36 found for oxidations with TCNE and DCBQ in acetonitrile are lower than the classical value of 7 expected for hydrogen atom transfer with a symmetrical transition state structure. Data given in the sixth column show quite large scatter, caused probably by experimental uncertainties. Nevertheless the average $k_H/k_{H'}$ ratio of 1.097 ± 0.060 is very useful in interpreting these isotopic kinetic experiments in which only k_{HH}/k_{HD} and especially k_{HH}/k_{HT} ratios have been measured, since determination of k_{HH}/k_{TT} ratios require working with 100% pure R_2CT_2. A quite good agreement between ipr values based on product analysis and the p/s ratios derived from kinetic measurements is noticeable. All the deuterium isotope effect data presented in Table 4 call for a mechanism in which the carbon–hydrogen bond is broken in the rate-determining step. Spectroscopic and chemical

TABLE 4. Rates and deuterium kinetic isotope effects[a] in the oxidation of isotopic *N*-methylacridan molecules with various acceptors in acetonitrile (AN) at 25 °C[115]

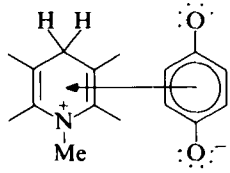
Acceptor and solvent	$k_{HH}(M^{-1}s^{-1})$	k_{HH}/k_{HD}	k_{HH}/k_{DD}	k_{HD}/k_{DD}	$k_H/k_{H'}$	k_H/k_D	$k_{H'}/k_D$	ipr
BQ in 60% AN[b]	1.42×10^{-2}	1.919	9.595	5.00	1.075	8.925	8.302	8.14 ± 1.4
BQ in 75% AN[b]	5.51×10^{-3}	1.900	11.479	6.042	1.039	11.044	10.626	9.1 ± 1.9
BQ in 90% AN[b]	1.86×10^{-3}	1.875	12.00	6.40	1.019	11.781	11.567	9.4 ± 2
BQ in AN	5.79×10^{-4}	1.956	14.088	7.202	1.055	13.349	12.648	—
TCNQ in AN	2.32×10^{-1}	1.966	7.227	3.676	1.169	6.183	5.290	—
TCNQ in AN[b]	2.33×10^{-1}	2.009	7.373	3.671	1.201	6.141	5.115	—
CA in AN	1.17×10	1.980	8.731	4.410	1.136	7.685	6.763	6.2 ± 0.7
TCNE in AN	1.01×10^{2}	1781	5.206	2.923	1.096	4.750	4.334	4.5 ± 1.4
DCBQ in AN	8.67×10^{3}	1.806	5.819	3.221	1.086	5.357	4.931	4.7 ± 0.1
		1.910 ± 0.078			1.097 ± 0.060			

[a] The notations are those given in equations 77–78.
[b] Containing 0.01 M AcOH.

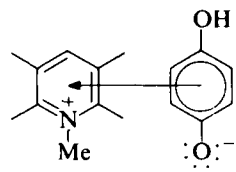
evidence indicates that the slow hydride transfer in the oxidation is preceded by a reversible formation of a charge-transfer (CT) complex between the hydride donor DA and the hydride acceptor A. Some fractionation of isotopic hydrogen in the CT complex formation in the case of (**184**) -9,9-hd is to be expected. The complexation constants K differ for the different isotopomeric methylacridans. It is proposed that the transition state of the oxidation has a structure intermediate between the donor–acceptor face-to-face orientation (**187**) and the products of electron (**188**) or hydride (**189**) transfer. The magnitude of deuterium primary isotope effect and the solvent effect favour a one-step hydride transfer mechanism although they do not exclude a sequential electron–hydrogen atom transfer mechanism.



(**187**)

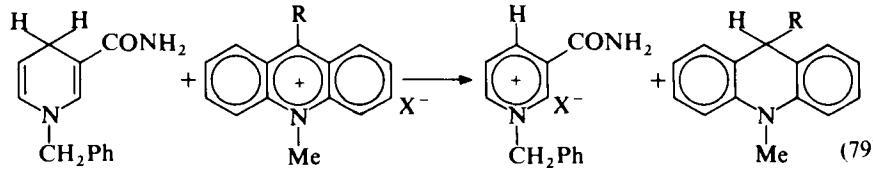


(**188**)



(**189**)

In connection with the problem of hydride transfer discussed above it is noteworthy that good agreement was recently found[116b] between the kinetic deuterium isotope effect k_H/k_D of 4.4–4.5 in the oxidation of 1-benzyl-1,4-dihydronicotinamide (BNAH, BNAH-4,4-d_2 and BNAH-4-d_1 systems) with 10-methyl- and 10-methyl-9-phenylacridinium ions (equation 79) and the mass spectrometrically determined isotope partitioning ratio in the $AcPh^+$/BNAH system of 4.5 in acetonitrile and 4.7 in 9:1 v/v acetonitrile–water.



(**190**) (BNAH) (AcR^+) (BNA^+) (AcRH) (79)

7. *Hydride transfer from 1-benzyl-1,4-dihydronicotinamide to p-benzoquinone derivatives*

In the course of studies of the mechanism of the irreversible hydride transfer from 1-benzyl-1,4-dihydronicotinamide (**190**) (an NADH model compound) to a series of *p*-benzoquinones 'Q', the primary kinetic isotope effects, k_H/k_D have been determined at 298 K in acetonitrile and correlated with redox potentials of quinones $E°(Q/Q^{-\cdot})$. The results are listed in Table 5. The rate constants k_{HH} of BNAH (**190**) and the rate constants k_{DD} of BNAH-4,4-d_2 were used for calculation of k_H/k_D ratios with $\pm 5\%$ error. It has been assumed that the secondary α-deuterium isotope effects are unity, since a secondary α-deuterium kinetic isotope effect value of 1.0 ± 0.1 has been deduced from the rate constants k_{HH} of BNAH, k_{HD} of BNAH-4-d_1 and k_{DD} of BNAH-4,4-d_2 in their reactions with *p*-chloranil, *p*-bromanil and 2,6-dichloro-*p*-benzoquinone. The majority of the k_H/k_D values (of entries 3–11 in Table 5) are located in the range 5.2–6.2. The maximum value of 6.2 for the hydride-transfer reaction with *p*-benzoquinone is again quite close to the theoretical

TABLE 5. Redox potentials, $E^{\circ}(Q/Q^{-\cdot})$ of Q, rate constants k and primary deuterium kinetic isotope effects, k_H/k_D, for the hydride transfer from BNAH to *p*-benzoquinone (*p*-BQ) derivatives in MeCN at 298 °K[117]

p-Benzoquinone	$E^{\circ}(Q/Q^{-\cdot})$	$k(M^{-1}s^{-1})$	k_H/k_D
2,3-Dichloro-5,6-dicyano-*p*-BQ	0.51	8.4×10^6	1.5
2,3-Dicyano-*p*-BQ	0.28	7.2×10^5	2.6
p-Chloranil	0.01	1.0×10^3	5.3
p-Bromanil	0	7.3×10^2	5.2
2,6-Dichloro-*p*-BQ	−0.18	7.5×10	5.6
2,5-Dichloro-*p*-BQ	−0.18	5.0×10	5.5
Chloro-*p*-BQ	−0.34	7.6	6.1
p-BQ	−0.50	1.3×10^{-2}	6.2
Methyl-*p*-BQ	−0.58	2.3×10^{-3}	5.9
2,6-Dimethyl-*p*-BQ	−0.67	8.4×10^{-5}	5.6
Trimethyl-*p*-BQ	−0.75	1.3×10^{-5}	5.6
Tetramethyl-*p*-BQ	−0.84	Very slow	—

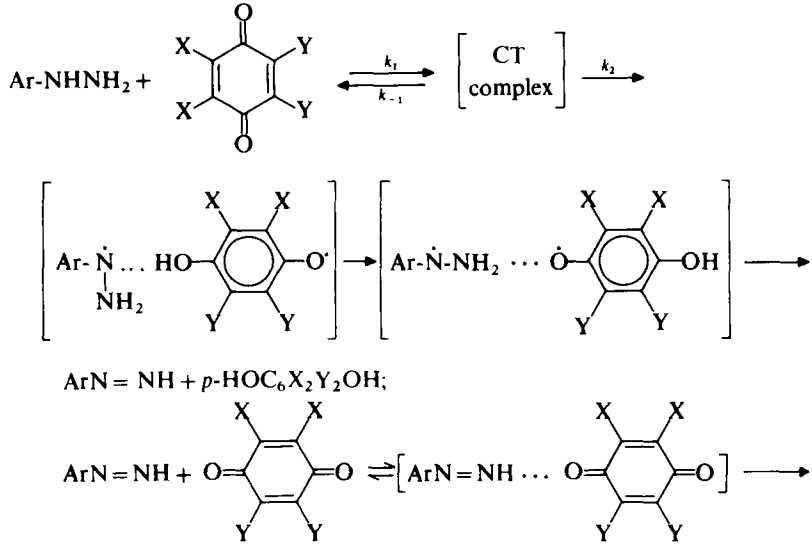
value of 6.7 calculated for C–H/C–D bond cleavage, neglecting tunnelling. A plot of the k_H/k_D ratios versus the redox potentials of Q, $E^{\circ}(Q/Q^{-\cdot})$ gives a Bell-shaped dependence with a Westheimer maximum. (There is a linear correlation between pK_a of semiquinone radicals and the redox potential $E^{\circ}(Q/Q^{-\cdot})$. It would be interesting to confirm the low k_H/k_D values of 1.5 and 2.6 obtained in the fast reactions with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone and 2,3-dicyano-*p*-benzoquinone by determining the ipr ratios in both cases using BNAH-4-d_1. Tritium isotope effects would also be useful as an additional test of the Bell-shape dependence obtained in this hydride transfer reaction for the first time. The authors[117] have shown that transient CT complexes are formed in the course of the hydride transfer reaction studied. Their absorption spectra, with maxima in the 670–735 nm range, were similar to the reflectance spectra of the 1:1 complexes of BNAH with *p*-chloranil, *p*-bromanil and 2,6-dichloro-*p*-benzoquinone isolated from benzene or toluene solutions under nitrogen atmosphere. It is proposed that the reaction proceeds according to the 'sequential electron–proton–electron transfer mechanism'. The radical ion pair $[BNAH^{+}\cdot\cdot\cdot Q^{-\cdot}]$ is formed inside the CT complex and thereby no free radical species are involved in the process (equation 80).

$$\begin{aligned}
&BNAH + Q \overset{K_{CT}}{\rightleftharpoons} [BNAH \cdots Q] \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [BNAH^{+\cdot} \cdots Q^{-\cdot}] \overset{k_H}{\rightarrow} \\
&[BNA^{\cdot} \cdots QH^{\cdot}] \overset{\text{fast}}{\rightarrow} BNA^{+} + QH^{-} \qquad (80) \\
&QH^{-} + Q \overset{\text{fast}}{\rightarrow} QH^{\cdot} + Q^{-\cdot} \\
&2QH^{\cdot} \overset{\text{fast}}{\rightarrow} QH_2 + Q
\end{aligned}$$

Reaction series 80 was used to correlate the k and k_H/k_D values with E° by the Marcus theory. This multistep mechanism is practically equivalent to a one-step hydride transfer from the CT complex since the formation constant of the 'radical ion pair' (k_1/k_{-1}) is much smaller than the formation constant of the encounter complex K_{CT} and it is impossible to detect the former by physical or chemical methods.

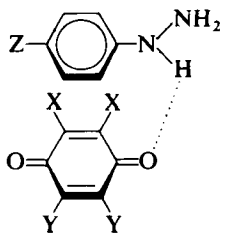
8. Oxidation of phenylhydrazines by quinones

Deuterium isotope effects have been used to investigate the mechanism of oxidation of phenylhydrazines by quinones[118-121]. The deuteriated phenylhydrazine, $PhNDND_2$, obtained by three-fold exchange of hydrazine with D_2O, contained > 95% deuterium in the hydrazine group. The $k_{(p\text{-}NO_2C_6H_4NHNH_2)}/k_{(p\text{-}NO_2C_6H_4NDND_2)}$ ratio for the oxidation of *p*-nitrophenylhydrazine with 1,4-benzoquinone in acetonitrile was 2.9 at 40°C. The $k_{(PhNHNH_2)}/k_{(PhNDND_2)}$ ratio for oxidation of phenylhydrazine with duroquinone in MeCN was 3.0 at 74°C, but in the reaction of hydrazine with 2,6-di-*t*-butyl-1,4-benzoquinone, 1,4-benzoquinone and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone the k_H/k_D ratios were much smaller, being 1.85 at 60°C, 1.30 at 29°C and 1.10 at 20°C, respectively. These effects were interpreted as primary isotope effects, corresponding to a mechanism which involves initially charge transfer complexation followed by a rate-determining hydrogen transfer with cleavage of the N–H bond (equation 81). A sandwich-type structure (**191**) in which the



(81)

π-electron ring orbitals of the electron donor hydrazine interact with the ring π electrons of the electron acceptor quinone was proposed for the CT complex. Application of reaction



(**191**)

sequence 81 for the reaction with duroquinone gave a calculated $k_{2(H)}/k_{2(D)}$ of 4.4 when the isotope effect on the equilibrium k_1/k_{-1} was neglected. It would be interesting to support sequence 81 by studying the ^{15}N kinetic isotope effect corresponding to the nitrogen–hydrogen bond rupture.

9. *Hydrogen transfer from metal hydrides to quinones*

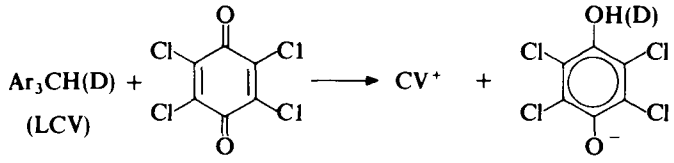
In completing the discussion of hydrogen transfer reactions to quinones we should mention also that in the spontaneous reduction of tetrachloro-, chloro- and the unsubstituted *p*-benzoquinone and TCNE with metal hydrides of the type HMR_3 (M = Sn, Ge, Si and R = Me, Et, *n*-Bu, *i*-Pr and Ph; equation 82), there is negligible (± 10 %, if any) deuterium isotope effect, defined[86] as $[(k_H/k_D)\text{-}1]\,\%$. In the reduction of TCNE with *n*-Bu_3SnH/D[122] $k_H/k_D = 1.0 \pm 0.1$ in cyclohexane, 1.3 ± 0.1 in methylene chloride, 1.4 ± 0.1 in ether and 1.5 ± 0.1 in acetonitrile. These very small isotope effects might represent

(82)

hydride transfers from the metal hydrides to TCNE proceeding either via very early or very late transition states. However, the slightly different from unity k_H/k_D ratios do not depend on the reduction potential E° in the range −0.8 to +0.5 volts of the various acceptors studied, contrary to the hydride transfer from *N*-methylacridan. In the oxidation of *N*-methylacridan both the second order rate constants and k_H/k_D values depend largely on the solvent polarity. In contrast in the reactions of *n*-Bu_3SnH only the second order rate constants increase by a factor of 10^3 by changing the solvent from cyclohexane to acetonitrile whereas the k_H/k_D ratio does not increase significantly. These differences are interpreted[122] as ruling out a radical chain and a hydride transfer reduction mechanisms with metal hydrides and as supporting the charge transfer mechanism in which the hydrogen transfer occurs after the rate-limiting electron transfer within the CT complex. The found k_H/k_D values of the order of 1.1–1.5, if real, are therefore secondary effects related to the electron transfer step (cf. Section II.C.11).

10. *The effect of pressure on the kinetic isotope effects*

A large primary kinetic deuterium isotope effect ($k_H/k_D = 12.3$ at 25 °C) was observed by Lewis and coworkers[123, 124] in the reaction of the colourless leucocrystal violet (LCV) with tetrachloroquinone (CA) in acetonitrile, which gives a cationic purple dye (CV^+) (equation 83). This reaction has been reinvestigated recently by Isaacs and coworkers[125] and by Nishimura and Motoyama[126] at pressures ranging from 0 to 2 kbar.



(83)

Ar = *p*-$Me_2NC_6H_4$ **(192)**

The results obtained by Isaacs and confirmed by Nishimura[126] are presented in Tables 6 and 7. They show that the deuterium isotope effect diminishes with increasing the pressure

TABLE 6. Deuterium isotope effect in the reaction of leucocrystal violet with chloranil[125]

Pressure bar	21	29	$T(^\circ)$ 40	29
		k_H/k_D in		
		Acetonitrile		Isobutyronitrile
0	12.3	11.2	9.1	11.5
500	11.6	9.5	8.6	10.3
1000	10.8	8.5	8.2	9.0
1500	10.1	8.2	7.8	8.2
2000	9.3	8.0		8.0

TABLE 7. Activation parameters for the reaction of leucocrystal violet H, D with chloranil in acetonitrile[125]

	LCV (H)	LCV (D)
E_A (kcal mol^{-1})		
1 bar	8.7 ± 0.5	10.3 ± 0.5
490	8.5	11.0
985	8.3	10.6
log A		
1 bar	7.2	7.3
490	7.3	8.1
985	7.3	8.0
$\Delta V^{\ddagger}_{\delta}$ (cm^3 mol^{-1})[a] in MeCN	-25 ± 2	-35 ± 2
$\Delta V^{\ddagger}_{\delta}$ (cm^3 mol^{-1})[a] in *i*-PrCN	-22	-29

[a] Calculated from: $-RT\partial \ln k/\partial p = (V_{\text{reagents}} - V^{\ddagger}) = \Delta V^{\ddagger}$.

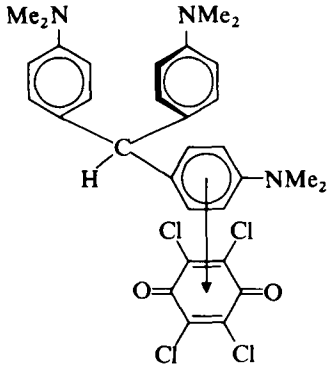
from a k_H/k_D value of 11–12 at atmospheric pressure to a value near 8 at 2 kbar. The precision of measurements was sufficient to observe a higher activation energy for the deuterium reaction but insufficient to estimate the effect of pressure upon the barrier dimensions. The very large primary deuterium isotope effect at low pressure, which is characteristic for hydrogen transfer processes occurring within highly hindered cage-like structures, is considered as a manifestation of a quantum mechanical tunnelling. In such cases the solvation of the hydrogen is poor and the effective masses of the hydrogen isotopes are close to their atomic masses. The pressure effect upon the k_H/k_D values is ascribed to increased solvation of the hydride ion and consequently an increase in its effective mass along the reaction coordinate with pressure which reduces the contribution of the quantum tunnelling. This view is strengthened by the pressure effect studies in the bulkier isobutyronitrile solvent, where the decrease of the deuterium isotope effect with pressure increase was found to be slightly less steep than in acetonitrile. In both solvents at a pressure of 2 kbar the value of k_H/k_D is around 8, approaching the value characteristic for processes caused by zero point energy differences between C–H and C–D bonds. Nishimura and Motoyama[126] proposed the two alternative reactions (equations 84 and 85) for the oxidation of LCV with chloranil (CA) which involve the participation of intermediate outer (X_1) and inner (X_2) charge transfer complexes and a polarized partial bond formation of the type $C^{\delta+}\ldots H\ldots^{\delta-}O$ in the transition state in equation 85.

$$LCV + CA \rightleftharpoons (X_1) \rightleftharpoons (X_2)$$

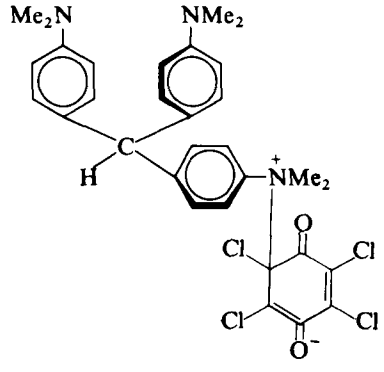
$$X_1 \text{ or } X_2 \xrightarrow{\text{slow}} CV^+ + (\mathbf{192}) \tag{84}$$

$$LCV + CA \rightleftharpoons (X_1) \rightleftharpoons (X_2) \xrightarrow{\text{slow}} CV^+ + (\mathbf{192}) \tag{85}$$

The complexes X_1 and X_2 might have structures **193** and **194**, respectively. The authors are inclined to conclude that the observed large kinetic pressure effect is more consistent with reaction 85 for the oxidation of LCV with CA, but the detailed reaction mechanism



(193)



(194)

requires further investigations. The effect of pressure on tunnelling was also investigated in the reaction of 2,4,6-trinitrotoluene with 1,8-diazabicyclo[5.4.0]undec-7-ene in aprotic solvents[127, 128a]. It is suggested[128a] that under a moderate pressure of a few kilobars the reduction of the 'free volume' of the solvent and the increase of the number of solvent molecules in the proximity of the reaction centre is the main pressure effect.

11. Concluding remarks

The experimental results presented in Section II.C demonstrate clearly that the hydrogen transfer step in the oxidation of organic compounds with quinones is the rate-determining one. The nature of the organic processes presented in this section was not always fully clarified. Many oxidations with quinones have been carried out at one temperature only and additional time-consuming kinetic determinations are needed to establish without ambiguity the degree of tunnelling and the structures of the transition states in the hydrogen transfer processes. Further studies of the pressure effect upon the primary kinetic deuterium isotope effect will be extremely helpful in that respect also. Heavy atom kinetic isotope effect studies of the hydrogen transfer process should provide an additional insight into the skeletal changes upon activation of the reacting molecules. A unique departure from the common mechanism of reduction of quinones with organic reductants was found with metal reductants. However, the physicochemical state of the metal hydride molecules in the solvent used and the nature of the 'spontaneous reduction' should be clarified before the decisive rejection of the hydrogen transfer step in the reduction process as the rate-determining, and formulating an electron transfer process

within the CT complex as the slowest one in the metal hydride reduction. The absolute magnitude of the deuterium isotope effect cannot be used for testing the heterolytic nature of the transition state. Kinetic isotope effects depend on the magnitudes of the force constants at the reaction centre (hydrogen) both in the precursors and in the transition states. The force constants corresponding to the C–H and N–H bonds differ from the force constants corresponding to the metal–hydrogen bonds in the metal hydrides used in studies of isotope effects in the reduction. The low values of deuterium isotope effects found in the latter reactions do not imply that electron transfer is the rate-determining step. Other possibilities related to the formation of new bonds with the central metal atom should also be investigated by using heavy atom isotope effects[128b].

III. BIOCHEMICAL SYNTHESES AND USES OF LABELLED QUINONES

Isotopically labelled quinonoid compounds have continued to be a subject of very active biochemical investigations and applications during the last 10–15 years. Several detailed monographs and reviews covering this field have already appeared. Mitchell[129] reviewed the radioactive drugs used in cancer 'radiochemotherapy' and 'immunoradiotherapy' including the applications of 2-methyl-1,4-naphthoquinol(bisdisodium phosphate), a radioactive drug of high molar tritium specific activity (abbreviated as T-MNDP-Synkavit), developed in Cambridge, England and used with some success in the treatment of inoperable cases of carcinoma. Biosyntheses of quinones, of the vitamin K and other natural naphthoquinones were reviewed by Bentley[130, 131]. Galimov[133] covered in his monograph the various problems of isotopic fractionations in 'nature' with a particular emphasis on the distribution of ^{13}C and ^{18}O isotopes in natural biological systems and in biochemical experiments conducted *in vitro*. He also dealt with the practical uses of isotope effects in unravelling the problem of the genesis of organic matter in nature and in the exploration of geological resources. In this section we review the biochemical studies in which labelled benzoquinones, naphthoquinones and anthraquinones have been isolated and identified by using radiochromatographic techniques. This is preceded by an introductory mathematical treatment of the kinetic isotope method developed by Neiman and Gal[133].

A. A General Treatment of the Applications of Isotopic Tracers in Biochemical Studies

Isotopes are extremely helpful in the elucidation of complex chemical and biochemical reactions, both at the preliminary reconnaissance stage of investigation characteristic for the present biochemical studies with quinones and in advanced physical studies of biochemical processes. In this section a brief presentation of the general relationships concerning intermediate formation and disappearance, derived for simple chemical sequences of reactions and applied chiefly in oxidation and decomposition studies[133a] is given.

1. Determination of the formation and consumption rates of an intermediate

Let us consider a sequence of consecutive chemical transformations comprising the intermediate 'X' to be investigated (equation 86).

$$A \rightarrow B \rightarrow C \xrightarrow{\omega_1} X \xrightarrow{\omega_2} D \rightarrow E \qquad (86)$$

We further assume that spectroscopic and analytical methods detect the occurrence of the intermediate in the reacting system and enable determination of its concentration changes

with time. The observed change of the concentration of X is the difference between its unknown rate of formation ω_1 and its unknown rate of consumption ω_2 (equation 87).

$$d[X]/dt = \omega_1 - \omega_2 \tag{87}$$

By introducing into the reacting system the labelled intermediate X and by observing the simultaneous changes of [X] and of the specific radioactivity α of X (defined by the quotient $\alpha = I/[X]$, where I is total radioactivity of the intermediate X, and [X] is total concentration of the intermediate), we obtain a second equation which enables to find two unknowns ω_1 and ω_2 of equation 87. A closer look at equation (86) shows that the rate of change of the specific activity of X* depends on the rate of formation ω_1 and on the concentration term [X] according to equation 88,

$$\frac{d\alpha}{dt} = -\frac{\alpha\omega_1}{[X]} \tag{88}$$

if small kinetic isotope effects for elements heavier than the hydrogen are neglected (Hevesy approximation). Equation 88 gives directly equation 89 for ω_1.

$$\omega_1 = -[X]\frac{d\ln(\alpha)}{dt} \tag{89}$$

Substitution of equation 89 into equation 87 leads to equation 90 for the rate of consumption of the intermediate:

$$\omega_2 = -[X]\frac{d\ln(\alpha)}{dt} - \frac{d[X]}{dt} \tag{90}$$

The rates of formation and consumption of an intermediate Y can also be determined by labelling the precursor X of the intermediate. The reaction sequence in this case is given in equation 91.

$$A \rightarrow B \rightarrow C \xrightarrow{\omega_1} \overset{\alpha}{X} \xrightarrow{\omega_2} \overset{\beta}{Y} \xrightarrow{\omega_3} D \rightarrow \tag{91}$$

The change of the specific radioactivity α of X is given as before by equation 88. The total activity, I_y, of the intermediate Y is a product of its specific radioactivity, β, and its concentration [Y] (equation 92).

$$I_y = \beta[Y] \tag{92}$$

Differentiation of equation 92 gives equation 93.

$$\frac{dI_y}{dt} = \beta\frac{d[Y]}{dt} + [Y]\frac{d\beta}{dt} \tag{93}$$

The left side of equation 93 is also the difference between the rate of formation of the labelled intermediate Y*, ω_2^*, and the rate, ω_3^*, of its disappearance (equation 94).

$$\frac{dI_y}{dt} = \omega_2^* - \omega_3^* = \alpha\omega_2 - \beta\omega_3 \tag{94}$$

Elimination of $d(I_y)/dt$ from equations 93 and 94 and replacement of $d[Y]/dt$ by $d[Y]/dt = \omega_2 - \omega_3$, leads to equation 95.

$$\frac{d\beta}{dt} = \frac{(\alpha - \beta)\omega_2}{[Y]} \tag{95}$$

At the beginning $\beta = \alpha$ and $(d\beta/dt)_{t=0} = 0$, but since α is decreasing with time, β is also decreasing, $d\beta/dt < 0$ and $\beta > \alpha$.

When the reaction between the intermediate Y and its precursor X is reversible (equation 96):

$$A \rightarrow B \xrightarrow{\omega_1} \overset{\alpha}{X} \underset{\omega_{-2}}{\overset{\omega_2}{\rightleftharpoons}} \overset{\beta}{Y} \xrightarrow{\omega_3} C \rightarrow \ldots \tag{96}$$

the observed changes of α, β, [X] and [Y] with time give the four differential equations 97–100 which allow evaluation of the four unknowns ω_1, ω_2, ω_{-2}, ω_3.

$$\frac{d\alpha}{dt} = -\frac{\alpha\omega_1}{[X]} + \frac{(\beta-\alpha)\omega_{-2}}{[X]} = \frac{-\alpha(\omega_1+\omega_{-2})+\beta\omega_{-2}}{[X]} \tag{97}$$

$$\frac{d\beta}{dt} = \frac{(\alpha-\beta)\omega_2}{[Y]} \tag{98}$$

$$\frac{d[X]}{dt} = \omega_1 + \omega_{-2} - \omega_2 \tag{99}$$

$$\frac{d[Y]}{dt} = \omega_2 - \omega_{-2} - \omega_3 \tag{100}$$

Many biochemical reactions include several reversible reaction steps and the strict solution of the kinetic equations is much more complicated than the simple case described above.

2. *Determination of the reaction sequence*

In order to show that intermediate Y is formed directly from the precursor X, one introduces into the reacting system a small amount of unlabelled Y together with the labelled X, and the changes of [X], [Y], α and β in the course of the reaction investigated are determined. The answer obtained is positive when the specific activities of X and of Y are changing with time as shown in Figure 1.

When Y is formed partly from the labelled precursor X and partly from one or more inactive precursors (K_i, K_1, K_2, K_3, etc.) (equation 101) then

$$A \rightarrow B \xrightarrow{\omega_1} \overset{\alpha}{X} \xrightarrow{\omega_{2a}} \overset{\beta}{Y} \xrightarrow{\omega_3} D \rightarrow \qquad \omega_{2bi} \uparrow K_i \tag{101}$$

the curve of β against time falls always below the curve of α against time as shown in Figure 2. By using equations 88 and 95 we obtain equation 102.

$$\frac{d\beta}{dt} = \frac{(\alpha-\beta)\omega_{2a}}{Y} - \beta\frac{\omega_{2b}}{Y} = \frac{\left[\alpha - \beta\left(1+\dfrac{\omega_{2b}}{\omega_{2a}}\right)\right]\omega_{2a}}{Y} \tag{102}$$

The condition for a maximum, $d\beta/dt = 0$, is given in equation 103,

$$\left(\frac{\alpha}{\beta}\right) = \frac{\omega_{2a}+\omega_{2b}}{\omega_{2a}} = \frac{\overline{AB}}{\overline{AC}} \tag{103}$$

which enables the evaluation of the respective rate ratios. If more than one unlabelled precursor K generates intermediate Y then the ω_{2b} term in equation 103 is replaced by the sum of the formation rates of Y, $\sum_i \omega_{2b_i}$.

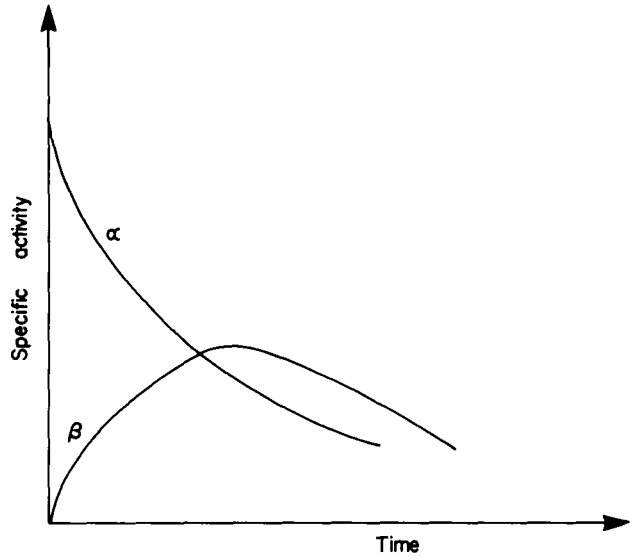


FIGURE 1. Time dependence of the specific activities of the precursor X(α) and of the intermediate Y(β)

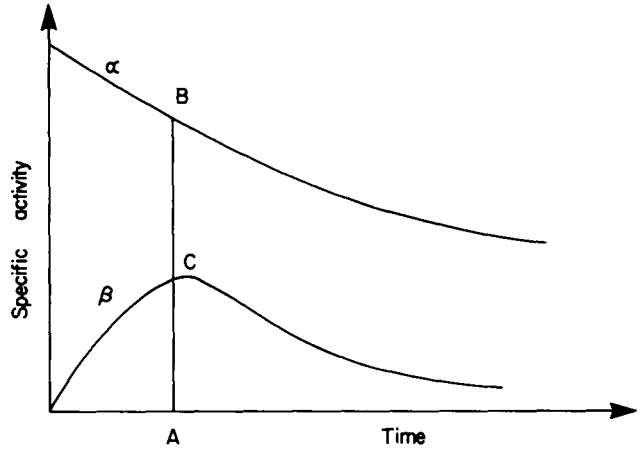
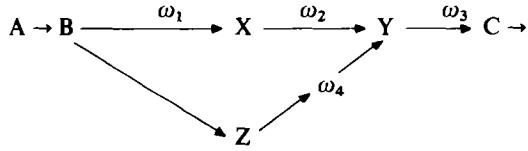


FIGURE 2. Time dependences of α and β when Y is formed also from an inactive precursor

In the case of a reaction sequence represented by equation 104,



(104)

the introduction of the labelled compound B into the reacting system and subsequent isolation of the intermediates [X], [Y], [Z] and measurements of their respective specific radioactivities α, β and γ allows the calculation of the ratio of the rates $\omega_2/\omega_4 = (\beta-\gamma)/(\alpha-\beta)$ which results directly from the condition for a maximum of the $\beta(t)$ time dependence (equation 105).

$$\frac{d\beta}{dt} = \frac{(\alpha-\beta)\omega_2 + (\gamma-\beta)\omega_4}{[Y]} = 0 \tag{105}$$

Usually a given intermediate participates in several different biochemical reactions taking place in the living organism investigated, and the direct use of simple relations 89–105 is of rather limited value. The technical and analytical difficulties also do not allow one to follow exactly the kinetics of the formation of the given compound and its intermediates in most cases. Finally, we will recall that the concentration of the intermediate $[X_t]$, defined by equation 106, can be calculated by graphical integration of equation 107 obtained in turn by substitution of equation 89 into 106.

$$[X_t] = \int_0^t \omega_1 dt \tag{106}$$

$$[X_t] = -\int_{\alpha_0}^{\alpha_t} [X]\, d(\ln\alpha) = \int_{\alpha_t}^{\alpha_0} [X]\, d(\ln\alpha) = 2.303 \int_{\alpha_t}^{\alpha_0} [X]\, d(\log\alpha) \tag{107}$$

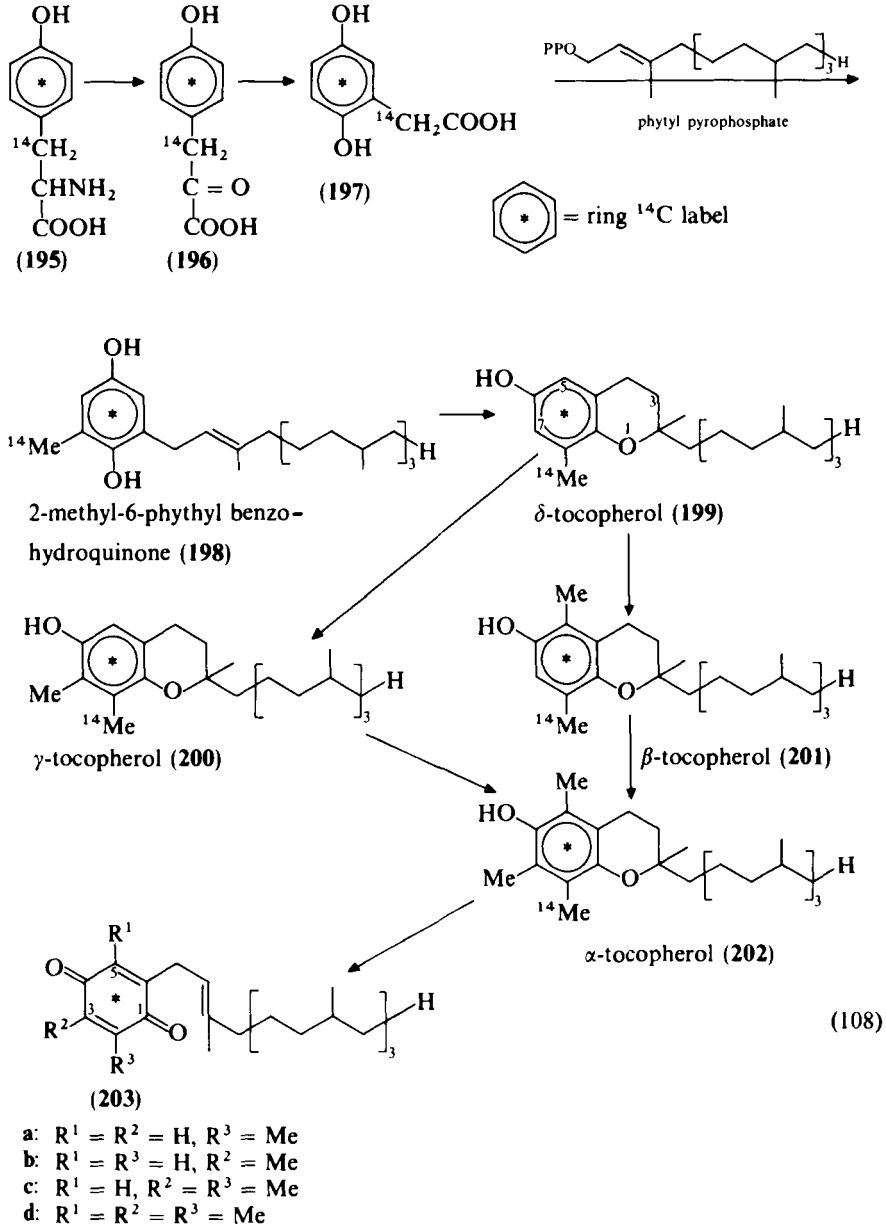
The difference between $[X_t]$ and [X] taken at any given time interval gives the 'consumed amount' of intermediate [X].

B. Biosyntheses and Uses of Labelled Benzoquinone Derivatives

1. Biosynthesis of plastoquinone-9 and tocopherols by ethiolated maize shoots

^{14}C-Isotopic tracer studies have established[134] that ^{14}C-tyrosine (**195**), [^{14}C]-*p*-hydroxyphenylpyruvic acid (**196**) and [α-^{14}C] and [U-^{14}C]homogentisic acid (**197**) are utilized by maize shoots for the biosynthesis of ^{14}C-labelled γ-tocopherol (**200**), β-tocopherol (**201**), α-tocopherol (**202**) and α-tocopherolquinone (**203**) (equation 108) and plastoquinone-9 (**204**) (equation 109). It is suggested that in the course of radioactive tocopherols production D-tyrosine is first converted into *p*-hydroxyphenylpyruvic acid[135] which in turn is degraded to homogentisic acid before incorporation into tocopherolquinone (**203a–203d**) (equation 108) and plastoquinone (**204**) (equation 109). The sequence of biochemical transformations of equation 108 is supported by several observations:

(1) [^{14}C]homogentisic acid is incorporated into tocopherols and into plasto- and α-tocopherolquinones more effectively than *p*-hydroxy[^{14}C]phenylpyruvic acid (**196**);



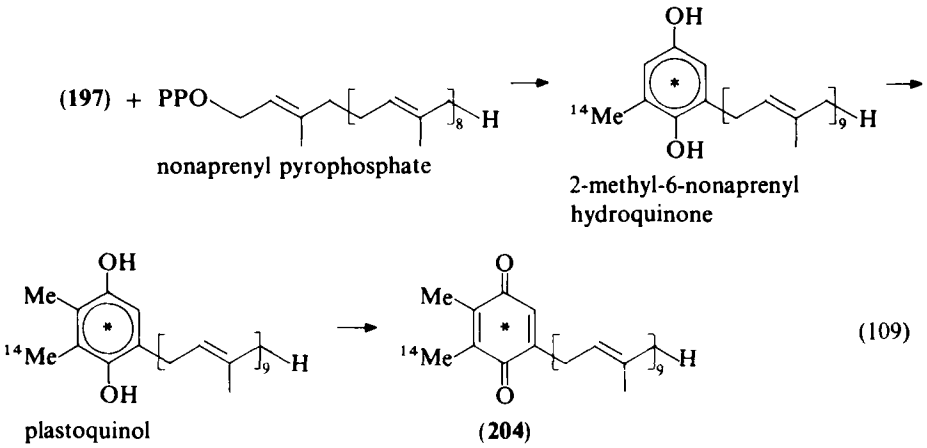
(108)

(2) in isotope competition experiments, addition of *p*-hydroxyphenylpyruvic acid of natural isotopic composition to the maize shoots culture markedly decreased the incorporation of radioactivity from DL-[β-^{14}C]tyrosine into plastoquinone; addition of homogentisic acid of natural isotopic composition into the culture diminishes significantly

the incorporation of radioactivity from *p*-hydroxy-[U-^{14}C]phenylpyruvic acid into plastoquinone-9, tocopherols and α-tocopherolquinone;

(3) *p*-hydroxyphenylacetic acid, as well as ^{14}C-labelled phenylacetic acid which could be considered as an intermediate in the conversion of *p*-hydroxyphenylpyruvic acid into homogentisic acid as well as 2-methylquinol-4-β-D-glucoside (homoarbutin) are not involved in the biosynthesis of labelled plastoquinone-9 (**204**), tocopherol and tocopherolquinone.

The chemical degradation of labelled isoprenoid quinones and chromanols showed that nuclear carbon atoms and the side-chain carbon atom adjacent to the nucleus of D-tyrosine, *p*-hydroxyphenylpyruvic acid and homogentisic acid are incorporated as a C_6–C_1 unit to the *p*-benzoquinone rings and as nuclear methyl groups of plastoquinone-9 (equation 109) and α-tocopherolquinone and as the aromatic nuclei and nuclear methyl groups of **200** and **203**. Ethiolated dark-grown 7-day-old maize shoots, excised and



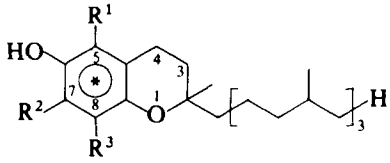
(109)

exposed with continuous illumination to D-[G-^{14}C]shikimate for periods up to 24 h produced ^{14}C-labelled dehydrophylloquinone, α-dehydrotocopherolquinone, α-dehydrotocopherol and γ-dehydrotocopherol[136]. It is suggested that the unsaturation occurs beyond the C(4′) position of quinones and beyond the C(1′) position in the case of chromanols. Dehydro compounds are accumulated in substantial amounts in ethiolated tissues, because these tissues are unable to carry out the complete reduction of all the molecules of geranyl–geranyl-substituted intermediates, and a mixture of dehydro and normal labelled products is formed.

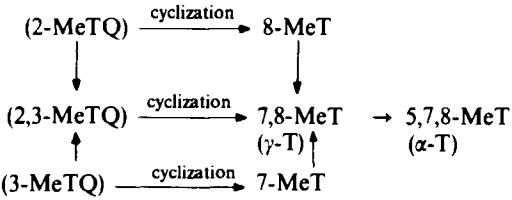
2. *Syntheses of ^{14}C- and tritium-labelled polyprenyl quinones and tocopherols by* Calendula officinalis

In the course of ^{14}C isotopic studies of the mechanism of the biosynthesis of polyprenyl quinones and tocopherols[137,138] by *C. officinalis*, using $^{14}CO_2$, [1-^{14}C]acetate, [2-^{14}C] mevalonate and [U-^{14}C]tyrosine as labelled precursors, the dynamics of the incorporation of tritium-labelled [2,3-^{3}H]phytol into tocopherols **199**–**202** and tocopherolquinones **203a**–**d**, produced in different cellular subfractions of *C. officinalis* leaves[139], has also been investigated. By isolating the individual tritium-labelled tocopherols and tocopherol-quinones from various cellular subfractions after 1, 2, 4 and 6 hours of feeding with [2,3-^{3}H]phytol protoplasts (obtained from 4 week old *C. officinalis* leaves) it has been shown[139]

that condensation of homogentisic acid with phytyl chain and formation of 2-MeTQ (**203a**) and 3-MeTQ (**203b**) takes place both in chloroplast and in microsomal fractions. Subsequent methylation and cyclization leads to the formation of 2,3-MeTQ (**203c**), or 8-MeT (**199**) and 7,8-MeT (**200**), which are methylated to 5,7,8-MeT (**202**) (equation 110).



8-MeT (**199**) $R^1 = R^2 = H$, $R^3 = Me$
7-MeT (**199a**) $R^1 = R^3 = H$, $R^2 = Me$
7,8-MeT (**200**) $R^1 = H$, $R^2 = R^3 = Me$
5,7,8-MeT (**202**) $R^1 = R^2 = R^3 = Me$

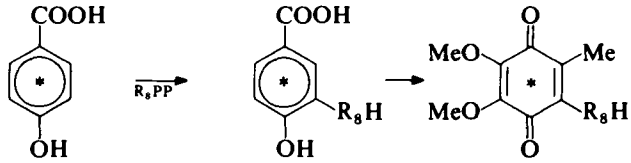


(110)

biosynthesis of tocopherols by *C. officinalis*

It is suggested that α-TQ (**203d**) does not participate in the biosynthesis of α-T (**202**) but results from the oxidation of α-T (**202**). A conclusion was also made that tocopherols and TQ (**203**) are transported to the mitochondria of plants from their place of synthesis. The biosynthesis of chloroplastidic terpenoid quinones and chromanols has been reviewed recently by Pennock[140].

Using [^{14}C]-4-hydroxybenzoic acid it has been also shown[141-143a] that *Escherichia coli* forms ubiquinone (**204**) which is synthesized by prenylation of 4-hydroxybenzoic acid with an all-*trans* polyisoprenoid side chain which consists predominantly of eight units (equation 111).



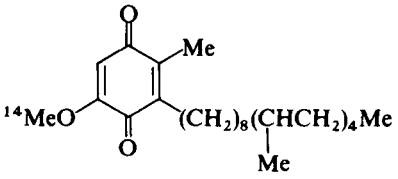
(111)

(**204**)

R_8PP-octaprenyl pyrophosphate
R_8-octaprenyl side chain

3. *Biosynthesis of* [^{14}C]*mavioquinone*

Carbon-14 labelled mavioquinone (**205**) has been biosynthesized[143b] by *Mycobacterium avium* in a growth medium containing [^{14}Me]-L-methionine, or [3-^{14}C]propionate and to a lesser extent from [1-^{14}C] or [2-^{14}C]acetate. Shikimic acid, a common precursor of the

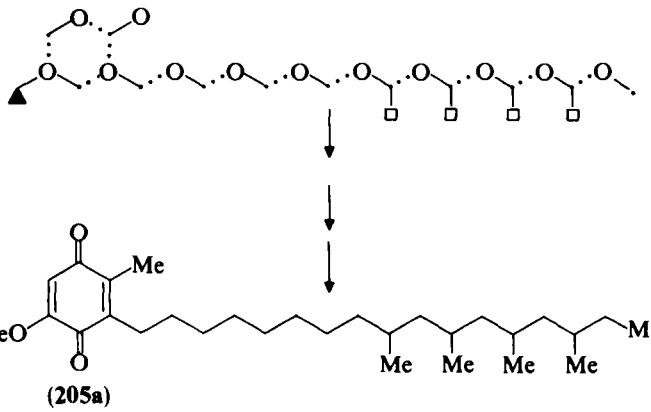


(205)

—o: MeCOOH

□—·—o: EtCOOH

▲: Me-from L-methionine



(205a)

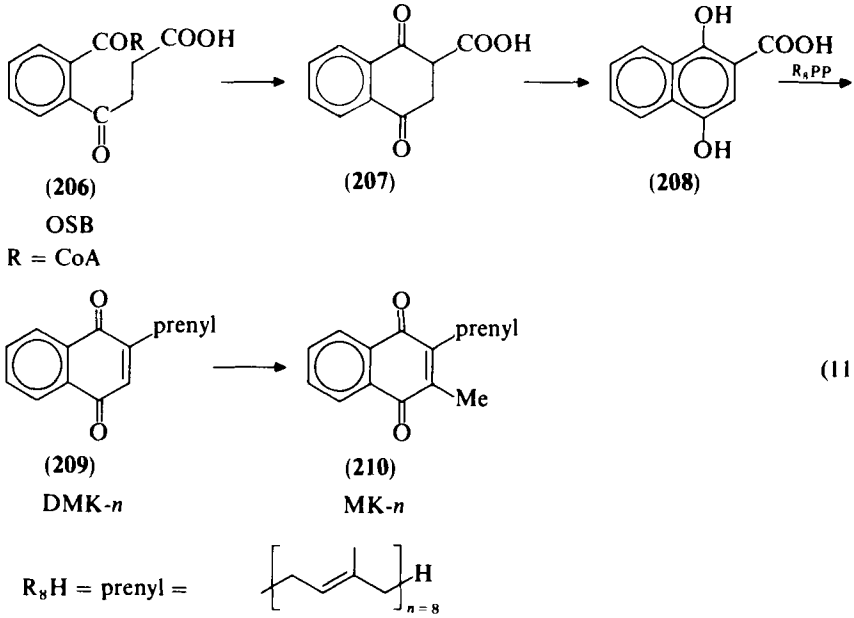
(112)

quinone ring of mena- and ubiquinones, and *p*-hydroxybenzaldehyde, a precursor of ubiquinones, were not incorporated into **205a**. The degradation experiments have shown that more than 75% of the label from [^{14}Me]-L-methionine is localized in the *O*-methyl group of mavioquinone, the rest being randomized in the side chain and in the ring. This specific incorporation of the Me group of methionine into an *O*-methyl group was also demonstrated by introducing [C^2H_3]-L-methionine into the growth medium. At least 75% of the ^{14}C from [^{14}C]propionic acid was found in the branched part of the side chain. The absence of incorporation of the methyl group of methionine in the ring C-methyl group and the failure to incorporate aromatic precursors into the ring carbon atoms suggest an acetate–methylmalonate condensation as the pathway for the biosynthesis of mavioquinone (equation 112).

C. Biosyntheses and Uses of Labelled Naphthoquinone Derivatives

1. *Menaquinone biosynthesis by* Escherichia coli *extracts*

The radiochemical evidence for the involvement of 1,4-dihydroxy-2-naphthoic acid in the menaquinones (**210**) biosynthesis by cell-free extracts of *E. coli* was presented by Bryant and Bentley[144, 147]. The addition of [2,3-$^{14}C_2$]-O-succinoylbenzoic acid (OSB, **206**), as the disodium salt to incubation mixtures of *E. coli* essentially cell-free extracts, containing naphthoate synthetase (coenzyme A having an approximate molecular weight of 45000) and ATP resulted in the formation of radioactive 1,4-dihydroxy-2-naphthoic acid (**208**). Supplementary addition of the side-chain precursor, farnesyl pyrophosphate, to the extract stimulated conversion of [2,3-^{14}C]OSB into menaquinones. The mechanism



(113)

n is number of isoprene units, equal for instance to 8 or 9

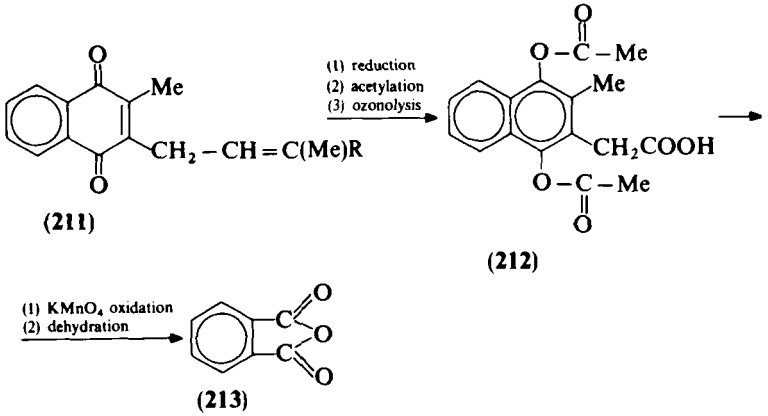
and the intermediates involved in the transformation sequences OSB → → → MK (**210**) are therefore as given in equation 113.

The Claisen condensation (i.e. elimination of water between a carboxyl and methylene group) which gives the ketotetralone (**207**) requires the formation of a CoA derivative at least of one carboxyl group. The biochemical mechanism of the conversion of 1,4-dihydroxy-2-naphthoic acid (**208**) to DMK (demethylmenaquinone (**209**)) and to menaquinone (MK, **210**) was investigated by Bentley[147] and Shineberg and Young[145]. Despite of the overall similarities, the biosynthetic paths of ubiquinone and menaquinones are different. Incubation of cell extract from *E. coli* with [^{14}C]-1,4-dihydroxy-2-naphthoic acid and solanesylpyrophosphate in the presence of Mg^{2+} and Triton-X-100 resulted in the formation of radioactive demethylmenaquinone-9 as well as radioactive menaquinone-8, by a concerted replacement of the carboxyl of 1,4-dihydroxy-2-naphthoic acid with a prenyl side chain. The isotopic tracer experimental evidence eliminates symmetrical intermediates such as naphthoquinone or its quinol[146]. Men A$^-$ mutants of *E. coli*, which are defective in the prenylation reaction, accumulate 1,4-dihydroxy-2-naphthoate rather than 1,4-naphthoquinone[143]. However, this strain had normal levels of 4-hydroxybenzoate octaprenyltransferase, the enzyme catalysing the analogous prenylation reaction in ubiquinone biosynthesis. This indicates that the two octaprenyltransferases are quite different. In the case of ubiquinone formation the substrate for prenylation is also the aromatic carboxylic acid, but 4-hydroxybenzoate is prenylated without decarboxylation. Another enzyme catalyses the decarboxylation in the next step and 2-prenyl phenol is formed.

2. *Biosynthesis of vitamin K_2*

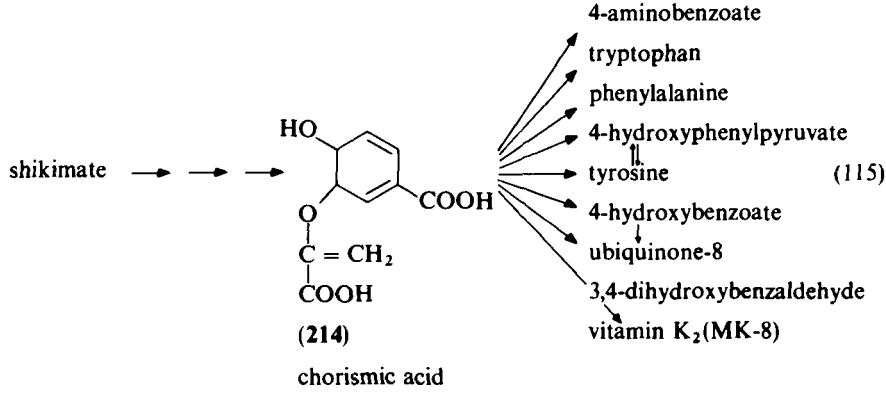
The role which shikimic acid plays in the biosynthesis of vitamin K_2 (MK-8), ubiquinone and in the aromatic synthesis in general in *E. coli* was investigated by Cox and Gibson[148]. In the preliminary experiments the *E. coli* cells were grown in the presence of

[G-^{14}C]shikimate during 6 h, harvested, extracted and the extracts were chromatographed on silica-gel thin-layer plates. The vitamin K and the ubiquinone appeared as yellow bands. Scanning of the plates for radioactivity showed that shikimate incorporates into both vitamin K and ubiquinone to about equal degrees. Following a kinetic investigation of the likely intermediates in the biosynthesis of vitamin K and ubiquinone, several suspected intermediates of natural isotopic composition were added in excess to the culture containing already labelled shikimate. Addition of unlabelled 4-hydroxybenzoate resulted in an almost disappearance of the radioactive peak corresponding to ubiquinone but did not affect the incorporation of radioactivity of shikimate into vitamin K. Addition of 3,4-dihydroxybenzaldehyde and adrenaline affected the incorporation of [^{14}C]shikimate into vitamin K since the peak of radioactivity corresponding to vitamin K on thin-layer plates largely disappeared. Compounds tested which do not affect the incorporation of [^{14}C]shikimate into either vitamin K or ubiquinone are catechol, 4-hydroxyphenylpyruvate, 2,3-dihydroxybenzoate, phenylpyruvate and menadione.



(211) (212) (213) (114)

Stepwise chemical degradation of vitamin K_2 (**211**), synthesized by *E. coli* from [^{14}C]shikimate showed that the benzene ring and carbonyl groups of the naphthoquinone arise from shikimic acid (equation 114). Specific ^{14}C activities of **211**, of 1,4-diacetoxy-2-methylnaphthalene-3-acetic acid (**212**) and of the phthalic anhydride (**213**) were nearly the same. Consequently the ^{14}C radioactivity of the original vitamin K was retained in the phthalic anhydride. When cells of *E. coli* were grown in a glucose–citrate–mineral salts medium to which [1,2-$^{14}C_2$]acetate was added, the extracted and purified vitamin K was



(214) (115)

chorismic acid

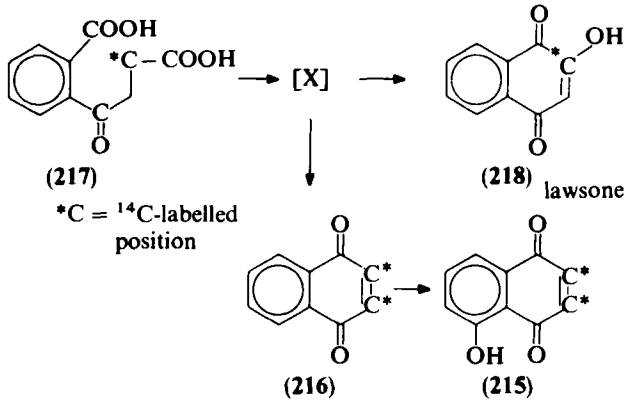
found to be radioactive. The degradation experiments showed that the specific radioactivities of compounds **211**, **212** and **213** are in 1.4:0.68:0.1 ratio.

The ^{14}C of the [Me-^{14}C]methionine fed to the culture also incorporates into vitamin K_2. After chemical degradation the specific activities of **211** and **212** were about equal. The question of whether quinone ring synthesis is direct from acetate or indirect through the shikimate intermediate is still open for discussion and requires further experimental investigation. Cox and Gibson[148a] suggested equation 115 as a probable pathway for the biosynthesis of aromatic compounds in *E. coli*.

Esmon, Sadowski and Suttie[148b] discovered that vitamin K plays a certain role in the incorporation of $H^{14}CO_3^-$ into plasma proteins in the course of synthesis of prothrombin (one of the four blood-clotting zymogens) by liver extract from vitamin K deficient rats (upon the addition of vitamin K).

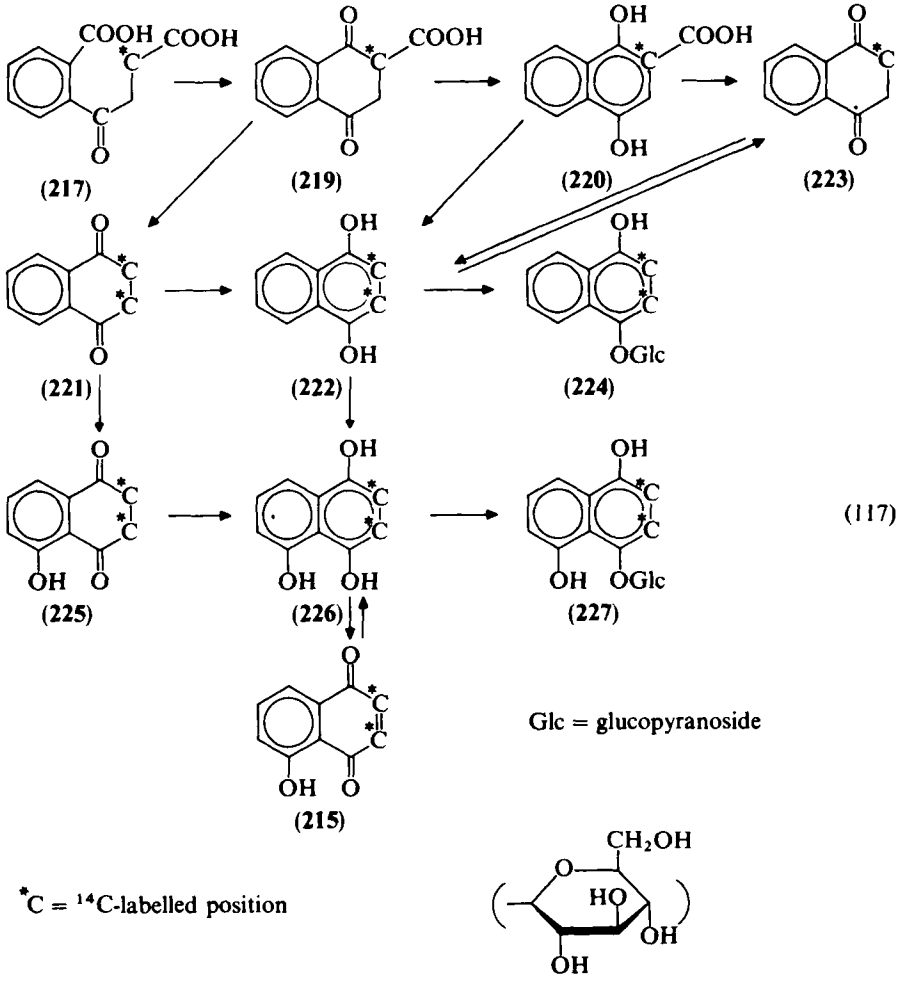
3. [^{14}C]*Juglone (5-hydroxy-1,4-naphthoquinone) biosynthesis*

Müller and Leistner[149] have shown that 1,4-naphthoquinone, one of the more than 120 naphthoquinones isolated from plants, is a natural intermediate involved in the biosynthesis of juglone in *Juglans regia*. Besides ^{14}C-labelled juglone (**215**), symmetrically ^{14}C-labelled 1,4-naphthoquinone (**216**) has been isolated from a young *Juglans regia* plant which was kept in contact with an aqueous solution of 4-(2'-carboxyphenyl)-4-oxobutyrate-[2-^{14}C] (**217**), for 25 h (equation 116). Its intermediacy was confirmed also



(116)

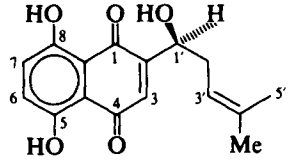
by growing the *Juglans regia* (and *Impatiens balsamina*) plants in aqueous solution of [1,4-^{14}C]-1,4-dihydroxy-2-naphthoic acid which was expected to be the intermediate [X] shown in equation 116. The naphthoquinone from *Impatiens* was inactive whereas 1,4-naphthoquinone from *Juglans* was radioactive. In a more careful radiobioexperiment[150,151] with *Juglans* plant, infused with ^{14}C-labelled *o*-succinoylbenzoic acid (**217**) and tritium-labelled [6-^3H]-D-glucose, the ^{14}C-labelled 4-oxo-α-tetralone (**221**), β-hydrojuglone (**225**) and glucosides **224** and **227** were also extracted. ^{14}C-Labelled glycosides such as 4-hydroxy-1-naphthalenyl-β-D-glucopyranoside as well as 1,4-naphthoquinone, juglone and 4,8-dihydroxy-1-naphthalenyl-β-D-glucopyranoside have been additionally isolated from fruits of different *Juglans* species[151]. A glycosyltransferase, catalysing the glycosylation of hydroquinone has been isolated from leaves of *J. regia* and callus culture of *J. major*. All the accumulated data are presented by the general equation 117 which shows the biosynthetic relationships between naphthalene derivatives in *Juglans*.



(117)

4. *Biosynthesis of* [^{14}C]*alkannin*

Alkannin (5,8-dihydroxy-2-((*S*)-1′-hydroxy-4′-methylpent-3-enyl)-1,4-naphthoquinone) (**228**), a coloured dyestuff found in the Boraginaceae, was ^{14}C-labelled heavily during



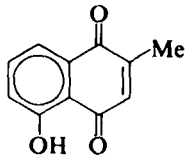
(228)

alkannin

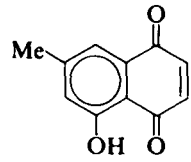
feeding *Plagiobothrys arizonicus* with phenylalanine-, or cinnamic acid-ring-[1-^{14}C], *p*-hydroxybenzoic acid-ring-[1,2,6-^{14}C], mevalonic acid-[2-^{14}C], and doubly labelled mevalonic acid-[5-^{14}C] and ^{3}H[152]. No significant incorporation of shikimic acid-[7-^{14}C] and tyrosine-[U-^{14}C] into the pigment was found. The distribution of carbon-14 within the labelled molecule of alkannin as well as data concerning the incorporation of supposed ^{14}C-labelled precursors of this 1,4-naphthoquinone suggest that alkannin is produced by a new biosynthetic sequence which involves the prenylation of *p*-hydroxybenzoic acid with two molecules of prenylpyrophosphate in succession, or with geranylpyrophosphate, subsequent decarboxylation and finally ring-closure of diprenylhydroquinone.

5. *Biosynthesis of* [^{14}C]*plumbagin*

In the course of study of the mechanism of the biosynthesis of 5-hydroxy-2-methyl-1,4-naphthoquinone (plumbagin, 2-methyl-juglone, **229**) in the genus *Drosera* and in the genus *Plumbago* it has been revealed that young shoots of *Plumbago europaea* L. do not incorporate shikimate-[7-^{14}C], L-[^{14}Me]methionine, DL-tyrosine-[β-^{14}C], DL-phenylalanine[ring-1-^{14}C] or DL-mevalonic acid-[5-^{14}C] into plumbago to a significant extent after 24 hours. However, acetate-[1-^{14}C], [2-^{14}C] and malonate-[2-^{14}C] labelled this naphthoquinone heavily. These findings suggested that **229** is formed via a polyacetate–malonate pathway. This conclusion was confirmed by extensive chemical degradation of plumbagin obtained by labelling with acetate-[1-^{14}C] or acetate-[2-^{14}C] feeding[153]. 7-Methyljuglone (**230**), co-occurring in *Drosera* plants is also formed by the

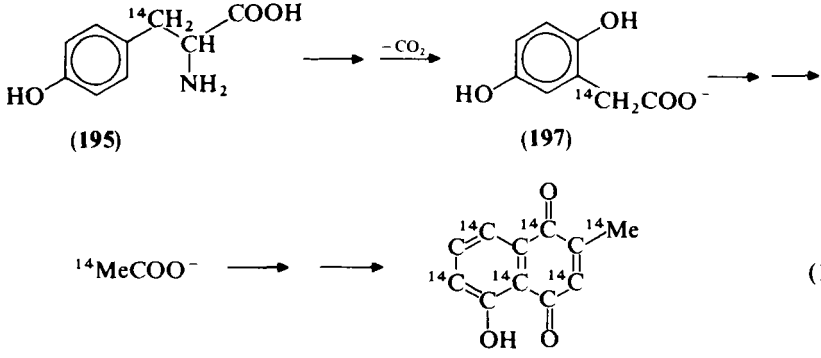


(**229**)



(**230**)

polyacetate–malonate route. In subsequent radiochemical isotopic studies of the biosynthetic routes leading to plumbagin in *Drosera*[154] it has been established that ^{14}C-labelled 2-methyljuglone is produced very efficiently in the young unrolling leaves of *Drosophyllum lusitanicum* from DL-tyrosine-[β-^{14}C] (**195**) via the acetate–polymalonate pathway (equation 118). Tyrosine is broken down to acetate through the homogentisate **197**, which is the central intermediate in this pathway.



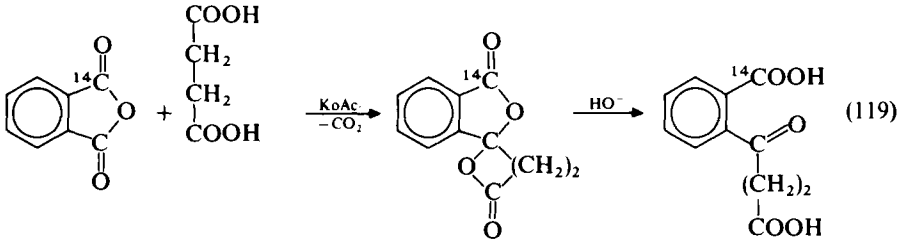
(**195**) (**197**) (118)

labelled plumbagin

Evidence for reaction 118 has been obtained by carrying out an extensive chemical degradation of the isolated ^{14}C-labelled plumbagin by Kuhn–Roth oxidation, alkaline hydrogen peroxide oxidation, etc. The established distribution pattern of the radioactivity within the plumbagin molecule, obtained after feeding DL-tyrosine-[β-^{14}C] to *Drosophyllum* leaves, almost coincides with the expected (16.7% or 0%) percentage if the acetate–polymalonate pathway is operative. In accordance with equation 118, acetate-[1-^{14}C] and [2-^{14}C] as well as malonate-[2-^{14}C], propionate-[2-^{14}C] and acetogenic amino acids were found to be excellent precursors of plumbagin. Carbon-14 of acetate-[1-^{14}C] is located in positions 2, 4, 5, 7 and 9 in agreement with the theoretically expected yield (20% in each of these positions). Carbon-14 of acetate-[2-^{14}C] gave the same labelling pattern as found after tyrosine-[β-^{14}C] feeding. Incorporation of other possible ^{14}C-labelled precursors and especially incorporation of homogentisic acid-[2-^{14}C] was about equal to that of tyrosine. The highest (ca. 30%) incorporation was found on feeding with intermediates which are formed after the oxidative cleavage of the aromatic ring of homogentisic acid, carried out by an iron-containing enzyme. In the presence of the chelating agent α,α'-bipyridyl which is an inhibitor of the homogentisate oxygenase, the pool of free homogentisic acid increased and the incorporation of the label into plumbagin was depressed. Thus it has been established that carnivorous plants and their cell suspension cultures are able to degrade phenolic compounds[155], like a number of animals and microorganisms, to acetate, both under sterile and non-sterile conditions. The acetate is subsequently incorporated into plumbagin and 7-methyljuglone probably via an intermediate having a hexaacetyl chain.

6. *The role of* [^{14}C]-o-*succinoylbenzoic acid (OSB) in the biosynthesis of* ^{14}C-*labelled naphthoquinones*

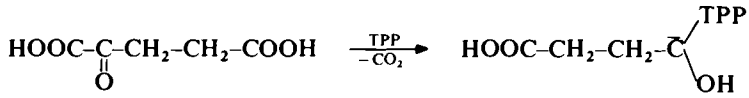
Dansette and Azerad[156] synthesized [^{14}C]-*o*-succinoylbenzoic acid (**231**) by condensing [^{14}C]phthalic anhydride with succinic acid (equation 119). The OSB formed was administered to *Mycobacterium phlei*, *E. coli* K_{12}, *Aerobacter aerogens* 62-1 and to young shoots of *Impatiens balsamina* or *Juglans regia*.



(119)

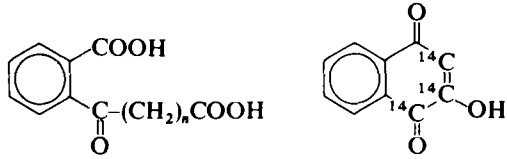
(231)

Degradative oxidation by $KMnO_4$ to phthalic acid of isolated MK-9 [II-H_2] (5'6'-dihydromenaquinone-*n*: abbreviation MK-9 [II-H_2]—the Roman numeral refers to the second isoprene unit out from the nucleus, $n = 9$ is number of isoprene units; **210**), menaquinone-8, demethylmenaquinone-8, lawsone, juglone and pseudopurpurine showed that the label is exclusively localized in C(1) and C(4) of the naphthoquinone ring. It has thus been concluded that OSB is a true intermediate in the biosynthesis of the naphthoquinone ring and a general scheme for its production has been proposed. According to Campbell[157] the first step in the OSB production is condensation, with dehydration of chorismic acid with the succinoyl–semialdehyde thiamine–pyrophosphate



(232) (120)

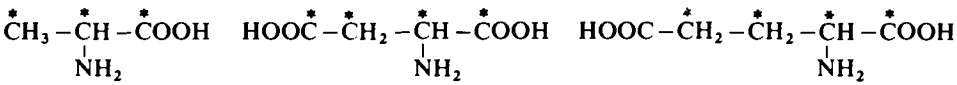
(TPP) carbanion (**232**) (equation 120). Grotzinger and Campbell[158] have also shown that **231** is an obligatory intermediate in the lawsone biosynthesis. When [U-^{14}C]glutamate was fed in aqueous solution to fresh *Impatiens balsamina* cuttings for 5 h, glycosidically bound and non-bound forms of ^{14}C-labelled lawsone were isolated from the organic extract of cuttings. The sensitive GLC–MS–proportional counter scanning method used in this study enabled the identification of 3-(2'-carboxyphenyl)-3-oxopropionate (**233**) as a second product of [U-^{14}C]glutamate metabolism[158].



(**233**) (**234**)

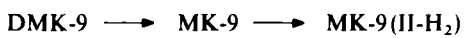
$n = 1$

Impatient balsamina plants produced ^{14}C-labelled lawsone (**234**) also from ^{14}C-labelled alanine (**235**) and aspartate[159] (**236**). Robins and coworkers have shown[160] that C(2), C(3)

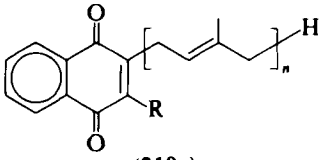


(**235**) (**236**) (**237**)

and C(4) atoms of the naphthalene nucleus of menaquinone of *E. coli* and *M. phlei* are derived from [U-^{14}C]glutamate (**237**). Azerard and coworkers[161] obtained 'radioactive dihydromenaquinone-9' and proved that cell-free extracts of *M. phlei* can catalyse the reaction shown in equation 121.



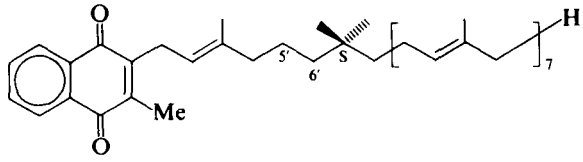
(**210a**) (**238a**) (121)



(**210a**)

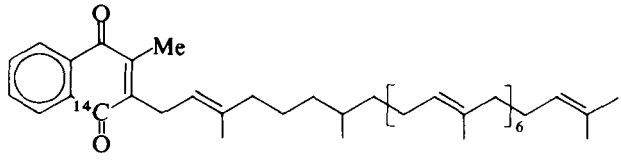
R = H, DMK-9 = demethylmenaquinone-*n*

R = Me, MK-9 = menaquinone-*n*



(238a)

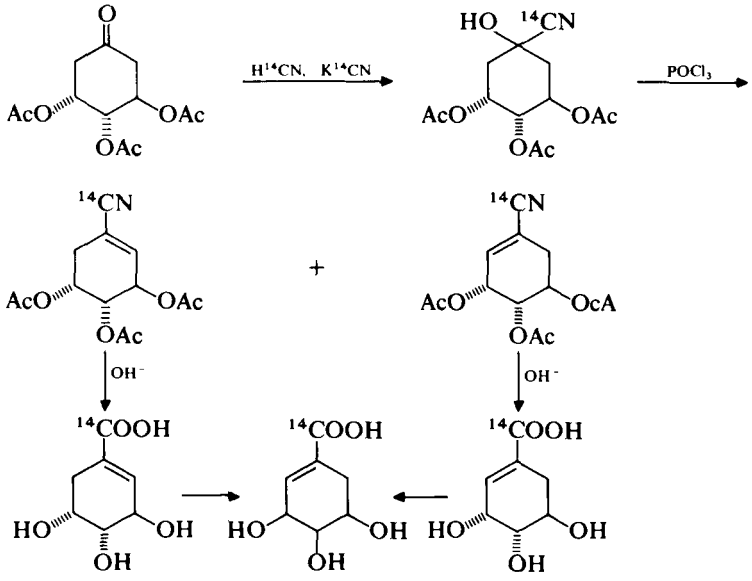
MK-9(II-H_2)



(238b)

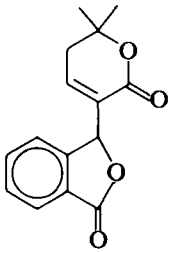
MK-9(II-H_2)

The mechanism of production of [4-^{14}C]-MK-9 (II-H_2; **238b**) in *Mycobacterium phlei* from [7-^{14}C]shikimic acid, synthesized in turn from (3*R*, 5*R*)-3,4,5-triacetoxycyclohexanone and H^{14}CN was investigated by Baldwin and coworkers[162] (equation 122).



(122)

The following ^{14}C-labelled naphthoquinone congeners were obtained[163,164] in the course of biosynthetic experiments in which 4-([carboxy-^{14}C]-2-carboxyphenyl)-4-oxobutanoic acid (**231**) was administered to callus tissues of *Catalpa ovata* grown for 2 weeks and incubated in the dark for 5 days: catalpalactone (**239**), α-lapachone (**240**), catalponone (**241**), menaquinone-1 (**242**), 3-hydroxydehydro-iso-α-lapachone (**243**), 1-hydroxy-2-methylanthraquinone (**244**) and lapachol (**245**). The above synthetic results and the



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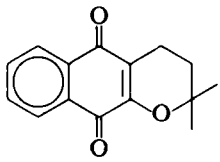

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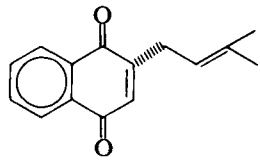

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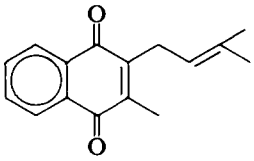

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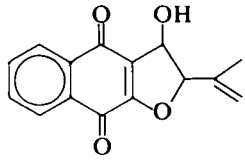
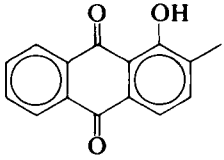


(243)



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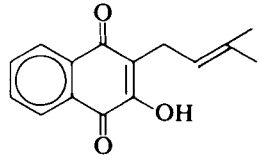

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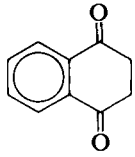

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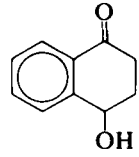
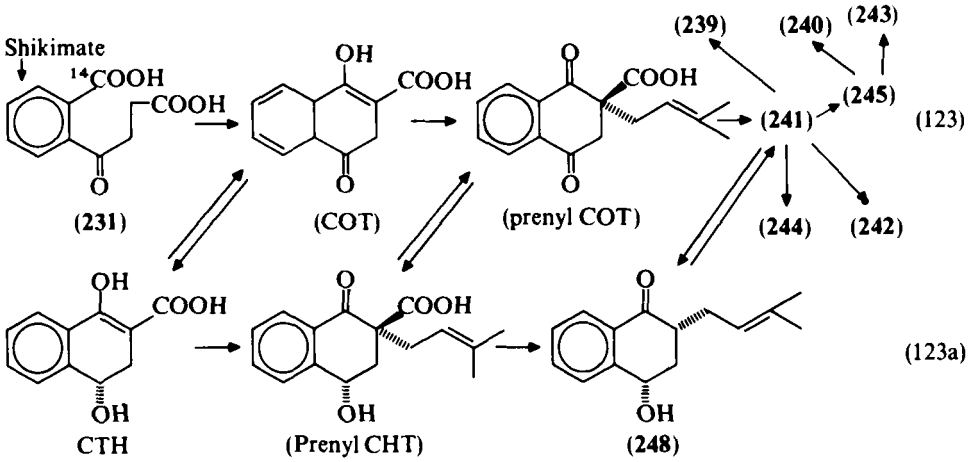


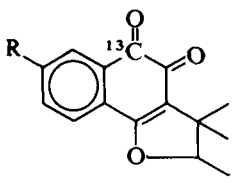
(247)

observation that **231** was incorporated into **246** in 3.75 times higher ratio than into **247** demonstrates that the naphthoquinones are biosynthesized stereospecifically in the callus tissues mainly according to the biosynthetic pathway of equation 123. It involves the intermediate compounds: 2-carboxy-4-oxo-1-tetralone (COT) and 2-carboxy-2-prenyl-4-oxo-1-tetralone (prenyl COT) while the route shown in equation 123a, involving 2-carboxy-4-hydroxy-1-tetralone (CHT) → 2-carboxy-4-hydroxy-2-prenyl-1-tetralone (prenyl CHT) → catalponol (**248**), is a subsidiary one. These conclusions were confirmed by administration of 4-([carboxy-^{14}C]-2-carboxyphenyl)-4-hydroxy[4-^{3}H] butanoic acid, obtained by reduction of [carboxy-^{14}C]-(**231**) with $NaB^{3}H_{4}$, to the callus cultures. Feeding of the doubly labelled compound to the wood of this plant was also performed in order to investigate the biosynthetic route in the wood. It has been demonstrated that COT is biosynthesized both in callus tissues and in wood by direct cyclization of **231** but not via



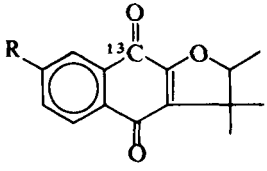
CHT. The observed formation of menaquinone-1 (**242**) from **241** suggests that vitamin K (especially plant origin phylloquinone) is similarly formed through the same prenylation mechanism shown above. All labelled intermediates and products were isolated from the growth medium as the stable methyl esters by isotopic dilution method.

Three unusually prenylated ^{13}C- and ^{2}H-labelled naphthoquinones, **249**, **250** and **251**, of *Streptocarpus dunnii* were biosynthesized by feeding *S. dunnii* cell suspension cultures with ^{13}C- and ^{2}H-labelled precursors, [2-carboxy-^{13}C]-4-(2-carboxyphenyl)-4-oxobutanoic acid (**252**) and [7-^{2}H]-lawsone (**253**), respectively[165a,b]. In the ^{13}C biosynthesis,



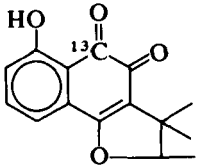
(**249**)

a: R = H
b: R = D

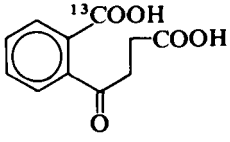


(**250**)

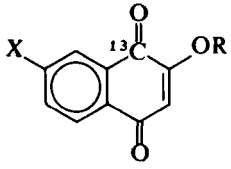
a: R = H
b: R = D



(**251**)



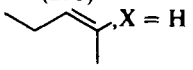
(**252**)

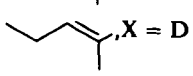


(**253**)

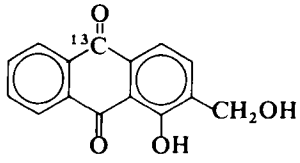
a: R = H, X = H
b: R = H, X = D

(**258**)

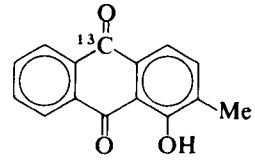
a: R=  , X = H

b: R=  , X = D

besides the dunniones **249a** and **250a**, the anthraquinones **254** and **255** labelled with ^{13}C in the 10-position were also obtained. Thus, it has been concluded that the naphthoquinones

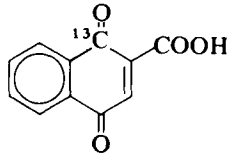


(254)

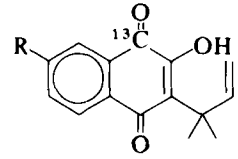


(255)

labelled with ^{13}C in the 1-position are biosynthesized from **252** via intermediates **256** and **253a**.



(256)

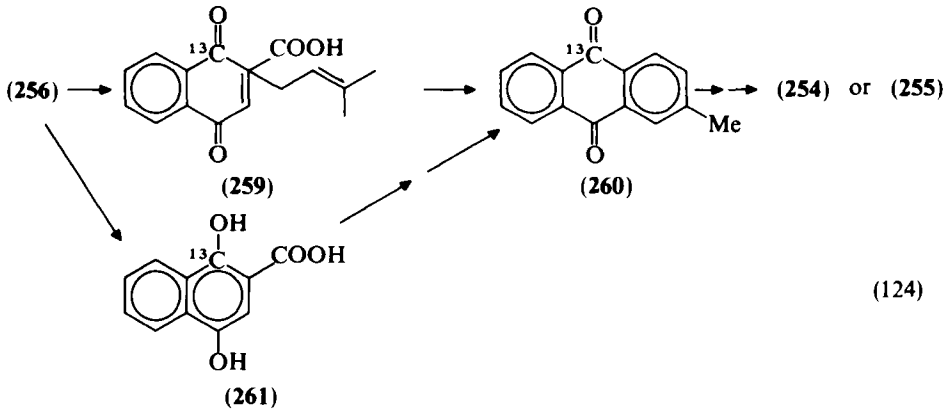


(257)

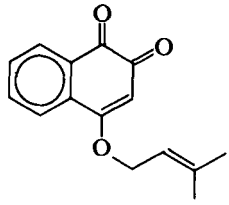
a: R = H
b: R = D

The lawsone **253a** was later prenylated at C(2) and the ether **258a** formed transformed via Claisen-type rearrangement to naphthoquinone (**257a**), which in turn was converted to labelled dunnione (**249a**), α-dunnione (**250a**) and 8-hydroxydunnione (**251**). Anthraquinones **254** and **255** are formed from **256** via the prenylation product **259** or the naphthoic acid (**261**) via the intermediate tectoquinone (**260**) (equation 124). The intermediacy of lawsone (**253**) in the naphthoquinone biosynthesis was established by feeding *S. dunnii* cultures with [7-^{2}H]-lawsone. Naphthoquinones **249b**, **250b** and **251** containing deuterium on C(7) were separated by silica gel chromatography.

No label was found in anthraquinones **254**, **255** and **260** derived from this culture. By adding the [7-^{2}H]-ether (**258b**) to the *S. dunnii* cell suspension cultures and isolating the intermediate **257b** and the deuterium-labelled products **249b**, **250b** and **251** from the post-reaction medium, the authors excluded the possibility of formation of the ether (**262**)



(124)



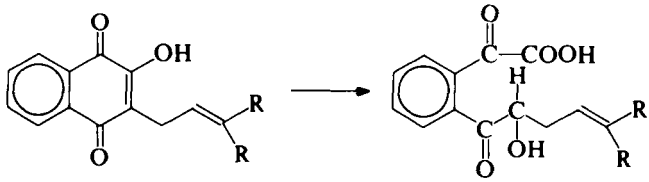
(262)

directly from **253** by prenylation, and its participation in the dunnione (**249**)-type naphthoquinone production[165].

Mass spectrometric evidence for 2-succinoylbenzoic acid and 1,4-dihydroxy-2-naphthoic acid as the menaquinone precursors and intermediates in menaquinone biosynthesis have been presented by Young[166]. The biosynthetic pathway leading to naphthoquinones, benzoquinones and anthraquinones has been reviewed by Leistner[167]. The structure of 1-hydroxy-2-(hydroxymethyl)anthraquinone (**254**), isolated from the leaves and roots of *Streptocarpus dunnii* has also been established by biosynthesizing labelled **254** using as potential precursors shikimic acid-[7-^{14}C], *o*-succinoylbenzoic acid-[2,3-^{14}C] and DL-mevalonic acid-[2-^{14}C][168a]. It has been shown that the OSB pathway is operative in the biosynthesis of this anthraquinone.

7. ^{18}O-Biooxidation studies with naphthoquinones

Lapachol (**245**) (possessing antitumour, antibiotic and antimalarial activities) and dichloroallyl lawsone (**245a**), incubated with several fungi and streptomycetes, undergo oxidative ring fission[168b] (equation 124a).

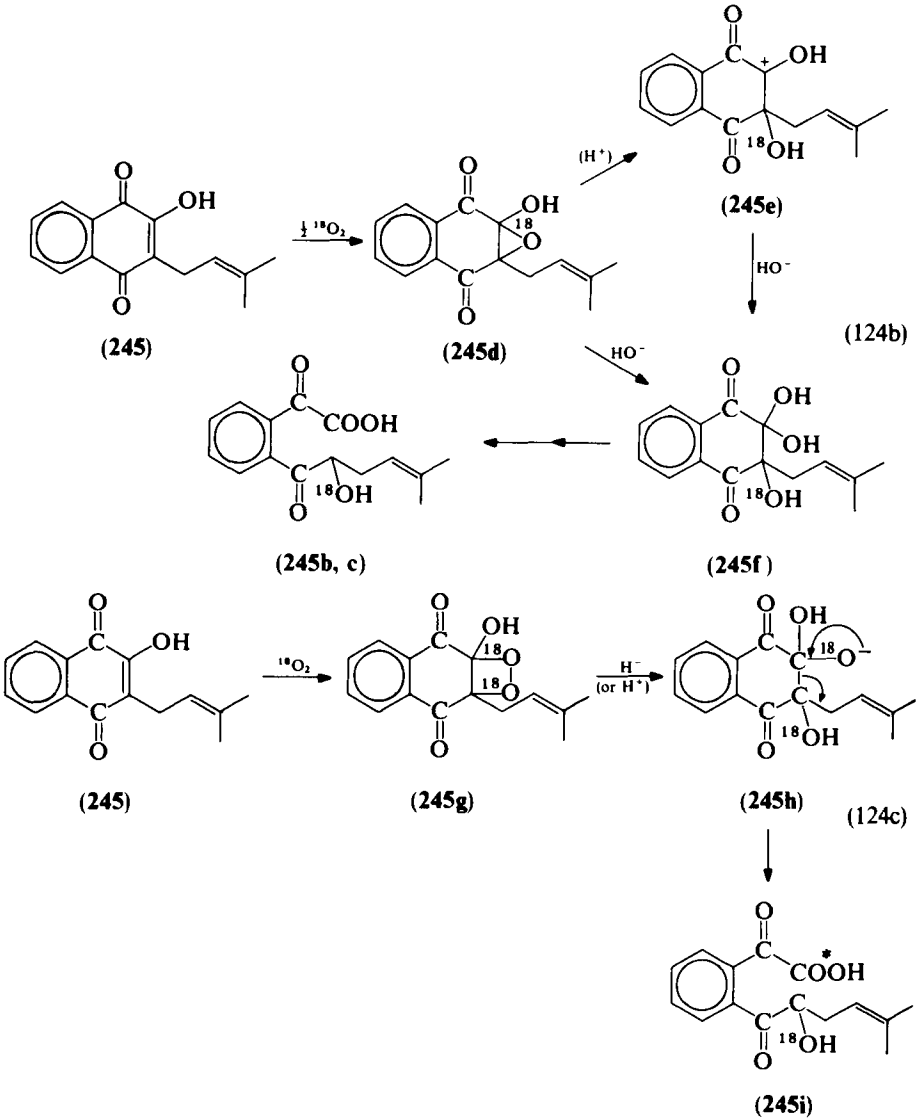


(124a)

(**245**) R = Me
(**245a**) R = Cl

(**245b**) R = Me
(**245c**) R = Cl

The compound **245c** was prepared also from dichloroallyl lawsone by treatment with H_2O_2 under alkaline conditions. Material obtained in chemical synthesis had the same infra red and mass spectra as the metabolite (**245c**) obtained in the biodegradation experiment. The mechanism of this process has been investigated by growing *Penicillium notatum* in $^{18}O_2$ atmosphere and subsequent mass spectral analysis of the oxygen-18 labelled ketol derivative (**245b**), obtained in the biodegradation of **245**. The location of heavy oxygen atom in the metabolite structure (**245b**) was accomplished by the use of the well defined mass spectral fragmentation pattern of the ketol metabolite (**245b**) prepared synthetically[168c] and metabolite derived from microbiological oxygenation of lapachol (**245**) by *P. notatum*. Analysis of mass spectral fragmentation pattern of **245b** showed that the ^{18}O label is located in the side chain hydroxyl group. No ^{18}O excess was found in the COOH moiety of **245b**. The conclusion was therefore made that molecular oxygen is introduced into lapachol via the monooxygenase pathway (124b), very likely by the initial formation of an epoxide (**245d**). In the acid or base-catalysed opening of the ring the oxygen atom is finally located as the secondary alcohol (**245b, c**).



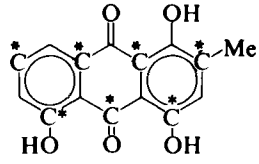
The second dioxygenase pathway (124c) of the metabolic conversion of **245** into the ketol derivative (**245i**) implies that two ^{18}O atoms, derived from molecular oxygen, are incorporated into a cyclic endoperoxy intermediate (**245g**) which, undergoing 'hydride or acid-catalysed opening', yields (**245i**) having excess oxygen-18 both in hydroxyl and in carboxylic acid groups. The lack of the noticeable excess of heavy oxygen in the carboxyl group forced the authors[168b] to reject the reaction sequence (124c). A special room temperature test experiment showed that oxygen-18 exchange (^{18}O scrambling) between carboxyl group of the metabolite (**245i**) and water during 24 hours of incubation at 27°C and subsequent work up procedure in acidic conditions did not take place. The possibility

of the carbon–carbon double bond cleavage and location of the heavy oxygen as the secondary alcohol (**245b**) according to acyclic type mechanism, analogous to scheme 43, is not taken into account in the biochemical mechanistic considerations.

D. Biosyntheses and Uses of Labelled Anthraquinones

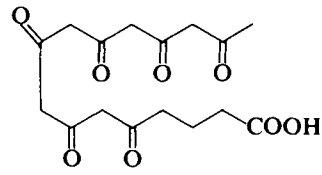
1. Biosynthesis of [^{14}C] and [^{13}C]islandicin

Carbon-14 labelled islandicin (**263**), a red pigment isolated from the mould *P. islandicum*, has been biosynthesized by Gatenbeck[169] from a polyketide chain precursor. Incorporation of $Me^{14}COONa$ into the *P. islandicum* culture resulted in the labelling pattern shown in **263**, which was confirmed subsequently[170] by incorporation of $Me^{13}COONa$ into the growing organism. Using 90% enriched ^{13}C doubly labelled acetate, $^{13}Me^{13}COONa$, it has been shown that islandicin is biosynthesized from the precursor **264**. The 2–2.5% incorporation level of ^{13}C was determined by adding $^{14}MeCOONa$ to [^{13}C]acetate. Prior to the ^{13}C-NMR resonance study[171] of the islandicin biosynthesized from $^{13}MeCOONa$, the isolated labelled product was converted with Ac_2O/py to the triacetate.



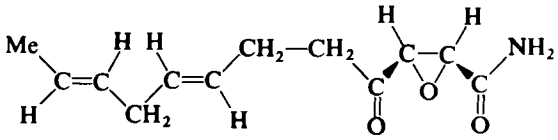
C* = ^{14}C or ^{13}C

(263)



(264)

The antibiotic cerulenin, (2*S*),(3*R*) 2,3-epoxy-4-oxo-7,10-dodecadienoylamide (**265**), isolated from the culture filtrate of the fungus *Cephalosporium caerulens*[172] is known as a specific inhibitor of fatty acid biosynthesis[173]. When added[174] to a culture in which



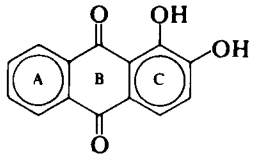
(265) cerulenin

vegetative mycelia of *Cortinarius orichalceus* were grown, it caused a simultaneous drastic decrease of the incorporation of the [1-^{14}C]acetate into both the mycelial triacylglycerols and the anthraquinone pigments emodin-6,8-dimethyl ether and anthraquinone physcion (produced also by the *C. orichalceus*). Cerulenin acts specifically on the polyketide formation. Hence the drastic decrease of the radioactivity incorporated into emodin-6,8-dimethyl ether in the presence of cerulenin confirms the suggestion that the biosynthesis of anthraquinones in higher fungi takes place via a condensation reaction of acetyl-CoA and malonyl-CoA, formation of an intermediate polyketo acid which undergoes intramolecular condensation, and cyclization.

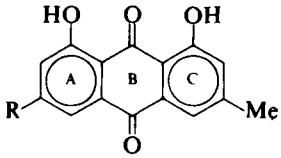
2. Biosynthesis of chrysophanol and emodin

Two different modes of incorporation of [^{14}C]acetate into structurally different types of anthraquinones were established[175] by biosynthesis of chrysophanol (**267**) and emodin

(**268**) in *Rhamnus frangula* and *Rumex alpinus* from [1-^{14}C]acetate and [2-^{14}C]acetate. Radioactivity from [^{14}C]acetate enters only into ring C of alizarin (**266**), while the radioactivity from [^{14}C]acetate was found to be equally distributed in chrysophanol. The outlined differences were explained by suggesting that ring C of alizarin is derived from mevalonic acid which itself originates from acetate, whereas the chrysophanol is synthesized from an anthraquinone precursor in the course of cyclization of the polyketide unit derived from labelled acetate by linear combination.



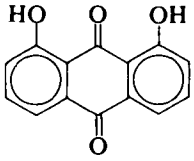
(**266**)



(**267**) R = H

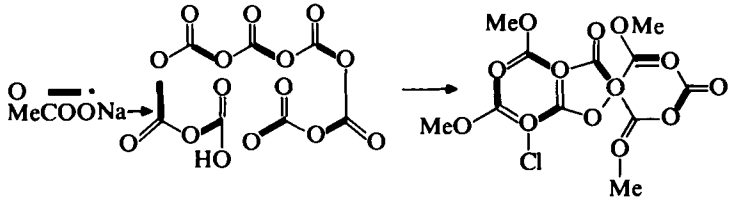
(**268**) R = OH

[^{14}C]Shikimate and [^{14}C]mevalonate did not incorporate into **267** or **268**. Carbon-14 labelled **267**, **268** and chryzasin **269** were also biosynthesized by *Rumex obtusifolius* from [1-^{14}C] and [2-^{14}C]acetates[176].



(**269**)

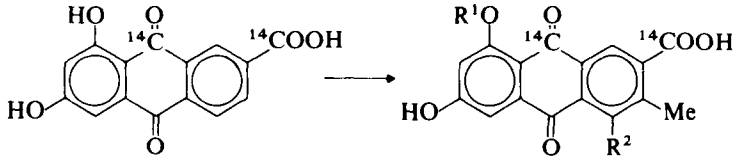
The isolated radioactive anthraquinones were degraded to phthalic and hydroxyphthalic acids. Comparison of the radioactivity present in the isolated acids and in the yellow quinones suggested that the acetate malonate route is used for producing anthraquinones in these higher plants. The metabolism of anthraquinones in the developing inflorescences was investigated by feeding radioactive anthraquinones, obtained from plants which had been grown in $^{14}CO_2$, to 20 young inflorescences. The results indicate that anthraquinones are rapidly utilized in the early stages of fruit formation. Their rate of conversion during the next period is slower though continues to be steady, similar to what has been found in developing fruits of *Cassia acutifolia* L.[177]. Singly and doubly labelled [^{13}C]acetates were also effectively[178] incorporated into griseofulvin (**270**), an important antifungal antibiotic, by a mutant strain of *Penicillium patulum*, by simple folding of a single heptaketide chain (equation 125). By feeding[179] the ammonium salt of



(125)

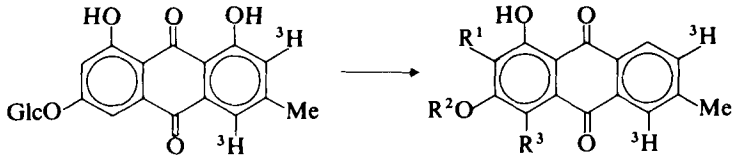
(**270**)

endocrocin (**271**) ^{14}C-labelled at C(9) and in the carboxyl group[180] to young mushrooms *Dermocybe sanguinea* it has been shown that **271** is the precursor only of the carboxylic acids **272** and **273** (equation 126). In a second experiment the labelled precursor [2,4-



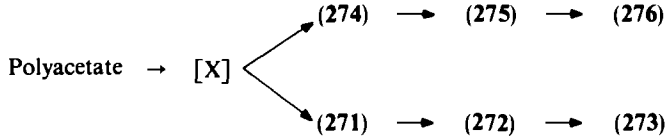
(271) (272) $R^1 = R^2 = H$ (273) $R^1 = Me$, $R^2 = H$ (126)

$^3H_2$]emodin-6-mono-β-D-glucoside (**274**) was administered to young *D. semisanguinea* (Bull. exFr). Only the tritium-labelled neutral pigments **276** and **275** were obtained (equation 127). It has therefore been suggested that anthraquinones are biosynthesized



(274) (275) $R^1 = OH$, $R^2 = Me$, $R^3 = H$ (276) $R^1 = R^3 = OH$, $R^2 = Me$ (127)

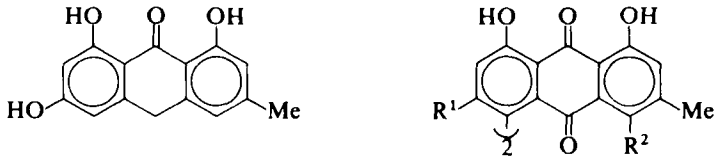
according to equation 128, which involves either endocrocin-9-anthrone or a compound in which the ring carrying the carboxyl group is not yet aromatic, such as the common precursor [X] of anthraquinones[179-181]



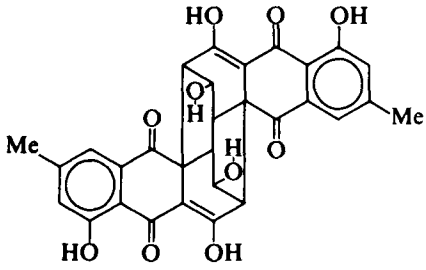
(128)

Emodin-6-mono-β-D-glucoside (**274**) labelled with tritium in the non-labile 2 and 4 positions has been obtained by tritium exchange reaction between emodin (**268**) and 0.7 N KOT water solution during 24 h at 110 °C. Tritium from the hydroxyl groups and from relatively labile 5- and 7-T positions of the emodin molecule has been washed out by heating hydroxyl-^3H and [2,4,5,7-$^3H_4$]tritium-labelled emodin with 0.7 N KOH during 3 h at 110 °C and converting the product, labelled in [2,4-$^3H_2$] positions, into the monoglucoside[181]. In the preliminary deuterium exchange experiment it has been found that at 100 °C the aromatic protons of emodin are completely exchanged with 0.7 N KOD in the following decreasing order: 7-H (during 15 min) > 5-H (ca. 60 min) > 2-H (ca. 12 h) > 4-H (ca. 24 h)[181].

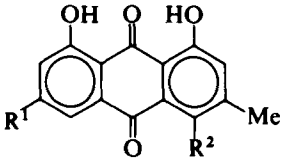
Efficient biosynthetic incorporation of ^{14}C-labelled emodinanthrone (**277**) as well as of [^{14}C]emodin into both dimeric skyrins (**278**, **279**) and (+) rugulosin (**280**), dimeric anthraquinonoids of *Penicillium brunneum* and *P. islandicum*, has been investigated by Sankawa and coworkers[182].



(277) (278) $R^1 = OH$, $R^2 = H$ (279) $R^1 = H$, $R^2 = OH$



(280)

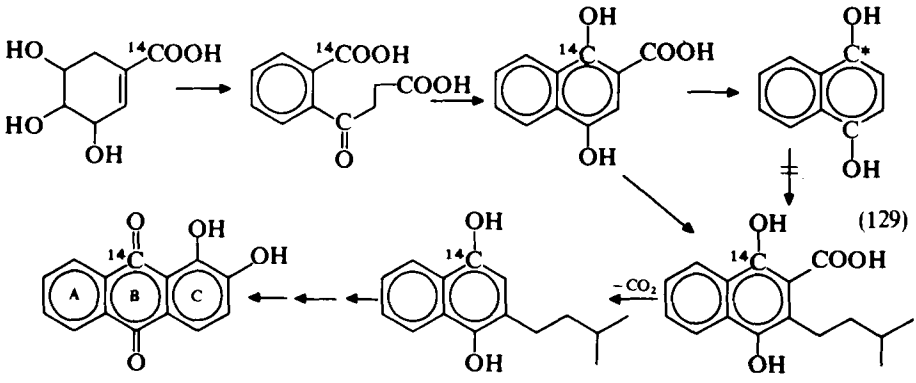


(281) $R^1 = R^2 = OH$
(263) $R^1 = H$, $R^2 = OH$
(267) $R^1 = R^2 = H$

No incorporation of [^{14}C]catenarin (**281**) into islandicin (**263**) was found and it has been suggested that the hydroxylation must take place after partial hydrogenation of the ring. Catenarin (**281**) produced biosynthetically does not undergo biohydrogenation.

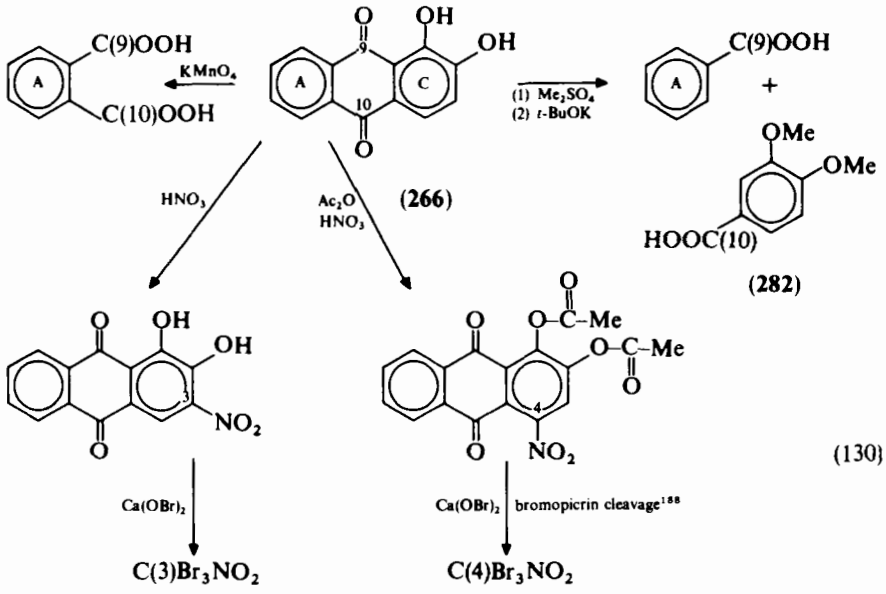
3. Biosynthesis of ^{14}C-labelled alizarin

The mechanism of biosynthetic incorporation of shikimic acid into alizarin (**266**) in *Rubia tinctorum* has been investigated[183] by using carboxyl-^{14}C-labelled shikimic acid which is known to be incorporated as an intact C_7 unit into vitamin K, juglone, lawsone and alizarin. In the case of 5-hydroxy-1,4-naphthoquinone (juglone, **215**) the carboxyl group of shikimic acid is incorporated into both keto-C-atoms to an equal extent[184]. In the case of alizarin biosynthesis in *Rubia tinctorum* a non-symmetrical incorporation of [^{14}C]carboxyl group of shikimic acid was found and the biochemical sequence given in equation 129 was suggested. The phthalic acid obtained in the degradation of [^{14}C]alizarin



(266) (129)

had the same specific radioactivity as the starting material, the benzoic acid obtained contained about 50% of the activity of alizarin, whereas veratric acid, whose carboxyl group corresponds to the keto-C(10) atom of alizarin was almost inactive. A symmetric compound like 1,4-naphthoquinol was thus excluded as an intermediate in the biosynthesis of [^{14}C]alizarin. After [1,2-^{14}C]shikimate feeding, the radioactivity in alizarin was confined only to ring A[185]. In a subsequent ^{14}C tracer experiment[186] the synthesis of alizarin was taking place in the cut off *Rubia tinctorum* roots fed with carboxyl-[^{14}C]-D-shikimic acid and [5-^{14}C]mevalonic acid. The labelled alizarin degraded according to equation 130. The results of degradation showed that:

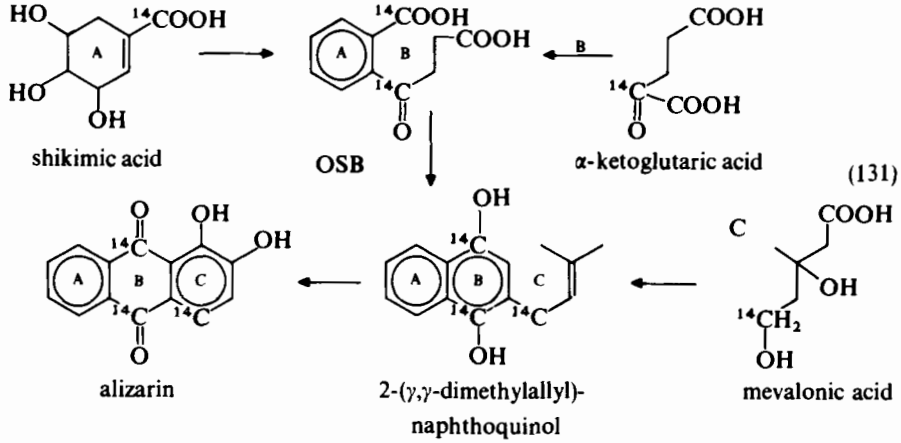


(130)

(1) After [7-^{14}C]shikimate feeding the carboxyl group of shikimic acid is exclusively incorporated non-symmetrically into the C(9) atom of alizarin. Veratric acid (**282**), the carboxyl group of which is derived from the C(10) atom of alizarin contains no radioactivity, while benzoic acid, formed by the degradation procedure of Davies and Hodge[187], contains all the radioactivity. Phthalic acid contained all the radioactivity corresponding to the keto-C-atoms of alizarin.

(2) After [5-^{14}C]mevalonic acid feeding, the activity from mevalonic acid enters specifically into position 4 of alizarin[188]. The C(3) atom did not contain any radioactivity. This suggests that ring C(1) to C(4) carbons are derived from mevalonic acid by way of γ,γ-dimethylallylpyrophosphate.

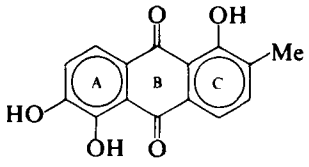
Further biochemical experiments with [2-^{14}C]glutamate indicated that its carbon-14 incorporates specifically into C(10) of alizarin. Therefore the general scheme of equation



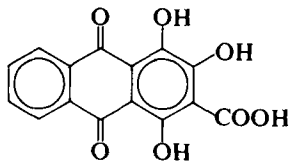
(131)

131 for radioactivity flow from different precursors to alizarin has been proposed. It does not include symmetrical intermediates like 1,4-naphthoquinone or 1,4-naphthoquinol.

Incorporation of ^{14}C-labelled compounds into morindone and alizarin anthraquinone skeleton by intact plants and cell suspension cultures of *Morinda citrifolia* has also been investigated[189]. In the case of anthraquinones produced by cell-suspension cultures, 1-methoxy-3-hydroxyanthraquinone-2-carboxaldehyde ('damnacanthal') was the most abundant, whereas alizarin and morindone (**283**) are produced in minor quantities.



(**283**)



(**284**)

Morindone is the most abundant anthraquinone in the intact 1-year-old plants. The main degradation product of morindone was veratric acid derived from ring A plus C(9). Alizarin was split into benzoic acid and veratric acid. The incorporation of [1-^{14}C]acetic acid, [2-^{14}C]-DL-mevalonic acid and [U-^{14}C]-D-glucose into both intact plants and plant suspension cultures of *Morinda citrifolia* was negligible. No incorporation was obtained with mevalonic acid. Highest incorporation of [7-^{14}C]-D-shikimic acid and *o*-(succinoyl-4-^{14}C) benzoic acid (OSB) carboxyl-^{14}C was found. ^{14}C Tracer degradation studies showed that the radioactivity from [7-^{14}C]shikimic acid and OSB carboxyl-^{14}C incorporates specifically into the C(9) position of alizarin and morindone. It is suggested that ring C of anthraquinones, biosynthesized in *Morindona citrifolia*, is derived from mevalonic acid and the hydroxy groups are introduced at a later stage of the biosynthetic pathway. This is similar to what has been found for the incorporation of OSB into juglone[156]. Purpurin carboxylic acid (**284**) is derived from shikimic acid, glutamic acid and mevalonic acid by way of OSB in a similar way to the alizarin biosynthesis of equation 131.

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CHAPTER 20

The solid state photochemistry of tetrahydronaphthoquinones: crystal structure–reactivity relationships

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I. INTRODUCTION

The photochemistry of quinones, including their photochemical behavior in the solid state, was reviewed in Part 1 of *The Chemistry of Quinonoid Compounds*[1]. The present chapter summarizes the photochemistry of a class of compounds that is closely related to the *p*-quinones, namely the tetrahydro-1,4-naphthoquinones. A great majority of the work described has been carried out in our laboratory over the past 12 years, and we include some results that have not been published previously. The article is concerned primarily with the crystal structures of compounds containing the 2-en-1,4-dione (ene-dione) chromophore and the photochemical reactions that these molecules undergo in the crystalline phase. The solution phase photochemistry of these systems, which has also been investigated in detail in our laboratory, will be discussed in this review only to compare and contrast it with the solid state results.

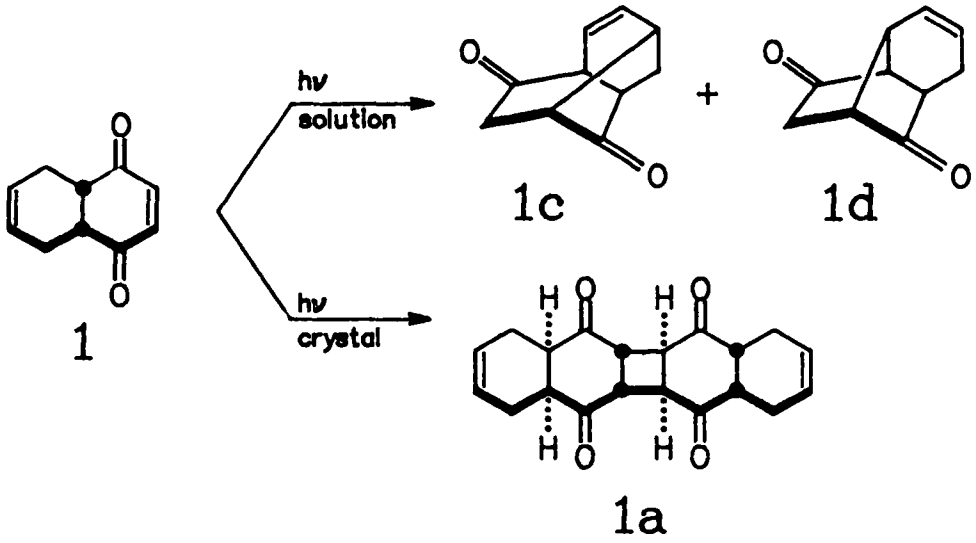
The study of chemical reactions in the solid state and the interpretation of the results in terms of the conformation and packing arrangement of the molecules that make up the crystal lattice have provided unparalleled insights into the mechanistic features of both bimolecular and unimolecular processes[2]. This arises from two properties that are unique to the crystalline phase: (1) determination of the crystal structure by X-ray diffraction methods provides a detailed, three-dimensional view of the reaction ensemble immediately prior to reaction, and (2) because of the relatively strong forces that hold crystals together, atomic and molecular motions are restricted, and chemical reactions in crystals tend to be least motion in character such that the transition states, intermediates and products closely resemble the reactants in shape and volume. As a result, the chemical reactivity of a given molecule in its crystalline phase frequently differs from its chemistry in liquid phases or the gas phase, and this provides a further impetus for carrying out chemical studies in solids.

The first investigation of ene-dione photochemistry in the solid state was carried out by Diels and Alder in 1929[3]. They found that exposure of crystals of the *p*-benzoquinone/1,3-butadiene adduct **1** (Scheme 1) to sunlight yielded a high-melting isomer or polymer. In 1964, Cookson and coworkers[4] briefly reinvestigated this reaction and concluded that intermolecular [2 + 2] photocycloaddition had occurred across the ene-dione double bond to give a dimer. The extreme insolubility of the dimer prevented its complete characterization or the determination of its stereochemistry. In the same paper[4], Cookson and colleagues reported that photolysis of **1** in solution 'gave only tars'. In the early 1970s, we became interested in the photochemistry of **1** and its derivatives, and it is this work with which the majority of this article is concerned.

II. INITIAL STUDIES

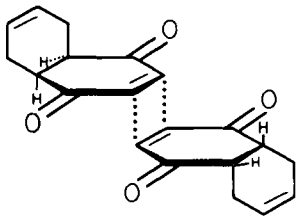
In agreement with the findings of Cookson and coworkers, we too observed extensive tar formation when **1** was photolyzed in benzene or *t*-butanol[5]. Careful examination of the crude reaction mixture, however, revealed that two rearrangement products, subsequently shown to be diketones **1c** and **1d**, were present in a combined yield of approximately 10% (throughout this review, the letters **a**, **b**, **c** etc. are used to refer to photoproduct structural types. Scheme 1 thus indicates that irradiation of ene-dione **1** gives no type **b** product). The structure of photoproproduct **1d** rests on a crystal structure determination[6]. Also in agreement with Cookson's report, we found that irradiation of crystals of **1** gave dimeric material[7]. The dimer was assigned the structure and stereochemistry **1a** on the basis of an X-ray crystal structure analysis[8] and the crystal and molecular structure of ene-dione **1** was also determined[9].

The results outlined in Scheme 1 raise two major questions: (1) why does ene-dione **1** react differently in solution and the solid state, and (2) of the many possible stereoisomeric dimers, why is only **1a** formed in the solid state? The answer to both questions is found in



SCHEME 1

the crystal structure of ene-dione **1**, in which two neighboring molecules are arranged as shown schematically below; the ene-dione double bonds of neighboring molecules are oriented in an arrangement very favorable for [2 + 2] photocycloaddition; the double bonds approach each other in a parallel, top-to-bottom fashion with a center-to-center distance of 3.76 Å. Most significantly, the incipient dimer pair has a stereochemical relationship that is identical to that found in the photoproduct **1a**. Thus the dimer

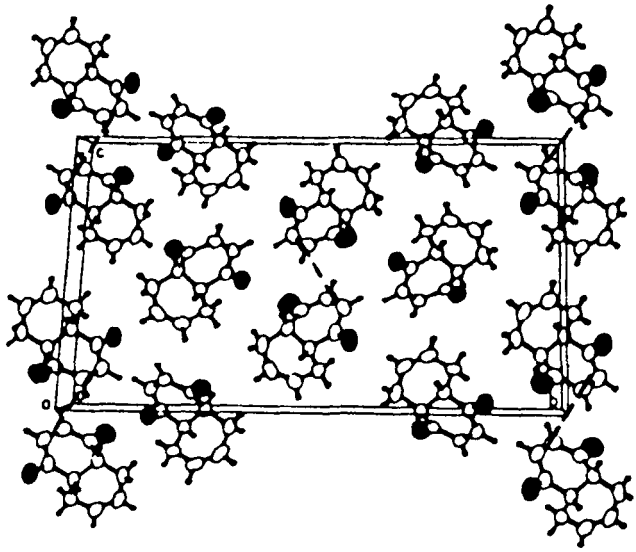


structure and stereochemistry are governed by the positions of the molecules in the crystal lattice (topochemical control), and this accounts for the stereoselectivity of the process. In solution, however, no fixed orientation exists between neighboring molecules, and they undergo unimolecular photorearrangement rather than dimerization. A discussion of the mechanism of the rearrangement is deferred to a later section of the review.

The photochemistry of ene-dione **1** is very similar in principle to the classic case of the cinnamic acids studied by Schmidt[2e]. In solution, the cinnamic acids undergo unimolecular photochemistry (*cis, trans* photoisomerization), whereas in the solid state they take part in [2 + 2] photodimerization owing to a favorable orientation between the double bonds of adjacent molecules. Based on the study of several examples, Schmidt suggested that a parallel, top-to-bottom approach with a center-to-center distance between double bonds of < 4.1 Å is required for efficient solid state photodimerization;

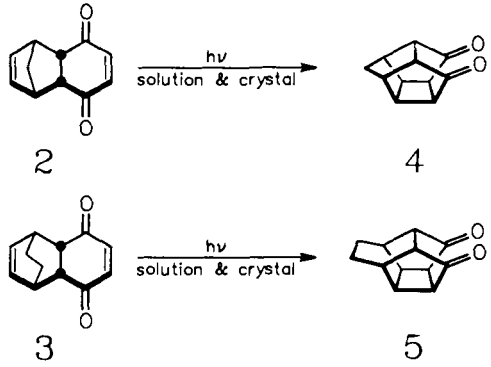
ene-dione **1** thus obeys Schmidt's rule, and this rule has been verified in a number of other instances as well[10].

An interesting aspect of the crystal structure of ene-dione **1** is that there are two independent molecules in the asymmetric unit as shown below. The two molecules have



shapes (conformations) which differ only slightly; however, they differ dramatically in packing arrangement. One (discussed above) forms pairs about centers of symmetry, with 3.76 Å between double bonds; the other molecule has a nearest neighbor, non-parallel double bond separation of 5.27 Å, and is unsuitable for dimer formation. Because the two molecules are present in equal amounts in the crystal, the maximum chemical yield of dimer **1a** is predicted to be 50%. The observation of yields considerably above 50% was taken as an indication that some dimer may be forming at dislocation sites and defects that are developed in the crystal during the later stages of reaction[7].

In 1964, Cookson and coworkers[4] also reported that irradiation of crystals of the ene-diones **2** and **3** (Scheme 2), affords high yields of the corresponding *intramolecular* [2 + 2]

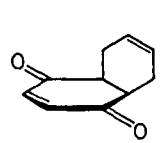


2 4

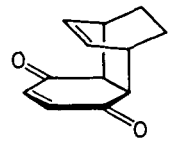
3 5

SCHEME 2

cycloadducts **4** and **5**. The same photoproducts were formed in solution, and no photorearrangement or intermolecular [2 + 2] photocycloaddition was observed. In order to investigate the reasons for these reactivity differences, Greenhough and Trotter[11] determined the crystal and molecular structure of ene-dione **3**. This showed that there are no close, parallel double bond contacts between lattice neighbors, hence no intermolecular [2 + 2] photocycloaddition in the solid state. This study also showed that the conformations of ene-diones **3** and **1** are quite different. These conformations are contrasted in the figure below. The carbon–carbon double bonds in **3** are parallel, with a center-to-center distance of 3.53 Å. This conformation clearly favors intramolecular photocycloaddition, as is observed. On the other hand, the conformer present in crystals of ene-dione **1** is not conducive to internal cycloaddition.

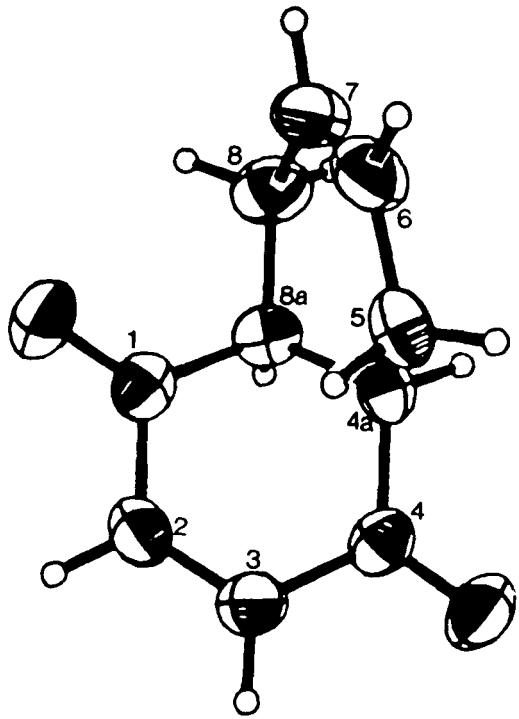


1



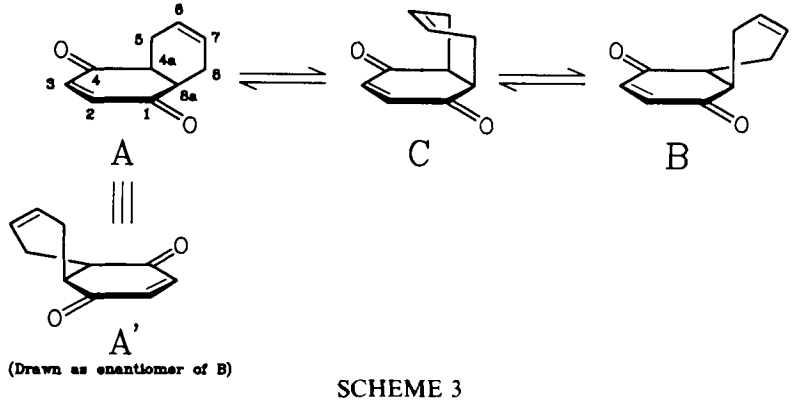
3

The conformations of ene-diones **1** and **3** in the solid state provide insight into the dynamic situation present in solution. The X-ray crystal structure study of **1** indicates that the molecule exists in a 'twist' conformation with staggered bridgehead hydrogen atoms (torsion angle of 60° about the C(4a)–C(8a) bond):



Both six-membered rings have half-chair conformations with approximately planar π-bond systems; bond torsion angles are 0–59°, mean 29° in the cyclohexene ring, and 2–52°,

mean 26°, in the ene-dione ring, so that the latter ring is slightly flatter. As illustrated in Scheme 3, two such 'twist' conformations (**A** and **B**) are possible for ene-dione **1**. Conformers **A** and **B** have equal energy (they are enantiomeric), and both are present in the racemic crystals of **1** and are related by a half-chair to half-chair conformational inversion of the cyclohexene ring. The equilibrium between **A** and **B** passes through the eclipsed conformer **C**. **C** can be either *endo* (shown) or *exo* (not shown); only *endo*-**C** is capable of intramolecular [2 + 2] photocycloaddition. The Diels–Alder adducts **2** and **3**, which are *endo*, are forced into conformation **C** by the one- and two-carbon bridges across positions C(5) and C(8), and this accounts for their photochemistry (internal [2 + 2] cycloaddition), both in solution and the solid state.

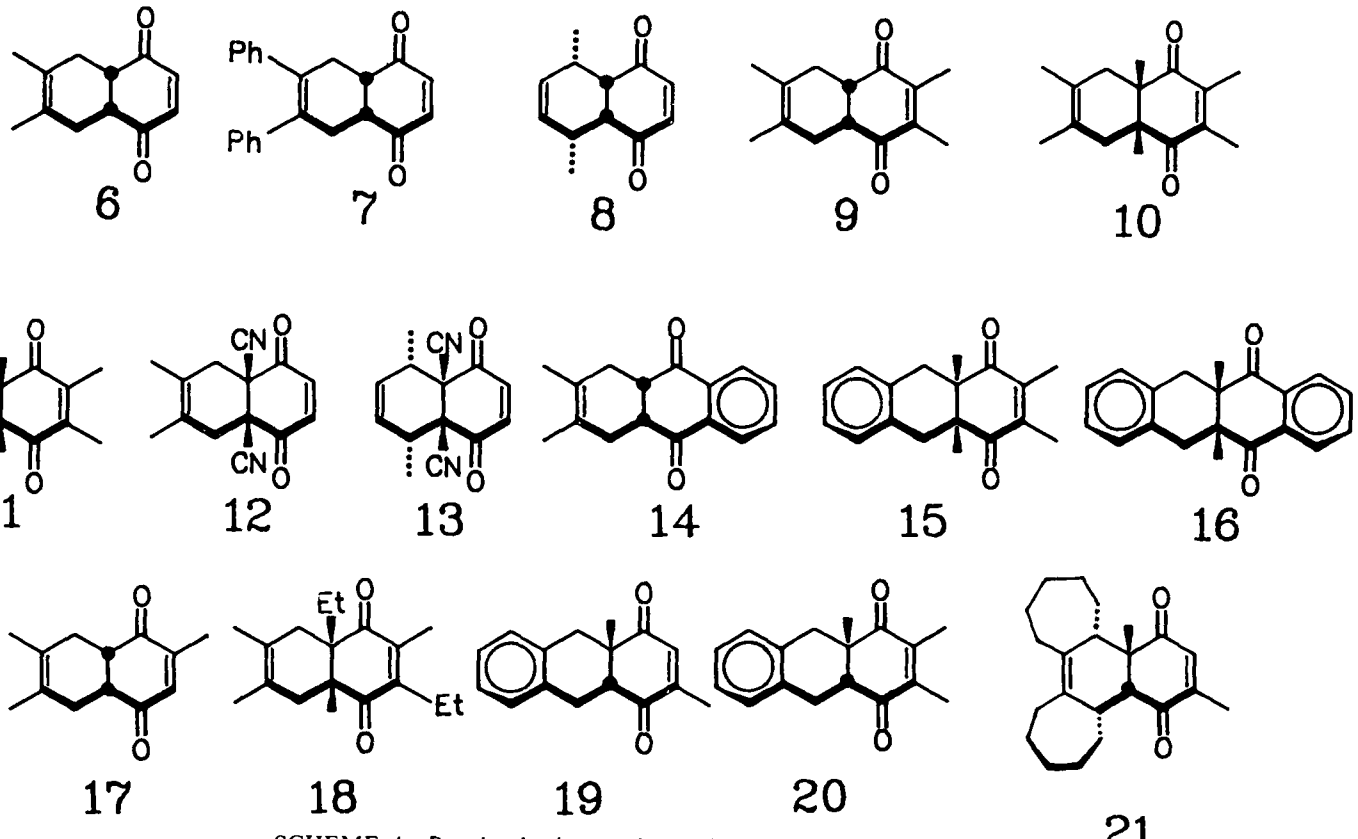


SCHEME 3

We have carried out variable temperature NMR studies on a number of ene-diones that give quantitative information on the energy barriers separating conformers **A** and **B**[12]. Because **A** and **B** lack symmetry, nominally equivalent atoms [e.g. C(1) and C(4)] are magnetically non-equivalent. However, if the equilibrium between conformers **A** and **B** is rapid on the NMR time-scale, an average plane of symmetry is established, and the spectrum is simplified accordingly. We found[12] that the equilibrium between conformers **A** and **B** for ene-dione **1** could not be frozen out at temperatures as low as −90°C. However, with the introduction of methyl groups at the bridgehead atoms C(4a) and C(8a), the coalescence temperature was in the −60 to −70°C range, and the free energy of activation for the conformational equilibrium was determined to be 8.7–9.2 kcal mol^{-1}. The *solid state* magic angle spinning ^{13}C-NMR spectra of **1** and substituted derivatives of **1** are also most informative[12, 13]. For instance, the number of independent molecules in the asymmetric unit can be established quickly by noting the signal multiplicity of nominally equivalent carbon atoms. In the case of **1** (two independent molecules per asymmetric unit), there are four carbonyl carbon signals, two for each independent molecule; ene-diones with only one molecule in the asymmetric unit show carbonyl carbon doublets.

III. COMPOUNDS STUDIED: SYNTHESIS OF STARTING MATERIALS

In this chapter we shall discuss the X-ray crystallography and solid state photochemistry of 17 separate ene-diones, **1** and **6**–**21** (Scheme 4). All were prepared through relatively straightforward Diels–Alder chemistry. Compounds **6**, **7**, **8**, **9**, **10**, **12**, **14** and **17** were known when this work began; the others (except for **21**) were prepared for the first time in our laboratory. The unusual ene-dione **21** was prepared, photolyzed and its crystal structure determined by Weisz and coworkers[14]. Ene-diones **15**, **16**, **19** and **20** required the



SCHEME 4 Regular, broken, or heavy lines indicate methyl groups.

use of *o*-quinodimethane as the Diels–Alder diene[15]. The general philosophy behind the choice of ene-diones **6–21** was to determine what effect the presence of substituents has on the crystal structures and photochemistry of the basic tetrahydronaphthoquinone system **1**.

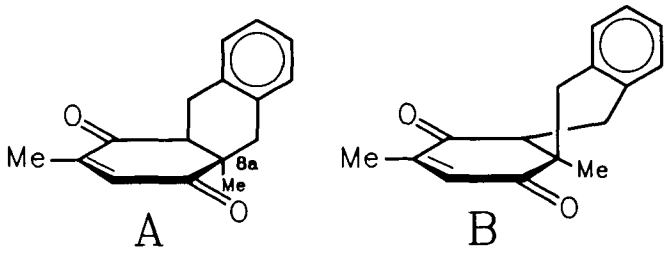
IV. CRYSTALLOGRAPHIC STUDIES

The crystal structures of ene-diones **1** and **7–21** have been determined by X-ray diffraction methods (Table 1, crystals of **6** were not suitable for crystallographic studies)[14, 16]. The striking result of the X-ray crystallographic investigations is that *all the compounds studied crystallize in twist conformations*, similar to that described above for **1**.

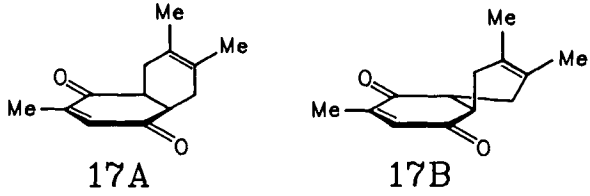
TABLE 1. Crystal data for compounds **1** and **7–21**

Ene-dione	Space group	**a** α	**b** β	**c** (Å) γ (°)	Z	R
1	$P2_1/c$	5.266	24.267 114.50	14.506	8	0.062
7	C2/c	27.092	6.527 120.56	22.112	8	0.053
8	$P2_1/c$	7.189	22.241 106.51	6.843	4	0.048
9	$P2_1/c$	5.245	29.452 106.44	8.278	4	0.072
10	$P2_1/c$	7.312	11.540 92.26	16.674	4	0.088
11	C2/c	24.930	7.795 101.13	14.472	8	0.070
12	$P2_1/c$	8.717	12.464 117.87	12.783	4	0.055
13	Pbcn	15.915	11.525	13.157	8	0.046
14	$Pna2_1$	15.643	5.160	15.568	4	0.040
15	Cc	6.877	22.377 101.68	9.972	4	0.037
16	$P\bar{1}$	9.907 80.54	12.094 85.03	13.049 89.73	4	0.044
17	$P2_1/n$	19.191	5.278 90.70	22.330	8	0.094
18	$P2_1/n$	21.557	7.932 95.79	9.525	4	0.039
19	$P\bar{1}$	6.834 85.46	9.817 73.48	10.071 76.71	2	0.041
20	$P2_1/a$	9.833	8.065 102.69	17.377	4	0.052
21	$P2_1/n$	18.389	15.398 90.22	6.370	4	0.061

Particularly noteworthy are the crystalline phase conformations of the asymmetrically substituted ene-diones **17–21**. In contrast to the symmetrically substituted ene-diones (**1** and **6–16**), in which conformers **A** and **B** (see Scheme 3) have equal energy and are present in equal amounts in the solid state (none of the compounds discussed in this review crystallizes in chiral space groups), the asymmetrically substituted systems have conformers **A** and **B** that are *not* isoenergetic. For example, the two possible twist conformations for ene-dione **19** are shown below. The main difference between them in



terms of their relative conformational energies is the environment of the methyl group at C(8a); in conformer **A** it is pseudoequatorial with respect to the cyclohexene ring, and in conformer **B**, it is pseudoaxial. The crystal structure of **19** reveals the presence of only conformer **A**. From this we conclude that the cyclohexene ring controls the conformation of this molecule. This is reasonable in view of the fact that the ene-dione ring is more nearly planar than the cyclohexene ring and thus interacts sterically to a lesser extent with the methyl substituent. The vinyl methyl group, which has no significant steric interactions with the rest of the molecule, appears to play no role in determining conformation. These arguments are strengthened by the crystal conformations found for ene-diones **19** and **21**. Both adopt conformations in which the bridgehead methyl group is pseudoequatorial with respect to the cyclohexene ring rather than the ene-dione ring. In the case of ene-dione **18**, the exclusive solid state conformation is the one that places the slightly bulkier ethyl group pseudoequatorial to the cyclohexene ring. The situation in the case of ene-dione **17** is unusual. This molecule is asymmetrically substituted, but contains no substituents that can be pseudoaxial or pseudoequatorial. As a result, the molecule crystallizes with *both* conformers **A** and **B** (below) present in equal amounts, presumably because the C(2) methyl group contributes very little to the molecular conformational energy, and the conformers are isoenergetic.



An exception to the rule is ene-dione **20**. This material crystallizes in a conformation that places the bridgehead methyl group *pseudoaxial* with respect to the cyclohexene ring. We believe this to be the less stable conformer because in solution reaction occurs predominantly from the conformation in which the methyl group is pseudoequatorial to

the cyclohexene ring (*vide infra*). As yet, we have not identified the crystal packing factors that favor the solid state conformation.

A general conclusion that emerges from the crystallographic studies is that for ene-diones, intrinsic conformational energy rather than crystal packing energetics usually, but not always, determines the conformations that are adopted in the solid state. With the exception of ene-dione **20**, the crystal conformations are those predicted by the rules of classical conformational analysis to be of lowest energy. This provides clear evidence for the idea that organic molecules generally crystallize in a single conformation that corresponds to the minimum energy conformation in solution[17].

Turning now to the crystal packing arrangements in ene-diones **6–21**, it was found that only compound **8** packs in an arrangement suitable for intermolecular [2 + 2] photodimerization. The photochemistry of **8** will be discussed in a later section, but we may note at this point that it *does* undergo dimerization in the solid state. A second type of photodimerization reaction is also possible. This is intermolecular hydrogen atom abstraction by a ketone oxygen atom followed by carbon–carbon bond formation between the radicals thus generated. This type of process has been demonstrated by Lahav and coworkers in crystalline inclusion complexes formed between deoxycholic acid and various aliphatic and aromatic ketones[18]. As far as we are aware, however, this reaction has never been observed in a homomolecular crystalline material. It was of considerable interest, therefore, that we encountered evidence for this process as a minor component of the solid state reactivity of ene-diones **17** and **20**. This is discussed in more detail in the sections that follow.

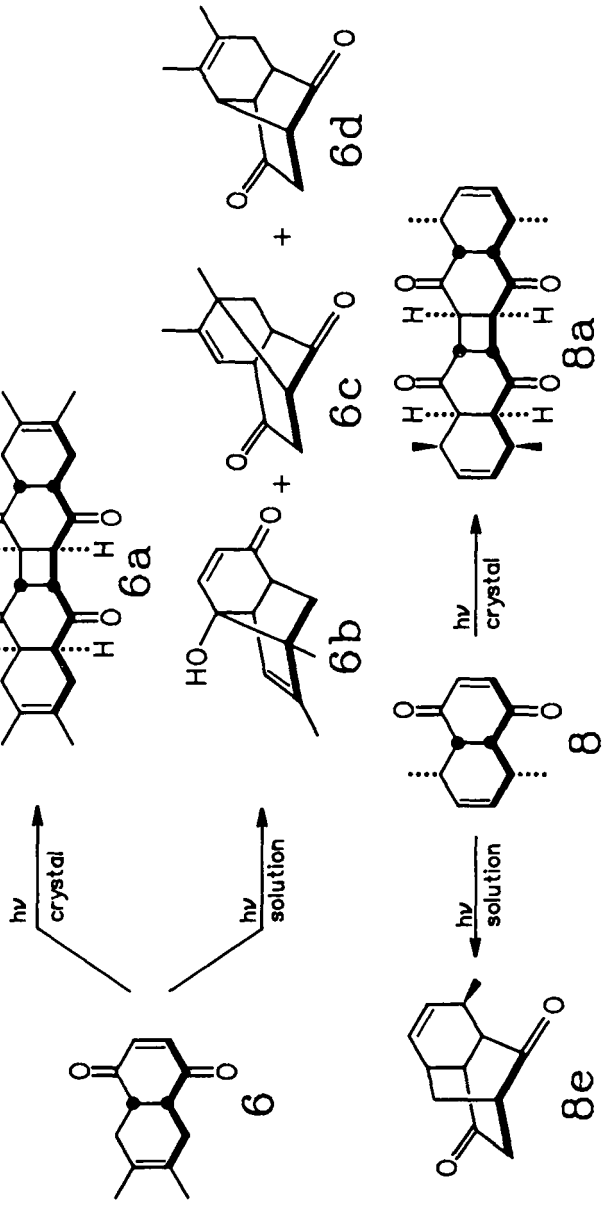
V. PHOTOCHEMICAL RESULTS: SOLID STATE STRUCTURE–REACTIVITY CORRELATIONS

The photochemistry (both solution and solid state) of each of the sixteen ene-diones whose structures are shown in Scheme 4 will be outlined in the sections that follow. In cases where two or more molecules exhibit similar behavior, they will be discussed together. Insofar as is possible, the differences between the solid state and solution results, as well as the mechanisms operating in the solid state, will be explained with the aid of the relevant X-ray crystal structure data.

A. Intermolecular [2 + 2] Photocycloaddition

Ene-diones **6** and **8** belong to this category[5a, 7]. Irradiation of crystals of ene-dione **6** leads to dimer **6a**; when **6** is photolyzed in solution, mixtures of the rearrangement products **6b**, **6c** and **6d** are obtained. Happily, the overall yield is ca. 90%, much higher than in the case of ene-dione **1**. Photolysis of ene-dione **8** in the solid state also affords dimeric material (**8a**), while in solution it affords the novel rearrangement product **8e**. These reactions are summarized in Scheme 5. The structure and stereochemistry of dimers **6a** and **8a** were determined by X-ray crystallography[19].

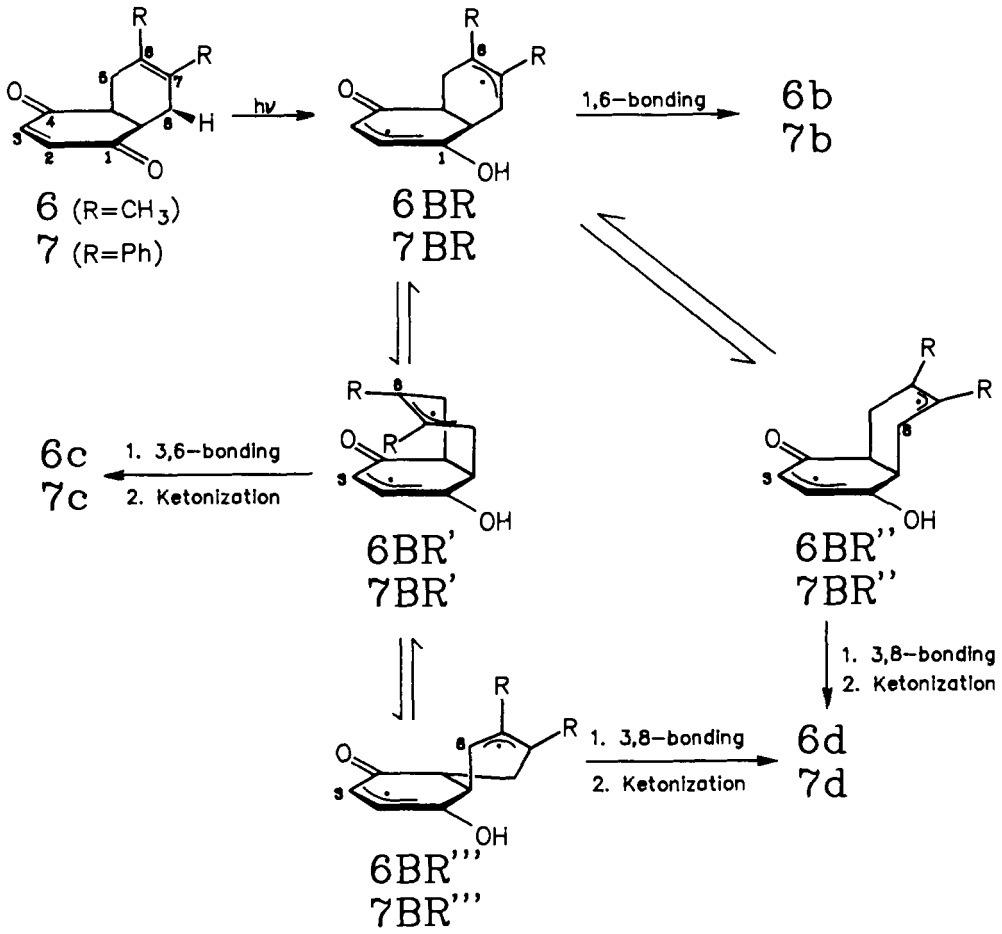
As was the case with ene-dione **1** discussed earlier, the X-ray crystal structure of ene-dione **8**[16] shows that it packs favorably for intermolecular [2 + 2] photocycloaddition. In accord with Schmidt's rule[2c], the distance between double bonds of centrosymmetrically related incipient dimer pairs is 4.04 Å. The dimer structure and stereochemistry correspond exactly to the packing of the incipient dimer pair in the crystal, showing that the reaction is topochemically controlled. One major difference between the packing in ene-diones **1** and **8** is that in **8**, there is only one molecule in the asymmetric unit. Thus, in principle, quantitative dimer yields are possible. High yields were, in fact observed[7]. Turning to ene-dione **6**, it will be recalled that crystals of this material were not suitable for crystallography. The examples of ene-diones **1** and **8**, however, leave little doubt that the


6
hν crystal
hν solution
6a
6b
6c
6d
8
8a
8e
hν solution
hν crystal

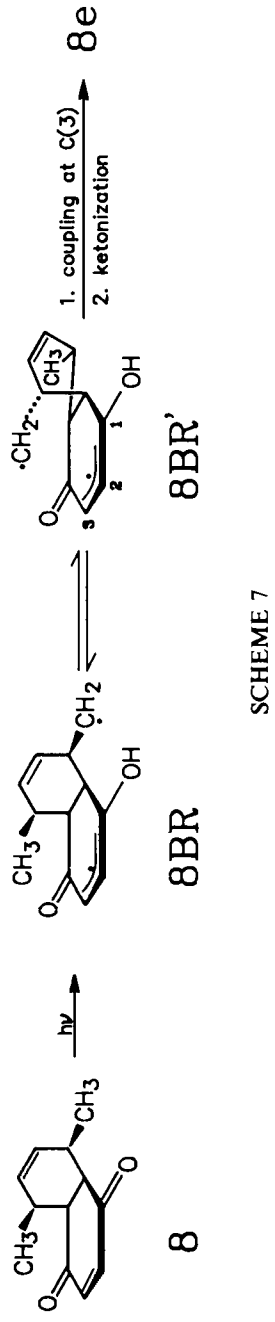
SCHEME 5

solid state photochemistry of **6** is also controlled by way of a crystal packing arrangement that favors dimerization.

Because ene-diones have similar conformations in solution and the solid state, we may use the crystal structure-derived conformations to help us understand the intriguing solution phase photorearrangement mechanisms. Ene-dione **6** undoubtedly adopts the preferred twist conformation common to all the ene-diones that lack bridged cyclohexene rings. This conformation is ideally suited for the first step of the photorearrangement process, namely, five-membered transition state (β) hydrogen atom abstraction of H(8) by O(1) (Scheme 6, R = Me). Abstraction leads to the bis-allylic biradical **6BR** which can close directly to photoproduct **6b**, or in solution, isomerize to **6BR'**. This can close either to **6c** or isomerize to **6BR'''**; closure of this latter species gives photoproduct **6d**. Photoproduct **6d** can also be formed from the *exo*-eclipsed biradical **6BR''**. This scheme also accounts for the products formed when ene-dione **1** is photolyzed in solution (see Scheme 1). Deuterium



SCHEME 6



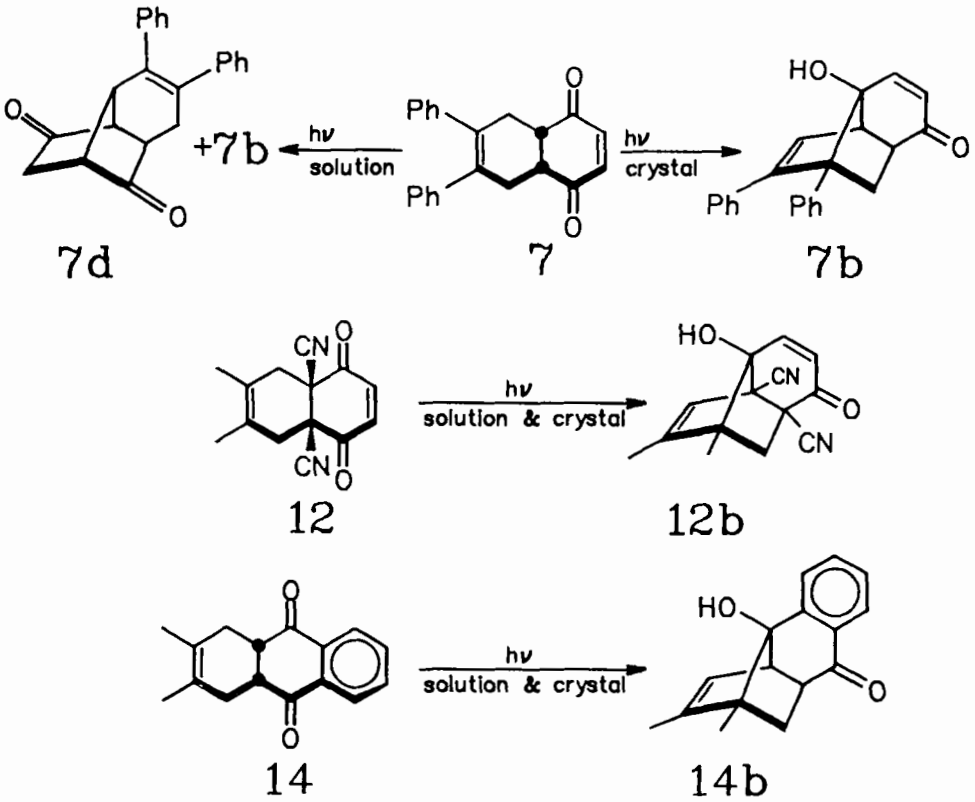
SCHEME 7

labeling and other mechanistic studies that establish these pathways have been published[5a]. As we shall see, for ene-diones other than **1**, **6** and **8**, abstraction also occurs in the solid state, and from the X-ray crystal structure data, we may obtain the distance and angular parameters for the process.

The conformation of ene-dione **8** in the solid state (and the favored conformer in solution) is the same as that of ene-dione **6**, except that the abstractable β-hydrogen atoms of **6** are replaced by methyl groups. Thus β-hydrogen atom abstraction is impossible in **8**, and instead, abstraction of a methyl γ-hydrogen atom is observed in solution (Scheme 7). This leads to biradical **8BR**, which, in solution, undergoes conformational isomerization to biradical **8BR'** and then closes to yield the enol form of the observed photoproduct **8e**[5a].

B. Enone-alcohol Formation

Ene-diones **7**, **12** and **14** belong in this category and behave similarly upon irradiation in the solid state; each gives the corresponding enone-alcohol type photoproduct **7b**, **12b** and **14b** (Scheme 8)[5, 7]. These products, which are analogous to photoproduct **6b** produced in the photolysis of ene-dione **6** (see Scheme 5), were the only products formed; no dimers of any kind could be detected. Enone-alcohols **12b** and **14b** were also the sole products formed when ene-diones **12** and **14** were photolyzed in solution; ene-dione **7**, however,



SCHEME 8

gave a mixture of enone-alcohol **7b** and a new photoproduct, **7d**, when irradiated in solution. Diketone **7d** is analogous to **6d**.

These results demonstrate that unimolecular, hydrogen atom abstraction-initiated photochemistry *is* observed in the solid state provided that the crystal packing does not favor [2 + 2] photocycloaddition. We note also that in the case of ene-dione **7**, fewer rearrangement products are formed in the crystal than in solution. This is explained readily with the aid of the mechanism outlined in Scheme 6 (R = Ph). Due to the restraints of the crystal lattice, the initially formed biradical **7BR** cannot undergo conformational isomerization to any of the other biradical intermediates. As a result, only photoproduct **7b**, which has the same basic conformation as that of ene-dione **7** and intermediate **7BR**, is formed in the solid state. No such restrictions exist in solution, however, with the result that both **7b** and **7d** are formed in this medium.

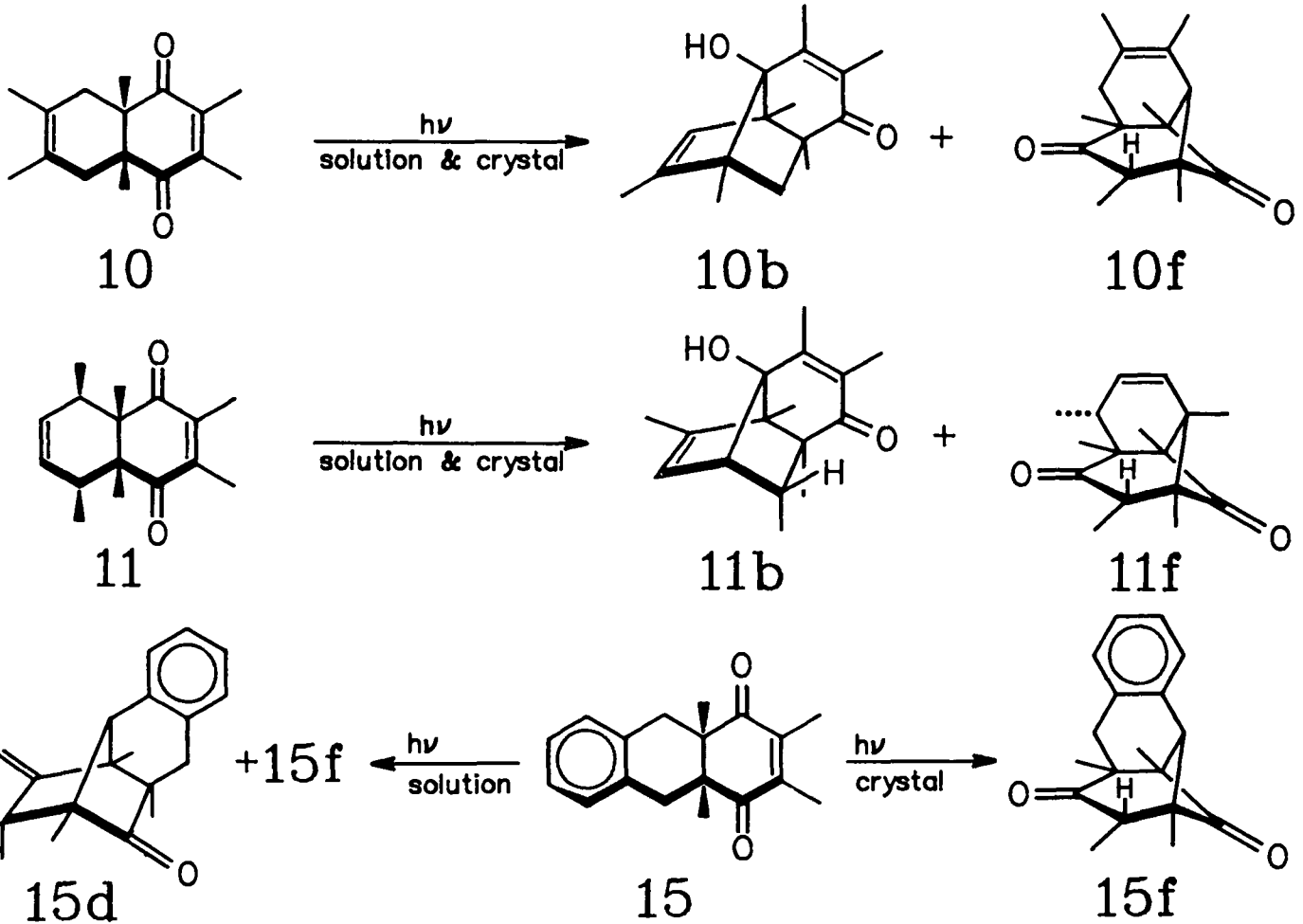
C. Cyclobutanone Formation

As outlined in Scheme 9, irradiation of crystals of ene-diones **10**, **11**, and **15** leads to a new type of photoproduct that contains a four-membered ring ketone moiety, hence the term cyclobutanone (products **10f**, **11f** and **15f**, respectively)[5, 7, 20]. In the case of ene-diones **10** and **11**, the cyclobutanone photoproducts are accompanied by lesser amounts of the corresponding enone-alcohols **10b** and **11b**; cyclobutanone **15f** was the sole product from the solid state photolysis of **15**. Very similar product mixtures were obtained in solution as in the crystal except for ene-dione **15**; solution photolysis of **15** gave **15d** and **15f**.

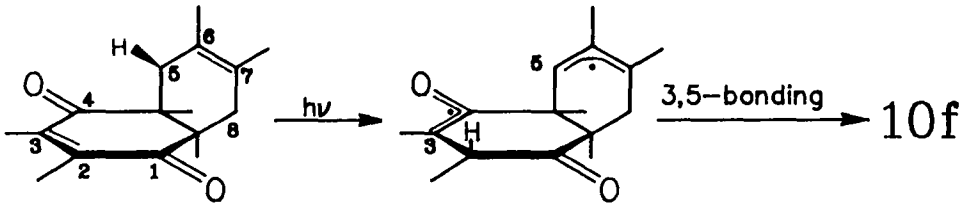
What is the mechanism of the formation of the cyclobutanone-containing photoproducts **10f**, **11f** and **15f**? As in the other solid state unimolecular photorearrangements, the conformation of the starting material in the crystal, determined by X-ray crystallography, provides the answer. Scheme 10 depicts the conformation of ene-dione **10** in the solid state; it exists in the now-familiar twist conformation. In this conformation, the *endo* allylic hydrogen atom on C(5) lies almost directly over the ene-dione carbon–carbon double bond. Transfer of this hydrogen (six-membered transition state) to C(2) of the double bond affords biradical **10BR**, and closure of this biradical by C(3) to C(5) bonding leads to the observed photoproduct **10f**. Like the solid state rearrangements of ene-diones **7**, **12** and **14**, the biradical and the final product have the same basic conformation as the starting material. Exactly the same mechanism and structure–reactivity correlation can be applied to the formation of photoproducts **11f** and **15f**.

With regard to the formation of enone-alcohols **10b** and **11b** from ene-diones **10** and **11**, respectively, the same mechanism as discussed earlier (Scheme 6) is operative. We note that no enone-alochol is formed in the case of ene-dione **15**, either in the solid state or in solution. This is due to the presence of the aromatic ring. Enone-alcohol formation requires C(1) $\cdots$ C(6) bonding in biradical **6BR**, a process which would disrupt aromaticity in the case of ene-dione **15**. Instead, the biradical analogous to **6BR** derived from **15** undergoes conformational isomerization in solution and gives diketone **15d**, the analogue of **6d**. This process does not disrupt aromaticity. Diketone **15d** is not formed in the solid state because the required conformational changes are not permitted by the crystal lattice.

An interesting point is that enone-alcohol formation and cyclobutanone formation involve the initial abstraction of *different allylic hydrogen atoms*. Abstraction of *endo*-H(8) by oxygen gives enone-alcohol and abstraction of *endo*-H(5) by carbon leads to cyclobutanone. The question thus arises, why do ene-diones **10**, **11** and **15** on the one hand, but not ene-diones **7**, **12** and **14** on the other, give rise to cyclobutanone-type photoproducts? The answer to this question comes from photophysical studies carried out in solution [5b, 20]. Quenching and sensitization studies on ene-diones **10** and **15** show that


hν
solution & crystal
HO
O
H
10
10b
10f
11
11b
11f
hν
solution
+15f
hν
crystal
15d
15

SCHEME 9



10 10BR

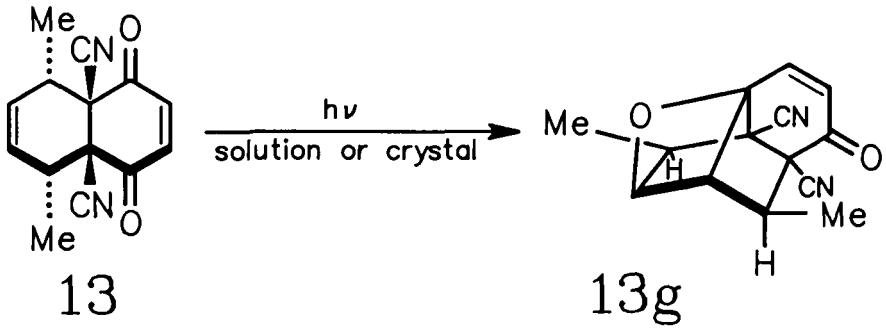
SCHEME 10

the cyclobutanone-type photoproducts are triplet-derived and that the enone-alcohol photoproducts as well as diketone **15d** come from singlet excited states. We assume that this holds in the solid state as well. It seems likely that the singlet excited state is n,π^* in nature and that the triplet is π,π^*. This is consistent with the $(\pi,\pi^*)^3$ being formed faster from the $(n,\pi^*)^1$ and having a lower energy relative to the $(n,\pi^*)^3$ as the result of ene-dione double bond methyl substitution[21, 22]. The mechanistic picture is thus clear: those ene-diones with methyl groups on the C(2)–C(3) double bond (**10**, **11** and **15**) undergo relatively rapid intersystem crossing to $(\pi,\pi^*)^3$ excited states that react to give cyclobutanones. In these cases, intersystem crossing is still sufficiently slow that some reaction (enone-alcohol or diketone **15d** formation) is observed from the initially formed $(n,\pi^*)^1$ excited state. In the absence of methyl substituents at C(2) and C(3), intersystem crossing is too slow to compete with reaction from the $(n,\pi^*)^1$ state and only products derived from the singlet manifold are produced. These excited state–reactivity correlations are entirely consistent with what is known concerning the photochemical hydrogen atom abstraction reactions of α,β-unsaturated ketones, namely that π,π^* excited states favor abstraction by the β-carbon atom, and that n,π^* excited states lead to hydrogen atom abstraction by oxygen[23]. The predilection of ketone n,π^* excited states to engage in hydrogen atom abstraction through the use of the oxygen n-orbital is well established[24].

It is interesting to ask why the $(n,\pi^*)^1$ and $(\pi,\pi^*)^3$ excited states of ene-diones **10**, **11** and **15** react differently from one another. One contributing factor may be the preference for triplet excited states to give biradical intermediates that have a greater separation between the radical centers than the biradical intermediates formed from singlet excited states. As Michl has pointed out[25], this stems from the zwitterionic character of singlet biradicals in which radical separation has to overcome coulombic attractive forces. Comparing biradicals **10BR** (Scheme 10) and **6BR** (Scheme 6), it can be seen that the radical centers in the latter (which is a singlet-derived) can approach each other more closely (two-bond separation) than they can in the triplet-derived biradical **10BR** (minimum three-bond separation). From studies in solution on the temperature dependence of the product in the photolysis of ene-dione **15**[20], a singlet/triplet activation energy difference $[E_a(\text{triplet}) - E_a(\text{singlet})]$ of 4.5 kcal mol^{-1} was determined. We assume that the rate-determining step in each case is hydrogen atom abstraction; the activation energy difference may be attributed to the fact that S_1 has a higher excitation energy than T_1, as well as to the greater resonance stabilization of biradical **6BR** as compared to biradical **10BR**.

D. Oxetane Formation

Upon irradiation in either the solid state or solution, ene-dione **13** gave only the intramolecular oxetane **13g** (Scheme 11)[5b, 7]. The structure of the oxetane was established by X-ray crystallography[26].



13 13g

SCHEME 11

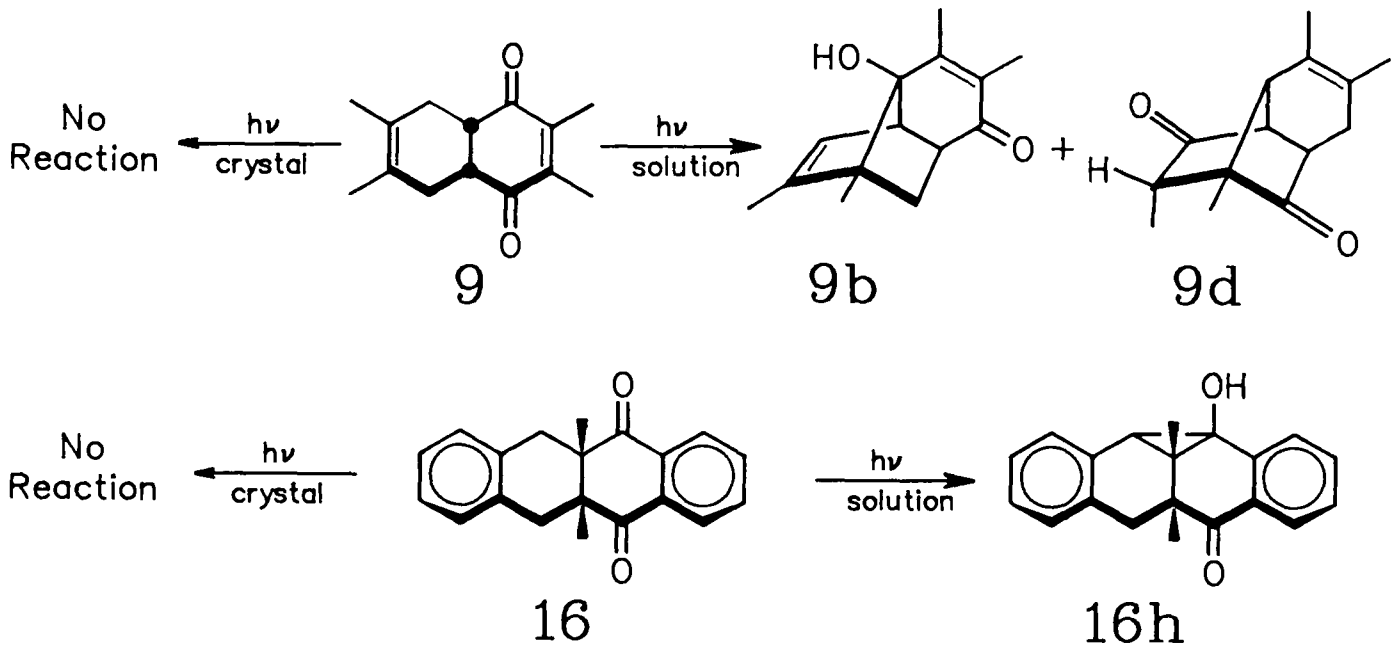
The crystal structure of ene-dione **13** shows that it has essentially the same conformation as ene-dione **8** discussed earlier (Scheme 7). The two differ only in the presence of two cyano groups at carbon atoms 4a and 8a, yet their solid state and solution phase photochemistry are completely different. In the solid state, ene-dione **13** does not photodimerize (as did **8**) because the packing precludes it. There are no abstractable allylic hydrogen atoms, therefore photoproducts of the **b**, **c**, **d**, or **f** type are not formed. Abstraction of a γ-hydrogen atom from a methyl group is possible, but the conformational isomerization of the resulting biradical required to form a stable photoproduct (see Scheme 7) is impossible in the solid state. The conformational isomerization of **13BR** is probably slower than that of **8BR** *in solution* as well, due to the bridgehead cyano groups. This may account for the fact that no photoproduct analogous to **8e** is formed in solution. As a last resort, the excited state of ene-dione **13** dissipates its energy by undergoing intramolecular oxetane formation. The fact that this reaction is geometrically feasible, but unobserved, for all of the ene-diones except those with aromatic rings fused in the C(6)/C(7) position, indicates that it is associated with an intrinsically low overall rate constant.

E. Compounds that React in Solution but not in the Solid State

Compounds **9** and **16** fall in this category[5a, 27]. In solution, ene-dione **9** affords products **9b** and **9d** upon irradiation. Photolysis of ene-dione **16** gives a photoproduct type not observed previously, namely the cyclopropanol **16h**. Neither ene-dione reacts when photolyzed in the solid state. These results are summarized in Scheme 12.

The photochemistry of ene-dione **9** is unusual in comparison with its close relative, ene-dione **10**. We expected that **9**, like **10**, would lead to substantial amounts of the corresponding, triplet-derived cyclobutanone (type **f**) photoproduct, both in solution and the solid state. This expectation was based on the fact that both **9** and **10** have methyl substituents on the C(2)–C(3) double bond, a feature that was suggested earlier to be important in bringing about cyclobutanone formation through facilitation of intersystem crossing to a low-lying $(\pi, \pi^*)^3$ excited state. On reflection, it is perhaps not too surprising that ene-dione **9** gives only singlet-type photoproducts. The balance between reaction from the singlet excited state and intersystem crossing is evidently a very delicate one for ene-diones **10**, **11** and **15**, and it is not unreasonable to suggest that the structural difference between ene-diones **9** and **10** (C(4a)/C(8a) methyl group substitution) could tip the scales one way or the other.

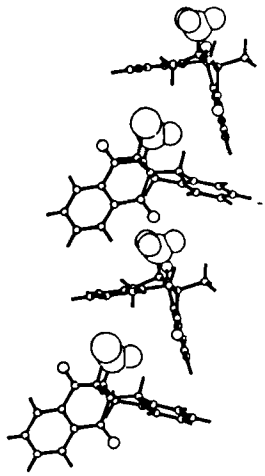
The solution phase photochemistry of ene-dione **16** is unique. None of the other ene-diones studied gave cyclopropanol-type photoproducts. Why does **16**? The answer is that


No Reaction
hν
crystal
hν
solution
HO
O
H
9
9b
9d
No Reaction
hν
crystal
hν
solution
OH
16
16h

SCHEME 12

formation of any of the other photoproduct types (**a** through **g**) would disrupt aromaticity. Photoproduct **16h** is the only product of biradical collapse that does not. Cyclopropanol **16h** is a stable, crystalline material that does, however, undergo an intriguing secondary rearrangement of its own upon photolysis[27].

The lack of solid state photochemistry in the case of ene-dione **9** is a mystery that tells us there are solid state effects on chemical reactivity that are yet to be discovered. The conformation and packing arrangement of ene-dione **9** appear to be little different from those ene-diones that react unimolecularly with alacrity in the solid state. On the other hand, there are two clear reasons for the unreactivity of ene-dione **16** in the solid state. The first can be appreciated by reference to Scheme 6. Cyclopropanol formation requires C(1) · · · C(8) bonding in one of the intermediate biradicals, but can only occur from either **6BR″** or **6BR‴**. As we have seen before, the conformational motions required to form these biradical intermediates are not permitted in the solid state. A more detailed understanding of the lack of cyclopropanol formation in the solid state emerges from an inspection of the packing diagram of ene-dione **16** (below). Crystals of ene-dione **16** contain two



independent molecules with slightly different conformations in the asymmetric unit, and these pack in stacks consisting of alternating conformers. A methyl group of a lower molecule projects directly into the space between the rings of an upper molecule. Cyclopropanol formation, however, requires that these two rings move considerably closer together, and this is prevented by the presence of the methyl group. Our calculations[27] show that were cyclopropanol formation to occur in the solid state, the methyl-carbon to aromatic-center distances would decrease from 4.1 and 4.8 Å to approximately 2.6 and 3.0 Å, an impossible steric situation in view of the fact that the sum of the van der Waals radii of a methyl group and an aromatic ring is 3.7 Å[28].

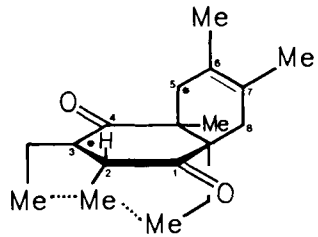
F. Conformation-Specific Solid State Photochemistry

The asymmetrically substituted ene-diones **17–21** belong to this category[29, 30]. As discussed earlier, the two possible twist conformations of these ene-diones are diastereomeric. In solution, both conformers are present in amounts that are of the same order of magnitude because the energy difference between conformers is relatively small. To a first approximation, the free energy difference between conformers **A** and **B** that have

a single methyl group at C(4a) or C(8a) is the axial/equatorial free energy difference for a C(4) methyl group in cyclohexene ca. 1 kcal mol^{-1})[31] minus the axial/equatorial free energy difference for a C(5) methyl group in cyclohex-2-ene-1,4-dione (value not known, assumed to be ca. 0.5 kcal mol^{-1}). This leads to an **A**/**B** free energy difference of ca. 0.5 kcal mol^{-1}, which corresponds at 25 °C to a mixture containing ca. 70% of the more stable conformer. With the exception of ene-dione **17**, however, only one of the two twist conformers is present in the solid state. Thus, in contrast to the liquid phase, the crystalline phase provides a medium for studying the chemistry of a single, pure conformer. We have termed this 'conformation-specific' chemistry[29].

We consider first the ene-dione **18**. As outlined in Scheme 13, irradiation in solution leads to a mixture of four photoproducts, two of the enone-alcohol type (**18b** and **18b'**) and two of the cyclobutanone type (**18f** and **18f'**). In contrast, photolysis of crystals of ene-dione **18** gives a single photoproduct, enone-alcohol **18b**. The explanation of these results is straightforward: the conformers **18A** and **18B** are present in roughly equal amounts in solution, and photolysis gives two products from each conformer. Note that the photoreactivity of ene-dione **18** is exactly the same as that of its close relative, **10**. In the crystal, only conformer **18A** is present and irradiation leads to enone-alcohol **18b**.

Why is cyclobutanone **18f** not formed in the solid state? We feel this is due to a unique solid state steric effect. The first step of cyclobutanone formation is transfer of an allylic hydrogen atom from C(5) to C(2). As illustrated below, this causes pyramidalization of C(2) with a concomitant downward movement of the methyl group attached to it. The X-ray crystal structure of ene-dione **18** shows that the ethyl groups at C(3) and C(8a) would sterically impede this movement (dotted lines). This steric effect can be avoided in solution because the ethyl groups can rotate out of the way. In ene-diones **10**, **11** and **15**, this effect is

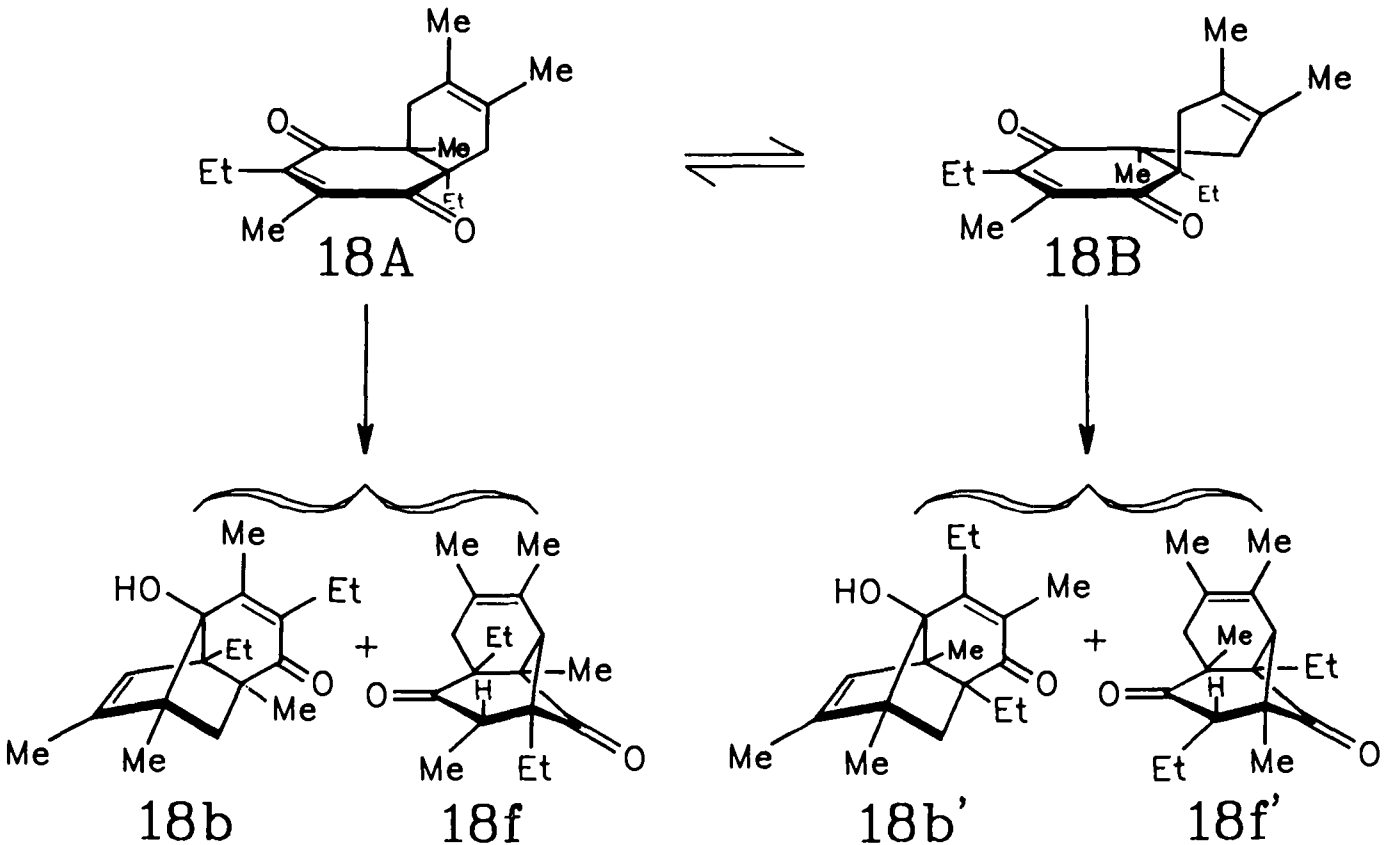


Biradical from 18A

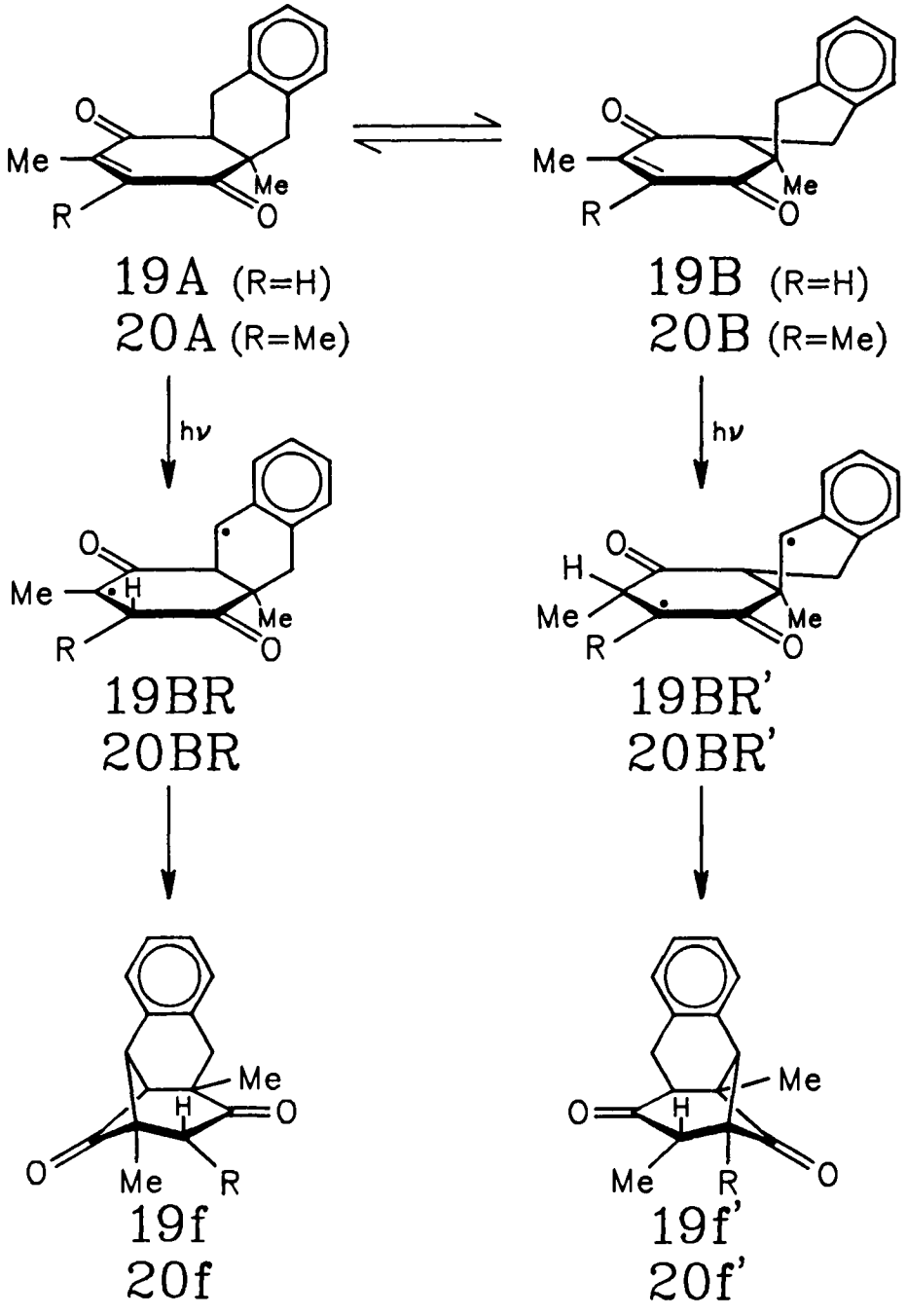
absent because there are no ethyl groups, and cyclobutanone photoproducts *are* formed in the solid state. Computer simulation of the pyramidalization motions verifies this effect in **18**, and we have termed it 'steric compression control'[29, 32].

Ene-dione **19** gives the same cyclobutanone type photoproduct (**19f**) in solution as it does in the solid state (Scheme 14); enone-alcohol type photoproducts are precluded in this case by the presence of the aromatic ring. The crystal structure shows that only conformer **19A** is present in the solid state. This explains the exclusive formation of cyclobutanone **19f** in this medium, but why is the other cyclobutanone isomer (**19f'**) not observed in solution? There are two reasons for this. First of all, conformer **19A** is the major conformer present in solution, and second, the biradical **19BR**, which gives rise to the observed photoproduct, has a tertiary center and is therefore more stable than its secondary isomer, **19BR'**.

Ene-dione **20** undergoes photolysis in acetonitrile to give two isomeric cyclobutanones, **20f** and **20f'** (Scheme 14), in a ratio of 57 to 43; in the solid state, only cyclobutanone **20f'** is formed. These unusual results stem from the fact, discussed earlier, that ene-dione **20**



SCHEME 13


Me
R
Me
O
19A (R=H)
20A (R=Me)
19B (R=H)
20B (R=Me)
hν
H
19BR
20BR
19BR'
20BR'
19f
20f
19f'
20f'

SCHEME 14

crystallizes in its *less stable* conformation, **20B**. In solution, conformer **20A** predominates and leads to the major photoproduct **20f**. In contrast to biradicals **19BR** and **19BR'**, intermediates **20BR** and **20BR'** have comparable radical stability and because **20B** is present in solution, some photoproduct **20f'** is formed in this case.

Just as we were beginning to feel that the solid state photochemistry of ene-diones could not provide any further surprises, Weisz and coworkers[14a] reported the synthesis and photochemical behavior of ene-dione **21**. As outlined in Scheme 15, irradiation of this material in ethyl acetate affords a mixture of the intramolecular [2 + 2] cycloaddition product **21h** and the unusual rearrangement product **21i**; photolysis of crystals of ene-dione **21** gives only **21i**.

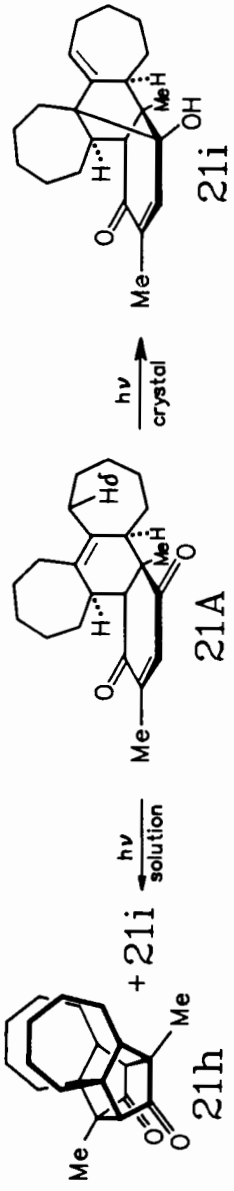
Formation of **21i** involves seven-membered transition state abstraction of a δ-hydrogen atom by oxygen atom O(1) from the lower energy twist conformer **21A**, followed by C(1) · · · C(6) bonding of the biradical so produced. This biradical closure step is identical to the topochemically allowed, second step of enone-alcohol (type **b**) photoproduct formation (see Scheme 6). Interestingly, the solid state reaction fails for ene-diones that contain one or two five-membered or six-membered rings fused to the cyclohexane moiety. This was ascribed to unfavorable O · · · H abstraction distances in the solid state[14]. The details of this aspect of the work are deferred to the section on the geometric requirements for hydrogen atom abstraction.

Finally, we briefly discuss the photochemistry of ene-dione **17**. Because, as mentioned earlier, both twist conformers of **17** are present in equal amounts in the crystal, no conformation-specific, solid state chemistry is observed, and irradiation of this material gives a mixture of photoproducts that is essentially the same in the solid state as in solution[5b]. Interestingly, the packing diagram of ene-dione **17** shows that it should be capable of intermolecular [2 + 2] photocycloaddition in the solid state. The ene-dione double bonds of neighboring molecules in the lattice are situated above one another in a head-to-tail, parallel arrangement; the center-to-center distance between double bonds is 3.9 Å, less than Schmidt's upper limit of 4.1 Å. A second notable feature of the packing in ene-dione **17** is that there is a close (2.5 Å) contact between a carbonyl oxygen atom of one molecule and a hydrogen atom on the C(2) methyl group of a neighboring molecule. As we shall see, this distance is within the upper limit for hydrogen abstraction. Thus a second mode of dimerization is possible for ene-dione **17**, namely, intermolecular hydrogen atom abstraction (photoreduction) followed by coupling of the radicals so produced. However, only a very small dimer peak was found in the mass spectrum of the crude solid state reaction mixture. The mass spectrum also exhibited a peak at 2M-18. This is consistent with the dimer being of the photoreduction type (loss of water from the tertiary alcohol produced by radical coupling). The results with ene-dione **17** show that a crystal packing arrangement that favors [2 + 2] photocycloaddition does not always cause this process to win out over unimolecular photochemistry.

The crystal packing of ene-dione **20** shows that potentially, it too is capable of photoreductive dimerization in the solid state, but that [2 + 2] photodimerization is not possible; the O · · · H contact between lattice neighbors in this case is 2.5 Å. The mass spectrum of the crude reaction mixture from solid state photolysis of ene-dione **20** again shows weak 2M and 2M-18 peaks, consistent with photoreductive dimerization; as yet we have been unable to isolate and characterize either photoreductive dimer.

VI. QUANTITATIVE STRUCTURE–REACTIVITY CORRELATIONS: THE GEOMETRIC PARAMETERS ASSOCIATED WITH HYDROGEN ATOM ABSTRACTION

The photochemical studies described above have uncovered two general types of hydrogen atom abstraction processes that occur in the solid state. The first is β or five-membered



SCHEME 15

transition state abstraction of an allylic or benzylic hydrogen atom by an ene-dione oxygen atom, and the second is γ or six-membered transition state allylic or benzylic hydrogen atom abstraction by one of the central carbon atoms of the ene-dione chromophore. Because these processes occur in crystals, where atomic and molecular motions are severely restricted relative to liquid media, the shape of the molecule undergoing reaction is likely to be very similar to that determined by X-ray crystallography, and detailed structure–reactivity correlations are possible. The question of what geometry changes are induced in ene-diones by electronic excitation will be dealt with later.

The structure–reactivity correlations will be discussed in terms of three parameters that characterize the geometric relationship between the abstracting oxygen or carbon atom and the hydrogen atom being abstracted. These are d, the oxygen $\cdots$ hydrogen or carbon $\cdots$ hydrogen abstraction distance, τ, the angle formed between the O $\cdots$ H or C $\cdots$ H vector and its projection on the mean plane of the carbonyl group or the ene-dione central double bond, and Δ, the C=O $\cdots$ H or C=C $\cdots$ H angle. These parameters are represented schematically in Figure 1.

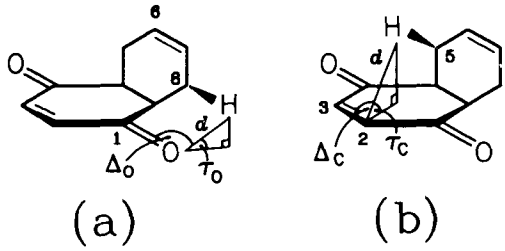
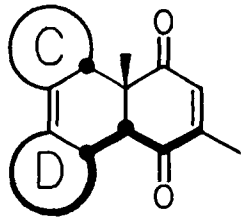


FIGURE 1. Definition of geometric parameters for hydrogen abstraction: d = abstraction distance; τ_0 = angle formed between O(1) $\cdots$ H(8) vector and its projection on mean plane of C(1)=O group; Δ_0 = C(1)=O(1) $\cdots$ H(8) angle; τ_c = angle formed between C(2) $\cdots$ H(5) vector and its projection on mean plane of C(2)=C(3) double bond; Δ_c = C(3)=C(2) $\cdots$ H(5) angle

The values of d, τ, and Δ for each of the compounds that undergo intramolecular hydrogen atom abstraction in the solid state are collected together in Table 2, which also lists a fourth parameter, the distance between the carbon atoms that become bonded to one another in the final photoproduct, and the types of photochemical reaction observed. The parameters for hydrogen atoms are less accurately determined by X-ray crystallography than for the heavier carbon and oxygen atoms, and fewer significant figures are quoted in the interatomic distances involving hydrogen atoms.

The data in Table 2 demonstrate that for ene-diones, intramolecular hydrogen atom abstraction occurs over distances that are less than or equal to the sum of the van der Waals radii of the atoms involved, 2.7 Å for O $\cdots$ H and 2.9 Å for C $\cdots$ H[28]. These distances are considerably longer than those previously considered feasible. The often-quoted limit of 1.8 Å for six-membered transition state hydrogen atom abstraction by oxygen stems from Djerassi's work on the mass spectrometric McLafferty rearrangement of steroidal ketones[33]. Evidently, excited state processes have less stringent distance requirements.

The suggestion that hydrogen atom abstraction occurs over distances less than or equal to the sum of van der Waals radii of the atoms involved has been substantiated by other studies from our laboratory[34]. It is also consistent with the studies on ene-dione **21** and related compounds[14]. These authors found, via X-ray crystallography, that the distance between the reactive δ-hydrogen atom and its nearest carbonyl oxygen atom varied with C/D ring size as shown below. Only ene-dione **21**, with an abstraction distance of 2.7 Å, the



Ring Size		SH ···· O Distance (Å)
C	D	
5	5	3.2
6	5	4.1
6	6	4.8
6	7	4.0
7	7	2.7

van der Waals radii sum, was photochemically reactive in the solid state.

With regard to the angular relationship between the abstracted and the abstracting atoms, we may expect that the most favorable arrangement will be defined by the spatial characteristics of the atomic orbital to which the hydrogen becomes bonded. In the case of hydrogen atom abstraction by oxygen, which occurs in ene-diones through the $(n, \pi^*)^1$ excited state, there is little doubt that the atomic orbital involved in abstraction is the non-bonding 2p orbital on oxygen[24]. This orbital lies in the plane of the carbonyl group and forms an angle of 90° with the C=O axis[35]. Thus the optimum values of τ_0 and Δ_0 for this process should be 0° and 90° respectively. The data in Table 2 reveal that ene-diones crystallize in conformations that, in terms of angle, *are nearly perfect for β-hydrogen abstraction by oxygen.* The average τ_0 angle is 4°, and the average value of Δ_0 is 84°. In the case of hydrogen atom abstraction by sp^2 hybridized carbon, it is the 2p AO that is involved. The preferred geometry of approach of the hydrogen atom here is 90° to the C=C axis and along the long axis of the AO rather than in the nodal plane. This gives optimum values of 90° for both τ_c and Δ_c respectively. The data in Table 2 show that ene-diones are less ideally arranged for carbon abstraction than for oxygen abstraction; the average τ_c value is 50°, and the average value of τ_c is 74°. This may be a third factor that contributes to the higher activation energy observed for this process in solution compared to abstraction of a β-hydrogen atom by oxygen.

The fourth geometric parameter listed in Table 2 is the distance between the carbon atoms that become bonded to one another in the final tricyclic photoproduct. The process of biradical closure is equal in importance to hydrogen atom abstraction to the success of the solid state reaction; if closure is topochemically disallowed, i.e. requires motions that are incompatible with the restraints of the crystal lattice, reverse hydrogen transfer leads to regeneration of starting material, and no net chemistry is observed. The carbon · · · carbon distances listed in Tables 1 and 2 range from 3.13 to 3.52 Å, with an average of 3.33 Å. Of course these distances refer to the ground state, not to the biradical intermediate, but these species certainly have similar gross conformations, and the fact that the distances are all close to the sum of the van der Waals radii for two carbon atoms (3.40 Å) is a strong

TABLE 2. Geometric parameters for intramolecular hydrogen abstraction

Ene-dione	d(Å)	τ_0(°)	Δ_0(°)	$C(1)\cdots C(6)$ (Å)	Reaction type[a] Solution	Solid
β-Hydrogen abstraction by oxygen and enone-alcohol formation, reaction type[a] 2 (refer to Figure 1a for definition of parameters)						
1[b]	2.5	4	80	3.43	2	1
6	—	—	—	—	2	1
7	2.5	3	81	3.51	2	2
8	2.4(γ)	15	101	3.4[c]	4	1
9	2.4	3	82	3.49	2	NR[d]
10	2.5	0	85	3.35	2+3	2+3
11	2.3	1	86	3.33	2+3	2+3
12	2.6	8	84	3.38	2	2
13		no abstractable hydrogen			5	5
14	2.6	5	81	3.46	2	2
16[b]	2.5	4	81	(2.51)[e]	2	NR[d]
17[b]	2.5	6	85	3.52	2	2
18	2.4	5	83	3.35	2+3	2
γ-Hydrogen abstraction by carbon and cyclobutanone formation, reaction type[a] 3 (refer to Figure 1b for definition of parameters)		τ_c(°)	Δ_c(°)	$C(3)\cdots C(5)$ (Å)		
10	2.8	52	73	3.17	2+3	2+3
11	2.7	50	74	3.17	2+3	2+3
15	2.8	51	74	3.13	2+3	3
19	2.9	47	75	3.26	3	3
20	2.9	50	74	3.20	3	3

[a] Reaction types: 1, dimerization; 2, β-H abstraction by O; 3, γ-H abstraction by C; 4 = γ-H abstraction by O; 5 = oxetane.
[b] Averages for two molecules in the asymmetric unit.
[c] Estimated after conformational inversion.
[d] NR = no reaction.
[e] C(1)···C(8) bond formation.

indication of a favorable arrangement for bonding. Another indication that the twist conformation is favorable for enone-alcohol and cyclobutanone formation is the alignment of the orbitals involved. The top lobes of the p orbitals at C(1) and C(6) (biradical collapse to enone-alcohol) point directly at one another (biradical **6BR**, Scheme 6), and the same is true of the orbitals at C(3) and C(5) in the biradical **10BR** (Scheme 10) leading to cyclobutanone-type photoproduct.

We turn now to a discussion of the important question of whether the *ground state* structural parameters can be correlated with *excited state* chemical reactivity. We believe they can. Based on spectroscopic and theoretical studies, there is general agreement that the $(n, \pi^*)^1$ states of α,β-unsaturated ketones have geometries that are essentially identical to their ground state geometries except for slight increases (< 0.1 Å) in the C=O and C=C bond lengths[36]. Assuming that enones and ene-diones have similar excited state characteristics, this indicates that the ground state structural data collected in Table 2 for the process of five-membered transition hydrogen atom abstraction by ene-dione oxygen also apply very closely to the reactive $(n, \pi^*)^1$ excited state. The situation in the case of the ene-dione $(\pi, \pi^*)^3$ excited state is less certain. Using enones again as a model, it was suggested initially that the $(\pi, \pi^*)^3$ excited states of cyclohexenones are twisted about the C=C bond, the torsion angle and consequent triplet energy varying as the structural constraints of the system[37]. More recent work, however, has disclosed a much more

complex situation[38] and at present there is no clear consensus as to the number, degree of twisting and the reactivity of the triplet states generated when cyclohexenones are photolyzed. Therefore, we prefer to leave the question of the shape of the reactive excited state responsible for γ-hydrogen atom abstraction by ene-dione carbon unresolved until further work is carried out. If this *is* a twisted species, we note that twisting may actually *facilitate* the process of abstraction by carbon by tilting the abstracting p orbital at C(2) directly toward the γ-hydrogen being abstracted.

VII. EXPERIMENTAL TECHNIQUES IN SOLID STATE PHOTOCHEMISTRY

A useful preliminary test to determine whether or not, as well as how, a given ene-dione will react in the solid state is to irradiate KBr pellets of the material and monitor the reaction by infrared spectroscopy. Prior to 1980, the pure crystal irradiations were carried out in a special variable temperature, evacuable apparatus consisting of an outer jacket with a Pyrex window and an inner, gold-plated reaction surface which is in contact with a reservoir containing liquid coolant[7]. The crystals were grown on the gold plated reaction surface of the inner vessel by slow evaporation of solutions of the ene-dione to be photolyzed. The last traces of solvent were removed by pumping on the sample, and the irradiations (450 W Hanovia lamp) were conducted in the absence of oxygen by maintaining the vacuum or by the introduction of nitrogen. The reaction temperature was chosen to be well below the eutectic temperature of the reaction mixture as determined by differential scanning calorimetry. The wavelength used was > 340 nm (Corning 7380 glass filter), which excites the low intensity ($\varepsilon < 150$), near-visible absorption band common to all the compounds studied. Conversions were kept low (< 30 %) so as to avoid destruction of the parent lattice and possible resulting loss of topochemical control, although in most instances, higher conversions could be achieved without noticeable loss of specificity or change in product ratio.

In recent years, we have turned to nitrogen lasers (337 nm) as the light source of choice in crystal irradiations. The collimated, monochromatic beams of lasers can be focused easily on small, carefully grown single crystals of the compound being studied, giving reasonable conversions in relatively short times without much sample heating. For low temperature photolyses, a specially designed, windowed Teflon cell is used. The temperature is controlled by passing vaporized liquid nitrogen through the cell; the temperature can be varied by adjusting the liquid nitrogen boil-off rate. Both solid state and solution samples are photolyzed using these techniques, generally to < 5 % conversion. In some cases the conversions are varied and the product ratios are extrapolated to 0 % conversion. We are well aware of the possibility that crystal defects, phase changes and changes in crystal packing can affect profoundly reactions occurring in the solid state. We recrystallize our samples routinely from different solvents and sublime them when possible to determine whether they exhibit polymorphism. To date, no ene-dione polymorphs have been identified. In addition to single crystal photolyses, parallel irradiations are conducted on polycrystalline samples to determine if crystal defects play a role in the reactions being studied; no effect of this type has been observed. The possibility that the reaction under investigation may be of the single crystal to single crystal type is also monitored carefully; so far, none has been found.

VIII. SUMMARY

The solid state photochemistry of *cis*-4a,5,8,8a-tetrahydro-1,4-naphthoquinone (ene-dione **1**) and 18 of its substituted derivatives has been reviewed and the results discussed with reference to the X-ray crystal structure data for 17 of the 19 compounds. All but one of the 17 ene-diones whose crystal structures were determined crystallize in a common 'twist'

conformation in which the cyclohexene moiety exists in a half-chair form *cis*-fused to a more-nearly planar cyclo-hex-2-ene-1,4-dione ring. The exception, ene-dione **3**, is prevented from adopting this conformation by a two-carbon bridge across positions C(5) and C(8). This leads to an eclipsed conformation in which the ene-dione double bond and the cyclohexene double bond are parallel and 3.53 Å apart; as a result, irradiation of crystals of ene-dione **3** affords quantitative yields of the intramolecular [2 + 2] cage product **5**. In the twist conformation, however, the ene-dione and cyclohexene double bonds are non-parallel and much further apart. Accordingly, intramolecular [2 + 2] cycloaddition is not observed when crystals of these materials are photolyzed.

Half-chair to half-chair cyclohexene ring inversion leads to two possible twist conformations for each ene-dione. Ene-diones with methyl groups attached to the central C(4a)–C(8a) bond have free energies of activation for inversion of ca. 9 kcal mol^{-1}. For symmetrically substituted systems, the twist conformations are isoenergetic and enantiomeric. In all cases of this type, however, the crystals are not chiral, as both enantiomers are present in equal amounts. Asymmetrically substituted ene-diones have twist conformations that are diastereomeric. In four of the five cases of this type studied, only one diastereomer (both enantiomers) was present in the crystal. In solution, both diastereomers are present in rapid equilibrium. The solid state medium thus permits the study of the reactivity of a single, pure conformer, a circumstance we term 'conformation-specific chemistry'. Three times out of four, it was found that the diastereomer present in the crystal is the one in which the perturbing substituent is pseudoequatorial with respect to the cyclohexene ring rather than to the ene-dione ring. The reverse was found for ene-dione **20**, indicating that the diastereomers have similar conformational energies (ΔG ca. 0.5 kcal mol^{-1}). In one instance (ene-dione **17**), where the perturbing substituent is on the ene-dione double bond, both diastereomers are present in equal amounts in the solid state.

Despite the fact that 16 of the ene-diones whose crystal structures were determined crystallize in a twist conformation, identical solid state photoreactivities were not observed. Eleven took part in intramolecular hydrogen abstraction processes, two underwent topochemically controlled, bimolecular [2 + 2] ene-dione double bond photocycloaddition, one gave rise to internal oxetane formation, and two were photochemically inert. The X-ray data showed that bimolecular [2 + 2] photoaddition occurred only when the crystal packing was such that adjacent molecules were oriented so that the reacting double bonds were parallel with center-to-center distances of less than 4.1 Å. Crystal packing of this type does not guarantee dimerization, however. Ene-dione **17**, with parallel ene-dione double bonds 3.9 Å apart, gives intramolecular hydrogen abstraction-derived products when irradiated in the solid state.

Three types of intramolecular hydrogen abstraction reactions were observed in the solid state: (1) abstraction by carbonyl oxygen through a five-membered transition state, (2) abstraction by C=C carbon via a six-membered transition state, and (3) in one instance only (ene-dione **21**), abstraction by carbonyl oxygen through a seven-membered transition state. All three processes are facile in the solid state owing to favorable geometric and distance factors. Also facilitating abstraction is the fact that in each case the hydrogen atom being abstracted is either allylic or benzylic. The structural parameters associated with these abstractions are summarized and compared to values previously estimated in the literature. This reveals that abstraction can take place over distances considerably greater than heretofore considered favorable and the data suggest that, with favorable geometry, these distances can be at least as great as the sum of the van der Waals radii of the abstracting and abstracted atoms (2.7 Å for C=O···H and 2.9 Å for C=C···H). Particularly noteworthy is the finding that the five-membered transition state abstraction process is favored by a nearly perfect angular relationship between the n orbital of the abstracting oxygen atom and the hydrogen atom being abstracted. Not only does the hydrogen lie within a few degrees of the mean plane of the carbonyl group and the n orbital,

but the C=O · · · H angle is very close to the ideal of 90°. The excited states giving rise to the hydrogen abstraction processes are tentatively identified as $(n, \pi^*)^1$ for abstraction by oxygen and $(\pi, \pi^*)^3$ for abstraction by carbon, and the general validity of formulating ground state structure–excited state reactivity relationships for these states is discussed. Equally important to the observation of the internal solid state hydrogen transfer reactions is the fact that the biradical intermediates produced by abstraction can collapse directly to stable products without the necessity for conformational isomerization. This is predicated on the reasonable assumption that the biradical has the same basic conformation as its ground state precursor, and the biradical coupling distances as estimated from the ene-dione structural data are all < 3.5 Å, of the order of the sum of the van der Waals radii for two carbon atoms (3.4 Å).

Intramolecular photochemical oxetane formation is observed only for the one substrate that has no neighbors in position to afford [2 + 2] photodimers and for which internal hydrogen abstraction is made geometrically impossible by replacement of the normally abstractable allylic hydrogen atoms by methyl groups. The fact that internal oxetane formation is geometrically feasible but undetected for all the other substrates studied indicates that it is the least favored of the solid state photoreactions. Finally, two of the ene-diones proved to be photochemically unreactive in the solid state. In the case of compound **9**, the reasons for this behavior are not known, but for ene-dione **16**, the photo-inertness is due to the fact that the biradical produced by hydrogen abstraction has no carbon–carbon bonding possibilities that do not either interrupt aromaticity or require a half-chair to half-chair conformational ring inversion, a motion that is impossible in the solid state. This type of reasoning also serves to explain the solid state/solution reactivity differences observed for many of the ene-diones studied. Irradiation in solution leads to biradical intermediates analogous to those formed in the solid state but which have much greater conformational freedom. Products are thus formed in solution that are not possible in the crystal, and in some instances, these become the major photoproducts.

IX. ACKNOWLEDGEMENT

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CHAPTER 21

Quinonediimines, monoimines and related compounds

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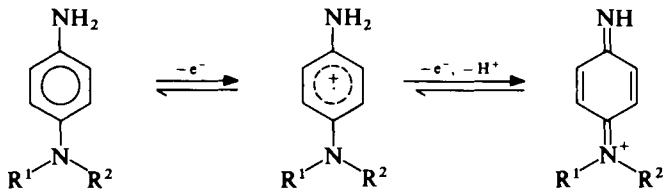
I. INTRODUCTION

The chapter on quinonediimines and related compounds, written by Finley and Tong[1] in the earlier volume of this series on the chemistry of functional groups, surveyed the

literature up to the late 1960s. Since that time many areas of the chemistry of quinonediimines have been extended in great detail. Quinonediimines and monoimines are important in many commercial applications, such as color photography and hair-coloring chemistry. Pertinent reviews in these two areas have been published[2,3]. Pharmaceutical chemistry, especially drug metabolism, is another important area of quinonediimine reactivity which has been studied since 1970; one example of this work is given later.

A major barrier to the quantitative study of quinonediimines is the elusive nature of the species. As Willstätter[4] pointed out, these compounds are unstable to light, water and acids. As a result, much recent work has relied on the oxidation of the precursor phenylenediamines and aminophenols to prepare the species of interest. These oxidations have been carried out using rapid mixing techniques with such chemical oxidants as ferricyanide[5], iodine[6], manganate[7], Mn(III)[8], permanganate in mild acid or alkali[6], persulfate, catalyzed peroxide, *N*-chloramine[9] and silver ion[4]. In photographic applications, exposed silver chloride or bromide is the oxidant[2]. Hair-coloring applications use hydrogen peroxide in mild alkali[3] as the oxidant. Other studies have made use of sophisticated electrochemical methods at inert electrodes to oxidize the precursor, phenylenediamine or aminophenol, to form the corresponding diimine or monoimine. The following chemical reaction coupled to the electrochemical step, perturbs the electrochemical response and forms the basis for studying the rate and mechanism of such reactions[10,11].

Regardless of the mode of oxidation, quinonediimines and quinonemonoimines are produced by two distinct one-electron oxidation steps[2] from the parent phenylenediamine or aminophenol, resulting in a radical intermediate semiquinone of varying stability. For some oxidants, the second oxidation step may be faster than the first, precluding any significant formation of radical when excess oxidant is used.



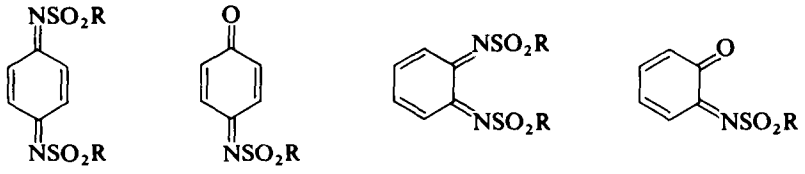
The stability of the semiquinone, S, depends on the nature of R^1 and R^2, and on whether *p*-quinoneimines or *o*-quinoneimines are formed. Semiquinone species of *o*-diimines and *o*-monoimines have been reported as transient species in such rapid oxidation techniques as pulse radiolysis and flow electron spin resonance (ESR) methods.

p-Semiquinones are much more stable, even for monoimines, when R^1 and R^2 are alkyl groups. These stable, often highly colored, intermediates confound mechanistic studies of diimines when oxidative formation is neither rapid nor complete[5,6].

Stable, isolable quinoneimines are formed when strongly electron-withdrawing groups are attached to nitrogen. Imines such as **1–4** have been studied extensively by Adams and Reifschneider[12], and more recently by Fujita[13].

Reviews of the chemistry of many *o*-quinonediimides have appeared recently by Heine and coworkers[14] and by Friedrichsen and Böttcher[15], and will not be repeated here.

The major goal of this chapter is to discuss the kinetics and mechanism of nucleophilic reactions of quinonemonoimines and quinonediimines after formation in a predominantly aqueous solution. The major reactions include deamination (attack by water or hydroxide), coupling reactions by carbanions to form dyes, sulfonation (addition of sulfite

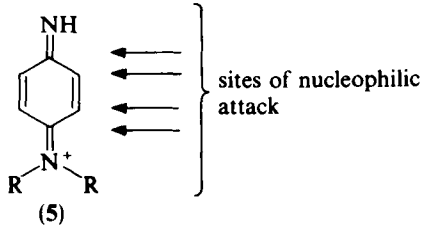


(1) (2) (3) (4)

and arylsulfinic acid), and intramolecular nucleophilic attack (self-coupling). Extensions of these same reactions to quinoneimides and diimides are also included. The role of redox equilibration, the semiquinone Michaelis equilibrium, is discussed briefly with regard to condensation reactions involving the quinoneimine with its precursor, phenylenediamine or aminophenol.

II. NUCLEOPHILIC REACTIONS OF QUINONEIMINES

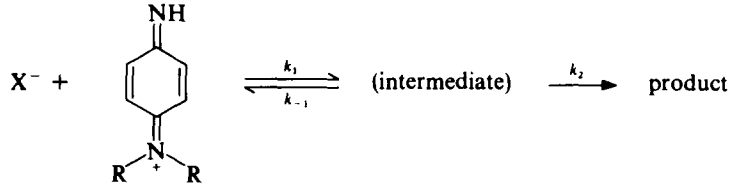
Addition and substitution reactions with quinonediimines or monoimines can occur at several sites on the molecule. In general, there are four reaction sites; the carbon atom attached to the unsubstituted nitrogen, the carbon atom attached to the substituted nitrogen, and the two ring positions, as illustrated for *N*,*N*-dialkylquinonediimine (**5**). The actual site of attack depends on several factors including the nucleophile and the structure of **5**.



(5)

Because of the competitive nature of nucleophilic attack, the product distribution will be determined by the site(s) that reacts fastest. The kinetics at any given site are determined by the electron density at that site, the stability of the products formed and steric considerations of both the electrophilic site and the approaching nucleophile.

The general reaction scheme for attack by the nucleophile, X^-, consists of two steps: (1) reversible formation of an intermediate and (2) irreversible formation of products.

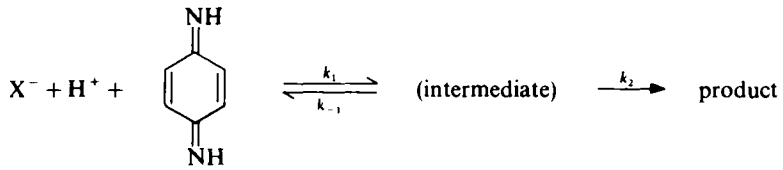


The reaction kinetics can be quite simple when very little intermediate accumulates and the steady-state assumption is used. When $[X^-]$ is in large excess or otherwise buffered, the observed first-order rate constant for loss of diimine or formation of product is given by equation 1.

$$k_{obs} = \frac{k_1 k_2 [X^-]}{k_{-1} + k_2} \quad (1)$$

If $k_2 > k_{-1}$, equation 1 becomes $k_{obs} = k_1[X^-]$ and the reaction is first order in $[X^-]$ as well as in diimine. Such is the case for attack by OH^- (deamination), as described later. When $k_{-1} > k_2$, equation 1 becomes $k_{obs} = Kk_2[X^-]$ where $K = k_1/k_{-1}$, the equilibrium constant for formation of intermediate.

Another extreme case occurs when the intermediate rapidly forms and maintains its equilibrium value. The kinetics of product formation now are determined only by k_2. The observed rate constant is still first order, but no longer depends on the concentration of X^-. By varying $[X^-]$, it is sometimes possible to obtain values for both k_1 and k_2 as described later for some dye-forming reactions.



(6)

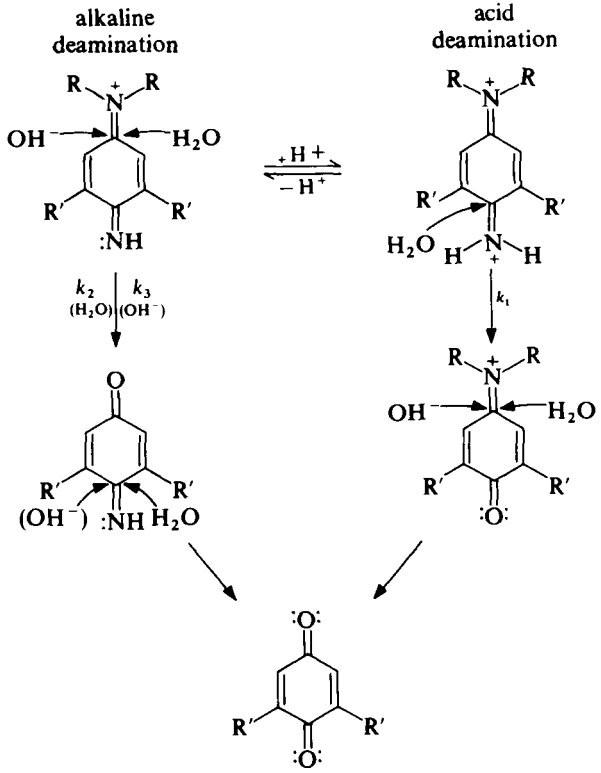
If the quinonediimine is neutral, as illustrated by **6**, the formation of an intermediate requires a proton, presumably on nitrogen. This is the case for deamination of quinonediimine in acid solution, where the attacking nucleophile, water, reacts with protonated diimine. Water is too poor a nucleophile to react at a kinetically significant rate with the neutral diimine except when it is the only species present.

The semiquinone species, which is involved in oxidative formation of quinonediimine, is not reactive in the nucleophilic reactions discussed here[16]. The major complication resulting from the presence of semiquinone is that of spectral interference in the observation of product formation or diimine loss. In addition, the diimine concentration as a function of time will be complicated by the redox reaction forming the species, instead of being controlled only by the attack of the nucleophile. Unambiguous analysis of the kinetics to determine k_{obs} in equation 1 is difficult under these conditions. The presence of semiquinone, particularly in acid solutions, further complicates kinetic studies, not because the oxidation of parent phenylenediamine is slow, but because it is incomplete.

III. DEAMINATION STUDIES

The nucleophilic attack of water and hydroxide is an important reaction of quinonediimines and monoimines, but the reaction often prevents isolation of the species under study. Tong[17] and, later, Corbett[18] used ferricyanide to oxidize *p*-phenylenediamines to the corresponding diimine in neutral or alkaline solution. Nickel, Jaenicke and their coworkers[5, 6, 19, 20] observed that, in acid solution, ferricyanide is not a sufficiently strong oxidant to completely form the diimine of most *N*-substituted compounds. They recommend using I_2[6], permanganate[19], Ce(IV)[20], or persulfate catalyzed by Cu(II)[20] to form the diimine or monoimine of interest rapidly and irreversibly. Electrochemical oxidation has also been used to form monoimines and diimines[11, 21–24]. These oxidation techniques in rapid flow or stopped-flow equipment, particularly the work of Nickel and Jaenicke[5, 6, 19, 20, 25], have led to a good understanding of the deamination (hydrolysis) mechanism for a large number of *para*-quinonediimines and monoimines.

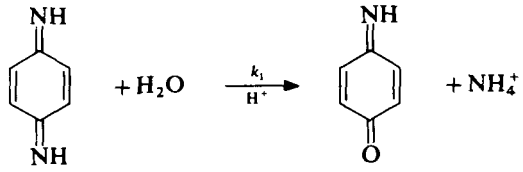
The overall path of diimine deamination is given by Scheme 1[19], giving *p*-benzoquinone as the product in both acidic and alkaline solution.



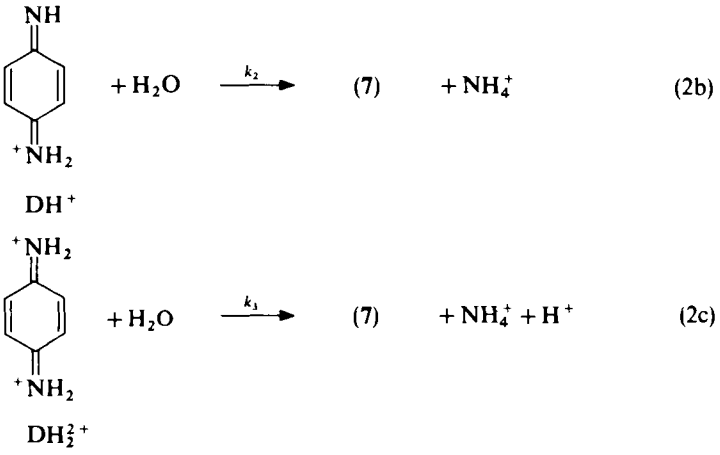
SCHEME 1. Overall path of deamination of diimines to quinone[19]

A. Unsubstituted Quinoneimines

For the unsubstituted quinonediimine (**6**), the kinetics of deamination have been reported by both Tong[17] and Corbett[18] over an extended pH range. The pH dependence of $\log k_{obs}$, obtained by following either the loss of diimine or the formation of monoimine spectrally in the ultraviolet, is shown in Figure 1. This dependence is the result of superposition of three parallel pathways for the attack of water on the three forms of the



D (**6**) (**7**) (2a)



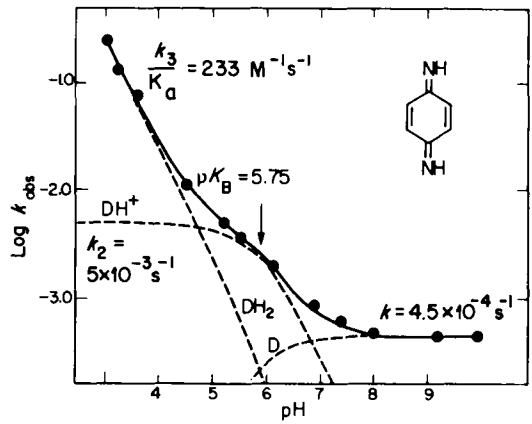


FIGURE 1. The effect of pH on the hydrolysis rate of *p*-benzoquinonediimine at 30 °C, showing the contribution of the hydrolysis of the individual species (broken lines) to the overall rate (full line) calculated, from equations 3 and 4. The points are experimental measurements[18]

diimine (equations 2a–c)[18]. Notice that, although a proton is required in equation 2a to balance the reaction, it is not required in the rate-limiting step, which is discussed in more detail later. The pH-dependent expression for the pseudo first-order rate constant, k_{obs}, in Figure 1 (solid line) is given by equation 3, where the values of k_1 through k_3 are given in Figure 1. These values include the water activity term ($\sim$ 55 M) so they are first-order rate constants. D_T is the total concentration of diimine. The relative concentration

$$k_{obs} = \frac{k_3\{DH_2^{2+}] + k_2[DH^+] + k_1[D]}{D_T} \tag{3}$$

of each form is given by equation 4, where K_a and K_b are the ionization constants of the doubly protonated and singly protonated species, respectively.

$$\frac{[DH_2^{2+}]}{D_T} = \frac{[H^+]^2/K_aK_b}{1+[H^+]^2/K_b+[H^+]^2/K_aK_b} \tag{4a}$$

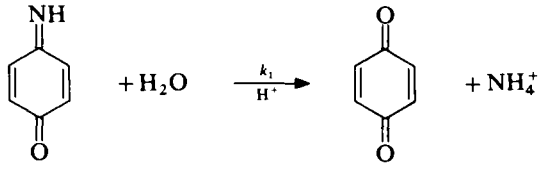
$$\frac{[DH^+]}{D_T} = \frac{[H^+]/K_b}{1+[H^+]/K_b+[H^+]^2/K_aK_b} \tag{4b}$$

$$\frac{[D]}{D_T} = \frac{1}{1+[H^+]/K_b+[H^+]^2/K_aK_b} \tag{4c}$$

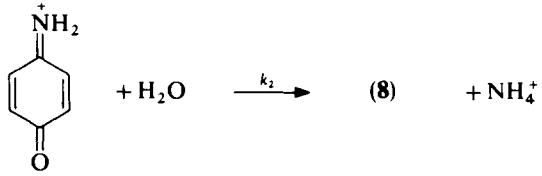
The ionization equilibria are $pK_a = 1.5$ and $pK_b = 5.75$, shown by the arrow pointing downward in Figure 1. The diimine is most stable in alkaline solution. In acid solution below pH 1, k_{obs} goes through a maximum[26] not shown in Figure 1, indicating the possibility of a more complex mechanism.

As evidence for the rate-limiting addition of water to the diimine in an alkaline solution, Tong and Glesmann[27] have measured the ionic strength dependence of the diimine hydrolysis. The rate is independent of μ up to 0.062 M, indicating no charge on the reactants in the rate-limiting step.

The monoimine (7) in equation 2 also undergoes deamination, to form *p*-benzoquinone (**8**). The pH dependence of log k_{obs} is given in Figure 2 from data taken from Tong[17] and Corbett[18]. Again, the pH dependence can be accounted for by superposition of parallel reactions of the neutral and protonated monoimine (equations 5a and 5b). The expression



M(7) (**8**) (5a)



MH^+ (5b)

for k_{obs} is given by equation 6, which is the sum of the rate constants for each of the two steps above;

$$k_{obs} = \frac{k_1[M]+k_2[MH^+]}{M_T} \tag{6}$$

where

$$\frac{[M]}{M_T} = \frac{1}{1+[H^+]/K_a} \tag{7a}$$

and

$$\frac{[MH^+]}{M_T} = \frac{[H^+]/K_a}{1+[H^+]/K_a} \tag{7b}$$

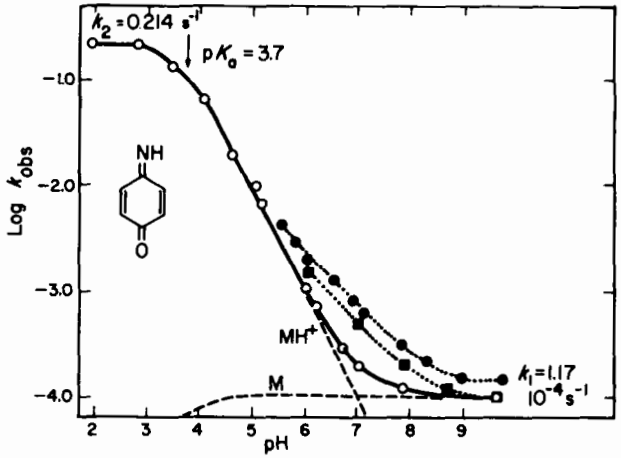
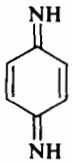
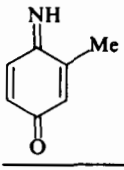


FIGURE 2. The effect of pH on the hydrolysis rate of *p*-benzoquinonemonoimine. ○ Acetate buffer at 30 °C[18]; ● phosphate buffer at 30 °C[18]; and ■ phosphate buffer at 25 °C[17]. The solid line is calculated from equations 6 and 7 using the rate constant values shown above

TABLE 1. Summary of deamination kinetics[17, 18]

Structure	pK_a	k_3 (s^{-1})	pK_b	k_2 (s^{-1})	k_1 (s^{-1})
	1.5	7.77×10^{3a}	5.75	0.005	4.5×10^{-4} 3.3×10^{-4b}
	—	—	3.7	0.214	1.17×10^{-4}
	—	—	—	—	1.0×10^{-4b}

[a] Maximum value of k_3, assuming $pK_a = 1.5$[18].
[b] Author's analysis of Tong's results[17].

The solid line in Figure 2 is calculated from equations 6 and 7 using the values obtained by Corbett[18] at 30 °C, as described in the figure caption. Comparison of k_{obs} with those in Figure 1 shows how similar the observed rate constants are, although individual species can have quite different values. The values of the individual constants are summarized in Table 1 for three compounds. The decrease in k_{obs} found electrochemically below pH 1 is probably due to additional complications in the mechanism[21,26].

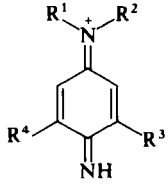
To be complete, there probably should be another term in equation 6 to describe the specific buffer effect of the phosphate shown in Figure 2. Insufficient study precludes describing this as a general base or general acid catalysis. Tong's data above pH 11, not included in Figure 2, show a rate increase, indicating that direct attack by hydroxide is responsible[17].

B. *N,N*-Dialkylquinoneimines

The mechanism is somewhat different for *N,N*-dialkyl *p*-quinonediimines. In alkaline solution, the logarithm of k_{obs} for hydrolysis increases linearly with pH, i.e. the reaction is first order in $[OH^-]$[17]. The positively charged diimines are attacked by OH^- to cleave *N,N*-dialkylamine, forming *p*-quinoneimine (7).

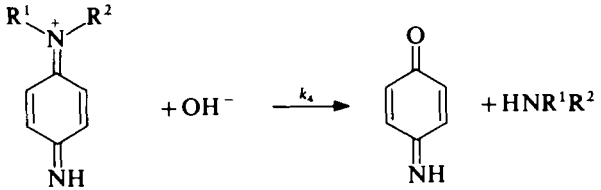
The second-order rate constant, k_4, was measured by Tong and coworkers[28] for several compounds of photographic interest and the data are summarized in Table 2. Increasing

TABLE 2. Deamination rate constants of *p*-*N,N*-dialkylquinone diimines



R^1	R^2	R^3	R^4	pK_a	k_2 (10^{-2} $M^{-1}s^{-1}$)	k_3 (10^{-5} $M^{-1}s^{-1}$)	k_4 (10^4 $M^{-1}s^{-1}$)	Reference
Me	Me	H	H	1.7 ± 0.1	1.1 ± 0.2	1.40	1.3	19[a]
				3.0[d]			1.5 ± 0.7	20
							2.5	17[b,c]
							1.1	23[e]
Me	Me	Me	H	1.74 ± 0.1	3.7 ± 0.4	—	—	19
Me	Me	Me	Me	1.48 ± 0.1	4.4 ± 0.4	—	—	19
Et	Et	H	H	1.60 ± 0.1	1.5 ± 0.2	0.5	0.9	19
							0.52	17
							1.0	28
Et	Et	Me	H	1.65 ± 0.1	3.1 ± 0.4	0.4	0.11	19
							0.16	17
Et	Et	Me	Me	—	—	0.10	0.02	19
							0.022	28
$-(CH_2)_4-$		H	H	—	—	—	0.60	28

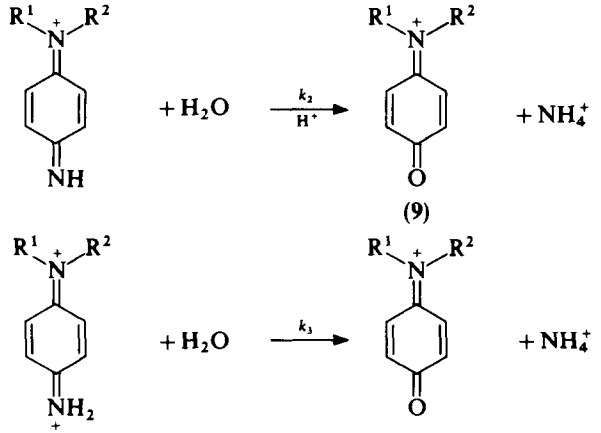
[a] 25 °C, variable ionic strength; second-order rate constants k_2 and k_3 have been obtained by dividing the observed rate constants (see Figure 3) by the water activity (~ 55 M).
[b] 25 ± 0.1 °C, 0.2 M phosphate.
[c] 25 ± 0.1 °C, $\mu = 0.375$, phosphate buffers.
[d] Ref. 30.
[e] 25 °C, $\mu = 0.4$ M phosphate, based on published k_{obs} vs. pH above pH 10.



(7)

ionic strength slows the reaction[27] in agreement with the mechanism of direct reaction of two unlike charged species.

It was later shown by Nickel and Kemnitz[29], and Lelievre and coworkers[30] that, in neutral and acid solution, the mechanism and products change. Deamination now occurs by the attack of water on the primary imine, or its protonated form, to produce an *N,N*-dialkylquinoneimine (**9**). The observed first-order rate constant, followed by indirect



(9)

methods[19], is small in neutral solution, increasing first order in $[H^+]$ to a constant value at a pH below the protonation equilibrium. The observed rate constant obeys an expression similar to equation 3, where the value of $k_1 = 0$ since no neutral diimine exists. The monoimine (**9**) is more stable than the diimine below pH 4 for R^1 and R^2 equal to alkyl, and can be observed spectrally[19]. The value of k_{obs} as a function of pH is plotted in Figure 3 for both *N,N*-dimethylquinonediimine and monoimine[19]. At high pH, the values reported by Tong[17] are in good agreement. The solid line, curve A, is given by equation 8

$$k_{obs} = \frac{k_3[H^+]/K_a[H_2O] + k_2[H_2O] + k_4[OH^-]}{1 + [H^+]/K_a} \tag{8}$$

with $pK_a = 1.7 \pm 0.1$. Notice that k_{obs} describe the formation of different products. The neutral monoimine (**7**) is produced in alkaline solution, represented by the term $k_4[OH^-]$. The *N,N*-dialkylmonoimine (**9**) is formed in acid solution, represented by the first two terms in equation 8. The product distribution will be 1:1 of **7** and **9** when the term $[H_2O](k_3[H^+]/K_a + k_2)$ equals $k_4[OH^-]$. This is near the pH of maximum stability of diimine, pH 6, represented by the minimum in curve A in Figure 3. The values of k_2 and k_3 in Table 2 are second-order rate constants since the water concentration is explicitly separated in equation 8[19].

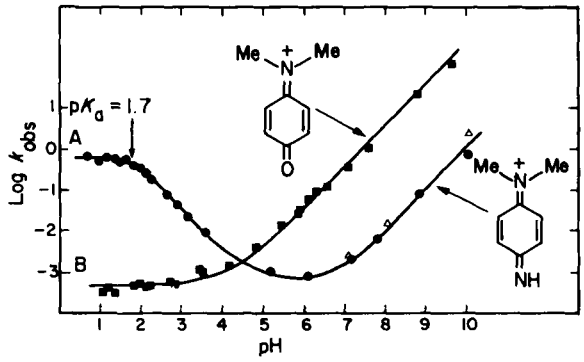
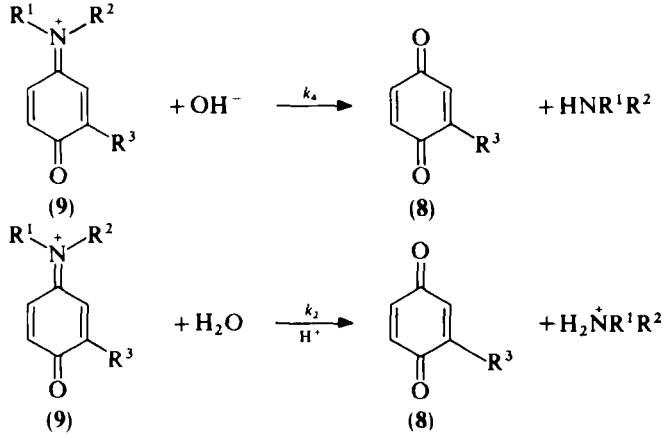


FIGURE 3. The effect of pH on the hydrolysis rate of *N,N*-dimethylquinonediimine (curve A) and monoimine (curve B)[19]. ● Diimine formed by Ce(IV) oxidation of diamine; O monoimine formed by I_2 oxidation of *p*-aminophenol; and Δ hydrolysis of diimine measured by Tong[17]. Curve A calculated from equation 8 using the values in Table 2. Curve B calculated from equation 9 using the values in Table 3

As methyl groups are added to the ring, the electron density on the charged nitrogen increases and k_4 decreases. Similarly, on going from Me to Et on this nitrogen, k_4 decreases.

The value of k_3 also decreases in the same manner, although the carbon to which the neutral amino group is attached is now the site of attack. Although the trend is small, k_2 actually increases slightly for deamination of the protonated amine as electron density increases. Given the variable ionic strength in the acid solutes (below pH 2) where these measurements are made[19], the differences may not be too meaningful.

Deamination of *p*-*N,N*-dialkylmonoimines has also been studied by Nickel and Jaenicke[20], and Tong and Glesmann[31]. The reaction product is a *p*-benzoquinone resulting from attack by OH^- in alkaline solution, or by H_2O in neutral and acid solution. The rate constant k_4 in alkaline solution is ~ 100 times larger than the value for the



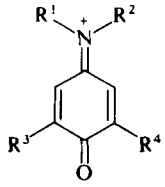
corresponding quinonediimine[31]. Nickel and Jaenicke[20] also studied acid solution and observed an additional influence due to buffer anions (general-base catalysis), particularly citrate. Their observed rate constants as a function of pH are given by equation 9, where

$$k_{obs} = k_4[OH^-] + k_2[H_2O] + k_5[B^-] \quad (9)$$

B^- represents a general base. At constant pH (pH = 4.5), the observed rate constant was proportional to the citrate concentration[20]. Above pH 6, the ionic strength dependence was consistent with the reaction of singly charged species of opposite sign; below pH 3, the dependence was very small[20]. A plot of log k_{obs} as a function of pH is shown in Figure 3 (curve B) for *N,N*-dimethylquinoneimine deamination. The rate is very slow in acid solution except when citrate ion is also present. Rate constants k_2 and k_4 are given in Table 3 for several compounds.

Comparing k_4 values in Tables 2 and 3, it is clear that the *N,N*-dialkylmonoimines are ~ 100 to 200 times more reactive toward hydroxide than are the corresponding diimines. In neutral-to-slightly-acid solution, they are slightly less reactive, although different products are formed. In a strongly acid solution, the diimine clearly is more reactive due to the formation of a protonated species.

TABLE 3. Deamination rate constants of *p-N,N*-dialkylquinonemonoimines

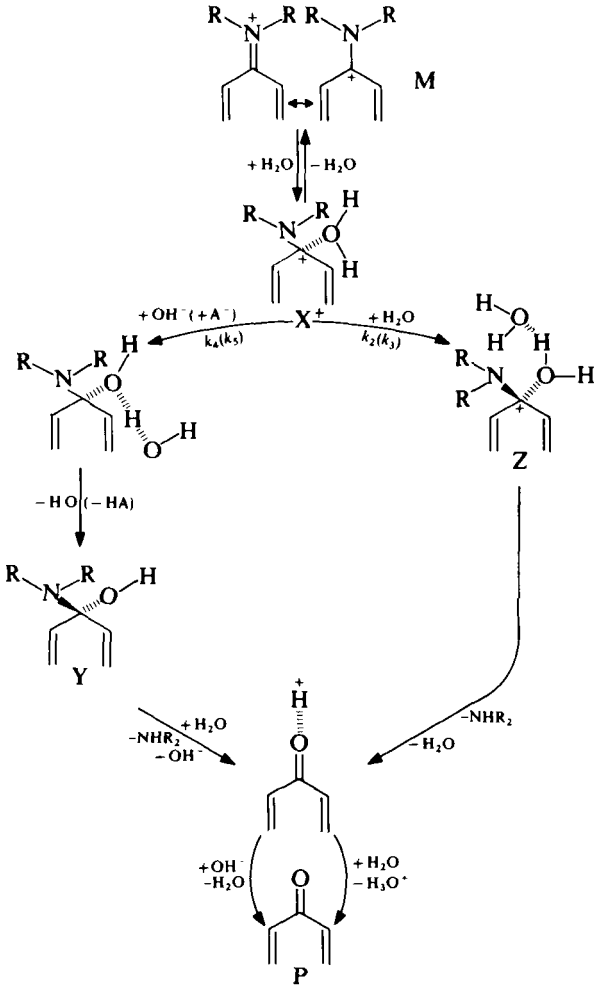


R¹	R²	R³	R⁴	k_4 (10^4 M^{-1} s^{-1})	k_2 (10^{-6} M^{-1} s^{-1})	Reference
Me	Me	H	H	240 ± 10	7.4 ± 0.6	20[a]
				200		[b]
Me	CH_2CH_2OH	H	H	310	—	31[c]
Me	Me	Me	H	26 ± 2	0.96 ± 0.09	20
Me	Me	Me	Me	3.1 ± 0.03	0.16 ± 0.03	20
Et	Et	H	H	100 ± 5	1.4 ± 0.2	20
Et	Et	Me	H	11 ± 1	0.17 ± 0.03	20
				15.8	—	31
Et	Et	Me	Me	1.3 ± 0.1	0.04 ± 0.02	20
$-(CH_2)_4-$		H	H	61.7	—	[b]

[a] 25 °C, $\mu = 0.3$
[b] E. R. Brown, unpublished work.
[c] 25 °C, $\mu = 0.37$.

The preceding results have prompted Nickel and Jaenicke[20] to propose Scheme 2 as the common reaction mechanism for loss of *N,N*-dialkylamine from *N,N*-dialkylquinonediimines and monoimines.

A preceding solvation equilibrium ($K > 10^{-5}$ M^{-1}) is assumed to occur. This solvation complex reacts via k_4 in alkaline solution, or via k_2 or k_3 in neutral and acid solution. In pathway k_4 a proton is transferred to OH^-, or to a general base, from the adduct X^+, which rapidly loses water to form Y in an irreversible step. The dialkylamine is split off by



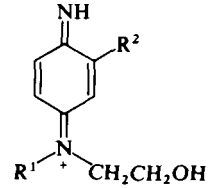
SCHEME 2. Common reaction mechanism for deamination of *N,N*-dialkylquinoneimines[20]

the attack of water and the loss of OH^-, forming a transient, positively charged intermediate which leads to product P. In acid solution, water attacks the adduct X^+, leading to the ring Z^+. This intermediate decomposes in a concerted reaction, losing both water and dialkylamine, to form the same positively charged intermediate which decomposes to P. In strongly alkaline solution, direct attack of OH^- (not shown in Scheme 2) upon the quinonediimine or monoimine is possible, without formation of the solvated species X^+ [17].

C. Pseudobase Formation

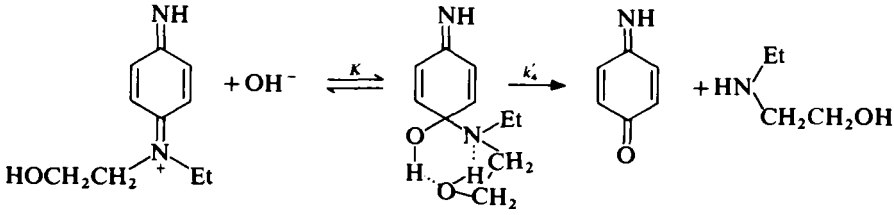
The positively charged quinonediimine, formed by the oxidation of *N,N*-dialkylphenylenediamine, can be stabilized toward deamination by internal cyclization

TABLE 4. Pseudobase equilibrium constants and deamination rate constants of *N*-β-hydroxyethyldiimines[28]



R^1	R^2	log *K*	$k_4'(M^{-1}s^{-1})$
Et	H	5.10	1.4×10^{-1}
CH_2CH_2OH	H	5.88	0.8×10^{-1}
Et	Me	4.18	2.5×10^{-1}
CH_2CH_2OH	Me	5.05	1.4×10^{-1}

when the alkyl group is replaced by a β-hydroxyethyl group, or a β-sulfonamidoethyl group. Such quinonediimines form pseudobases (**10**), probably through intramolecular hydrogen bonding, after the addition of base[28]. Such adducts form reversibly and deaminate several orders of magnitude more slowly than their dialkyl counterparts. The equilibrium constant for pseudobase formation and the deamination rate for several adducts of diimines were measured by Tong and coworkers[28]. Values for *K* and k_4' are given in Table 4 for several β-hydroxyethyl-substituted diimines. Comparison with values of k_4 in Table 2 shows that the rate constants are 10^4 to 10^5 times smaller for deamination of the adduct.

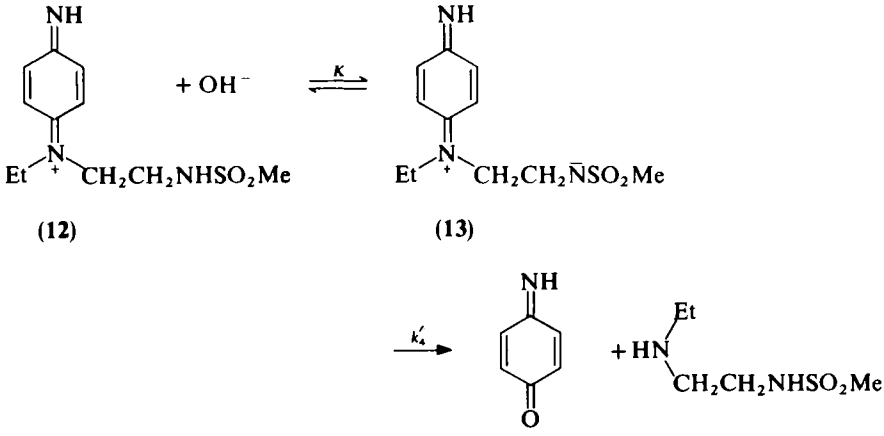


(**11**) (**10**) (**7**)

In the case of β-methyl sulfonamidoethyl substitution, the sulfonamido proton ionizes on the quinoneimine forming zwitterionic pseudobase (**13**)[17]. The rate constant for deamination in this case is only ~ 100 times smaller than the rate constant for deamination of **12**, due to the overall charge reduction on the diimine. The effect is much greater for monoimines, as shown in Table 5. The net effect of pseudobase formation is to yield observed kinetics that approach or become independent of pH as pH increases because the dominant species in solution, the pseudobase, is so stable.

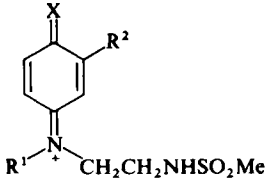
D. *N*-Alkylquinonemonoimines

These compounds react in base, but do not undergo deamination. Instead, they undergo slow ionization to a tautomeric Schiff base, which then cleaves by hydrolysis. The slow tautomerization of several compounds has been studied in alkaline phosphate buffer[32].



(12) (13)

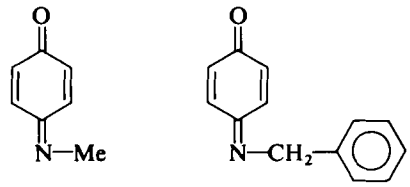
TABLE 5. Ionization equilibrium constants and deamination rate constants of *N*-β-methyl sulfonamidoethylimines



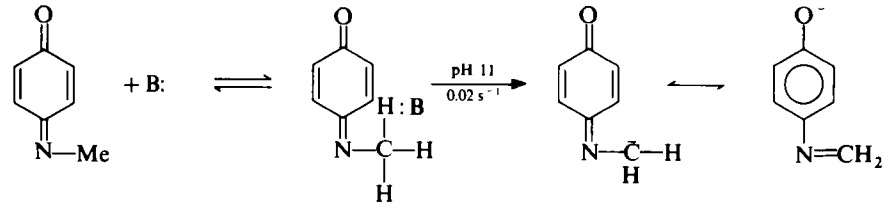
Structure R^1	R^2	X	log *K*	QDI$^+$ log k_4	QDI (ionized) log k_4'
Et	H	=NH[a]	5.13	4.30	2.34
Et	Me	=NH[a]	4.48	3.65	2.48
Et	H	=O[b]	8.15	6.69	1.75
Et	H	=O[b]	9.50	7.36	0.83

[a] Ref. 28.
[b] Ref. 31.

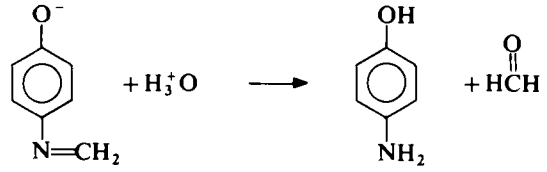
The observed rate constants for **14** and **15** are $\sim 0.02\ s^{-1}$ at pH 11, and the products are the corresponding Schiff bases (**16**), formed by general base-catalyzed ionization of the alkyl group.



(14) (15)

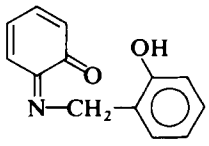


(14) (16)



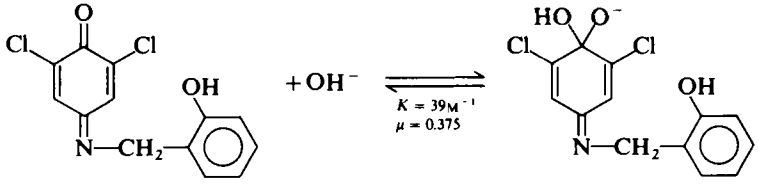
(16)

Upon acidification, rapid and quantitative formation of the corresponding aminophenol is observed along with the corresponding aldehyde, which in the case of **14** is formaldehyde, detected by chromotropic acid[32]. A detailed hydrolysis of the Schiff base of **17** has been published by Reeves[33].

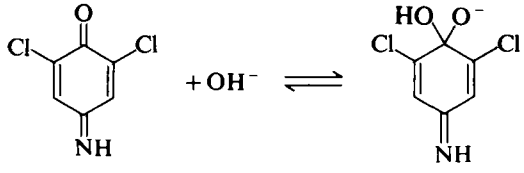


(17)

The pH dependence of tautomerization to the Schiff base is shown in Figure 4 for four monoimines in 0.375 ionic strength phosphate buffers. At high pH, log k vs. pH has a slope



(18)



(19)

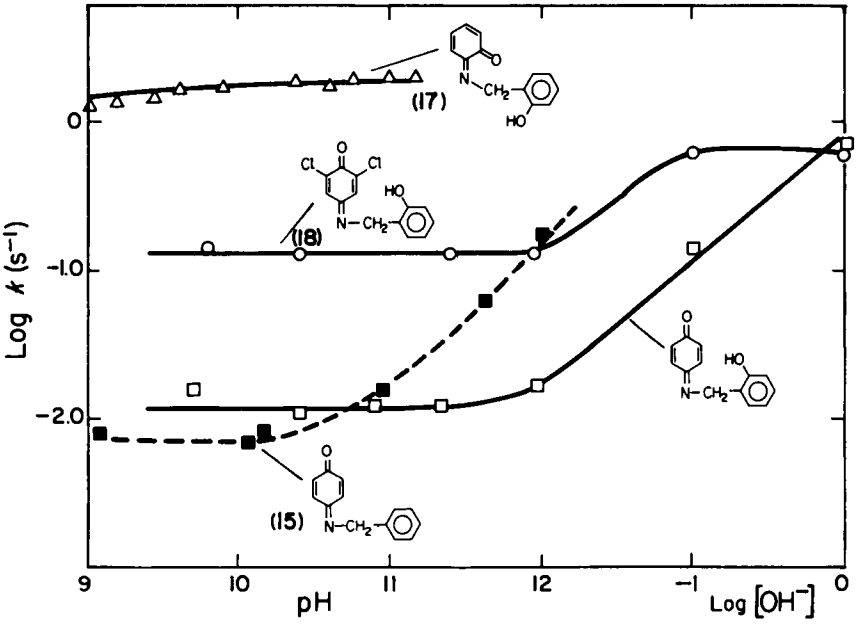
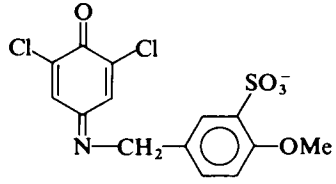


FIGURE 4. The effect of pH on the conversion of quinonemonoimines to the corresponding Schiff bases in phosphate buffer ($\mu = 0.375$)

of unity, indicating that OH^- is the most reactive base attacking the monoimine. The pH dependence of **18** is caused by formation of a reversible hydroxide adduct of the quinoneimine, observed spectrally[32]. The author has observed similar adduct formation with 2,6-dichloro-*p*-quinoneimine (**19**) at $\mu = 0.375$ with $K = 63\ M^{-1}$.

A more detailed study of the tautomerization of monoimine (**20**) has yielded the separate rate constants for each of the four different bases present in phosphate buffer in alkaline solution.



(20)

The rate constants listed in Table 6 are used to calculate the solid line in Figure 5 for the observed tautomerization rate constants (points) of **20**. The hydroxide adduct equilibrium for **20** is $39\ M^{-1}$, causing the observed rate constant to level off at high pH, as shown in Figure 5. Tautomerization of the corresponding *N*-alkyldiimines has not been studied.

Hartke and Lohmann[34] studied the reaction of primary and secondary amines with 1,2-naphthoquinone-4-sulfonate in aqueous solution. In order to explain their products, they

TABLE 6. Rate constants for base-catalyzed tautomerization of **20**[32]

Base	k_{base} ($M^{-1} s^{-1}$)
OH^-	159
PO_4^{-3}	0.75
HPO_4^{-2}	0.25
H_2O	0.02[a]

[a] Value of $k_{H_2O}[H_2O]$ in s^{-1}.

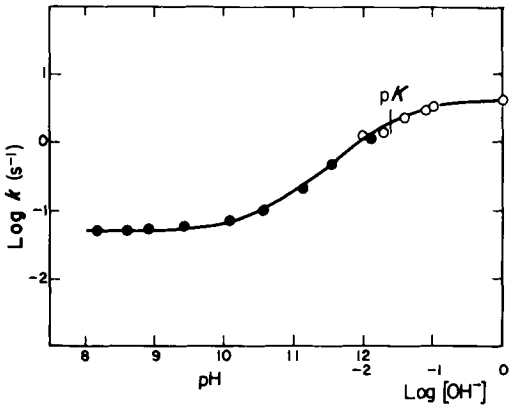
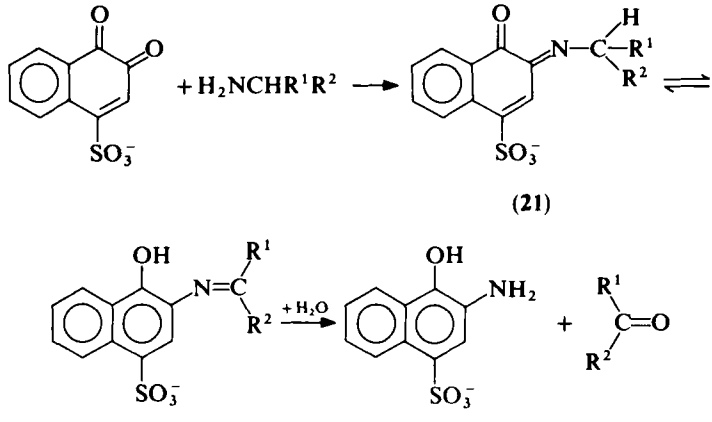


FIGURE 5. The effect of pH on conversion of monoimine **20** to Schiff base at 25 °C[32]. ● Phosphate buffer, $\mu = 0.375$; ○ NaOH solution, $\mu = 0.375$ with added NaCl. Solid line calculated using the rate constants in Table 6

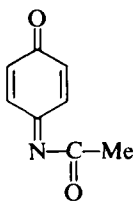
postulate the formation of an *o*-quinoneimine (**21**) which they suggest can tautomerize to the Schiff base (**22**). This unisolated intermediate then undergoes hydrolysis to the 2-



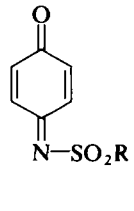
aminonaphthol-4-sulfonate (**23**). When the amine was benzylamine, benzaldehyde was detected in the reaction mixture. The corresponding carbonyl compound was also isolated when the amine was methylamine, ethylamine and *i*-propylamine.

E. Monoimides and Diimides

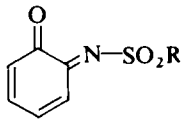
The hydrolysis of several monoimides and diimides has been studied in varying detail. The types of compounds discussed here are shown by structures **24**–**28** below. *N*-acetyl-*p*-quinoneimine (**24**) is the two-electron oxidation product of acetaminophen(*N*-acetyl-*p*-aminophenol), formed electrochemically[35, 36] on a carbon electrode in aqueous solution, or by oxidation with lead tetraacetate in benzene, or with freshly prepared silver oxide in either benzene or chloroform in almost quantitative yield[37].



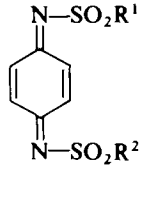
(**24**)



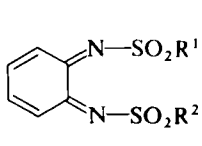
(**25a**)



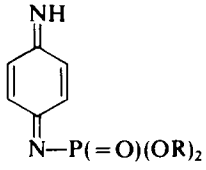
(**25b**)



(**26**)

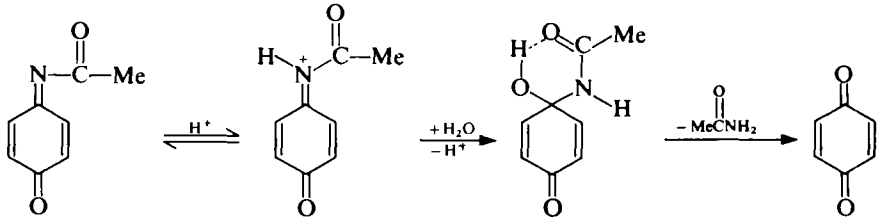


(**27**)



(**28**)

The hydrolysis mechanism of **24** in acid solution has been studied electrochemically in some detail by Kissinger and coworkers[35]. The initial attack by water on either **24** or its protonated form is the same as described for other diimines earlier (Scheme 1). The intermediate carbinolamide (**29**), however, is quite stable, decomposing to produce *p*-benzoquinone and acetamide on a much slower time scale than observed for the loss of **24**. The hydration kinetics to form **29** are shown in Figure 6 at $\mu = 0.5$ at 25 °C. The solid line through the points is given by equation 10, where the two terms represent attack by H_2O



(**24**) (**29**)

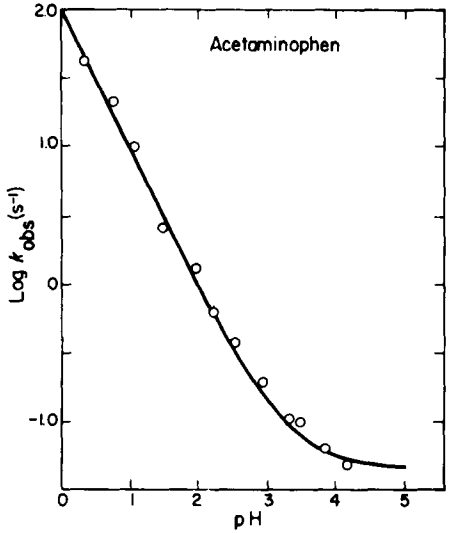


FIGURE 6. The pH dependence of the hydration rate constant of *N*-acetyl-*p*-quinoneimine (**24**) formed electrochemically[34]. Points experimentally determined at 25 °C, $\mu = 0.5$; line calculated using equation 10; $k_1 K_a = 98.2\ M^{-1}s^{-1}$; and $k_2 = 0.047\ s^{-1}$

on the protonated form of **24** (K_a is the protonation constant) and on **24** itself. The line is calculated using $k_1 K_a = 98.2\ M^{-1}\,s^{-1}$ and $k_2 = 0.047\ s^{-1}$. The protonation of **24** must

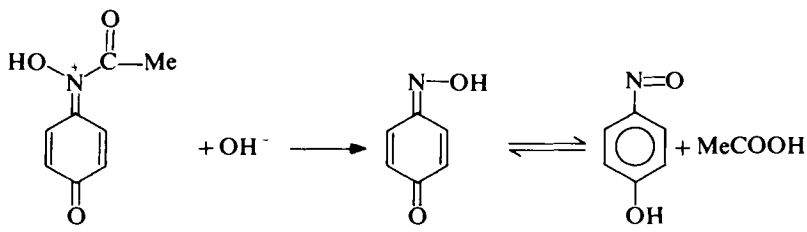
$$k_{obs} = k_1 K_a[H^+] + k_2 \tag{10}$$

occur well below pH 0, because the slope of the line in Figure 6 is still unity at 0.5 M $HClO_4$, the most acid solution studied.

Both HSO_4^- and phosphate ($H_2PO_4^-$) accelerate the rate in a linear fashion in this pH range. The effect is not general; citrate and SO_4^{2-} show no buffer concentration effect[35].

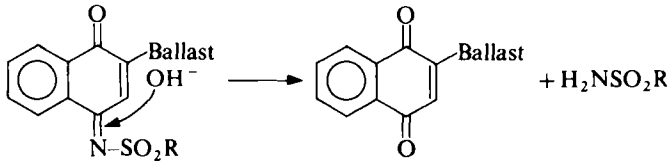
Deamidation of **29** to form quinone was studied only at 0.5 M and 0.1 M $HClO_4$. The rate constant increases with acid concentration, yielding a second-order rate constant, $k_{obs}/[H^+]$, of $0.25\ M^{-1}\,s^{-1}$. Details of the deamidation at higher pH are not available.

A brief study of the hydrolysis of a related compound, *N*-hydroxy-*N*-acetamido-*p*-quinoneimine (**30**), shows that acetic acid is rapidly released, forming nitrosophenol. The reaction is shown as an attack by hydroxide, because nitrosophenol appears in greater quantities at pH 6 than in 0.1 M $HClO_4$ in the electrochemical generation of **30**[36].

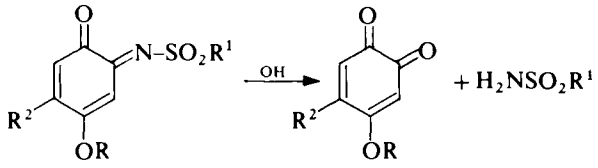


(**30**)

The hydrolysis of *N*-arylsulfonyl-*p*-quinoneimines (**25a**), R = Ar, and the related *p*-naphthoquinoneimines (**31**) with high molecular weight 'ballast' groups has been described by Hanson[38] for the use of these compounds in photographic imaging, where R is a dye species. Similar utility of the *ortho* analogs (**32**) has been described by Fujita[13, 39], along with synthesis and isolation of the appropriate quinoneimides[13]. The hydrolysis kinetics of the quinoneimides have been studied only in alkaline solution where hydroxide is the reactive species, attacking the sulfonimide group to release that group, and forming the corresponding quinone.

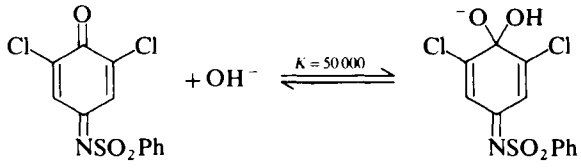


(**31**)



(**32**)

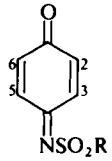
The reaction of *p*-quinonesulfonimides is first order in OH^- and goes to completion[40]. Electron-withdrawing groups on the ring, or on R when it is an aryl group, accelerate the reaction, whereas electron-donating groups decrease the rate constant. Table 7 shows the second-order rate constants ($k_{obs}/[OH^-]$) obtained from rate-constant measurements between pH 8 and 11 in phosphate buffer ($\mu = 0.375$). The rate constants vary over two orders of magnitude, depending on the substituent. Notice that *p*-naphthoquinonesulfonimide is about as reactive as 2-methyl-*p*-benzoquinonesulfonimide. Changing from phenylsulfonimide to methylsulfonimide has only a minor effect on the rate constant. 2,6-Dichloro-*p*-quinonesulfonimide (**33**) undergoes reversible adduct formation at pH 9.3 ($K = 50\,000$) and the adduct is only about 1/8 as reactive as the parent compound.

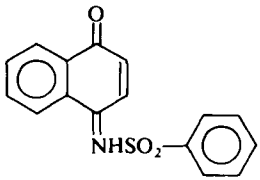


(**33**)

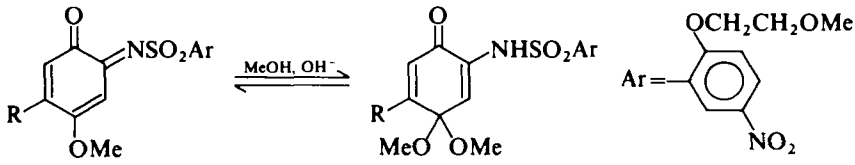
The hydrolysis of *o*-quinonesulfonimide is more complicated, and several species are formed. In alkaline methanol, Fujita[13] found significant amounts of the *p*-quinone monoacetal (**34**) formed initially, slowing the release of sulfonamide. The substituent R

TABLE 7. Bimolecular rate constants for deamidation of *p*-quinonesulfonimides in phosphate buffer[a]



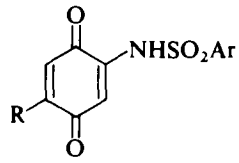
Substituent		R	k (10^4 M^{-1} s^{-1})
2-position	3-position		
H	H	Ph	2.6
H	H	Me	2.1
H	Me	Ph	2.6
Me	H	Ph	0.70
2,6-Cl_2	H	Ph	7.95 1.17 for OH^- adduct
H	H	4-O_2NPh	5.2
H	H	3-O_2NPh	3.7
			0.52

[a] Quinonesulfonimide is formed by oxidation of the corresponding *p*-sulfonamidophenol with two or four equivalents of ferricyanide in phosphate buffer ($\mu = 0.375$)[40].

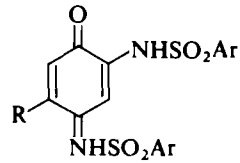


(34)

also affects the reaction. When R is methyl only ~ 60% of the sulfonamide is released, but when R is *t*-butyl > 80% is released. Two other products were identified, both a result of 1,4 addition to the ring. Compound **35** results from attack by hydroxide and **36** results



(35)



(36)

from attack by the sulfonamide released from the original *o*-quinonesulfonimide. As much as 12% **36** is produced when R is methyl. Rates of sulfonamide release in alkaline methanol were slow with a $t_{1/2}$ = 0.4 h for R = methyl and $t_{1/2}$ = 1.3 h for R = *t*-butyl[13]. No kinetic studies for the hydrolysis of bis-sulfonimido-*o*-quinone (**27**) have been reported.

Quinoneimine phosphonamides (**28**), where R = Ph, have been formed by oxidation of the corresponding *p*-aminophenol with ferricyanide at pH 11[41]. No detailed kinetic study was performed, but both the quinone and the phosphate fragment were isolated from the reaction mixture by thin-layer chromatography and comparison with authentic compounds. The half-life for deamidation at pH 11 is < 0.3 s in phosphate buffer.

IV. COUPLING CHEMISTRY

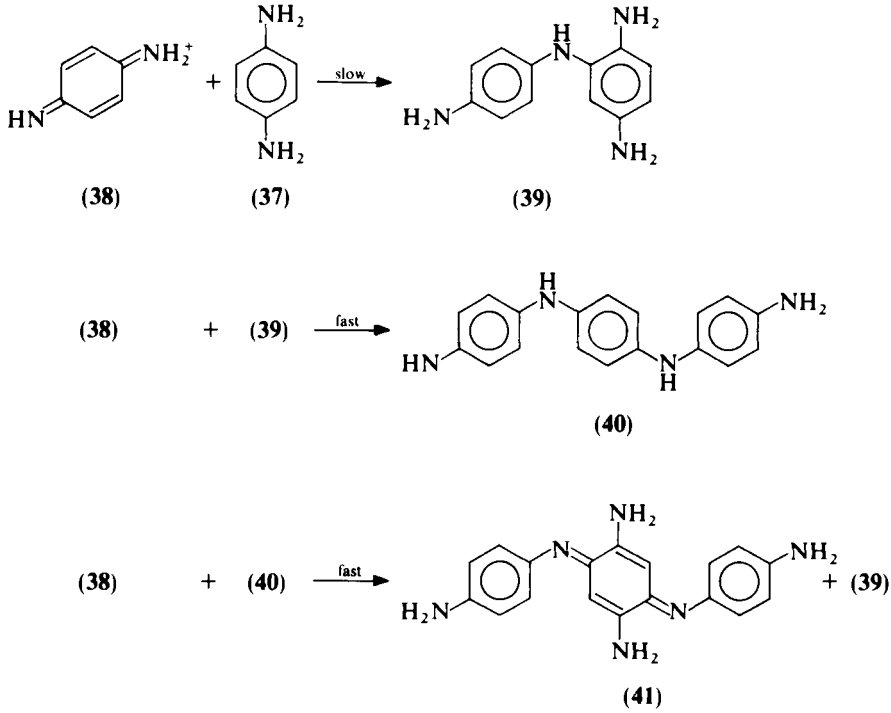
Coupling of quinoneimines to nucleophiles has generally been studied by chemical or electrochemical oxidation of the parent aminophenol or phenylenediamine to form the corresponding quinoneimine. This means that the quinoneimine often exists in the presence of starting material, which is, itself, a reasonable nucleophile and can react in competition with other nucleophiles in the system. These self-coupling reactions have been studied in some detail to identify products, which are often highly colored dyes, and to determine the exact coupling mechanism.

A. Self-coupling

The oxidative coupling of *p*-phenylenediamine (**37**) produces the trimeric species, Bandrowski's base (**41**), originally isolated from alkaline oxidation of the starting material by ferricyanide[42] or oxygen[43]. The structure was identified later by Corbett[44] and Dolinsky and coworkers[45] and the mechanism was studied by mixing less than two molar proportions of ferricyanide with *p*-phenylenediamine as a function of pH[46]. The reaction is first order in both diamine and protonated diimine (**38**), but the diamine concentration remains constant throughout the reaction, yielding an observed pseudo-first-order reaction. The pH dependence of the second-order rate constant is consistent with the attack of protonated diimine (**38**) on the neutral diamine, as described in Scheme 3. The reaction consumes three diimine species for each molecule of **41** formed, regenerating one molecule of diamine. The observed second-order rate constant increases linearly as the pH drops from pH 10 and pH 7.5, after correction for the deamination reaction described in Section III.

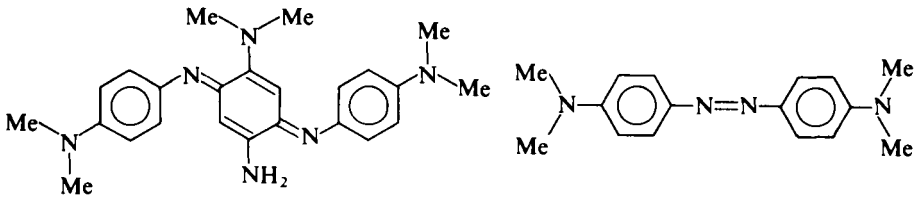
At low pH, the reaction is complicated by the formation of the intermediate radical cation, causing a decrease in the observed rate constant. Correcting for this effect, and for the amount of the reactive species in solution at each pH, Corbett[46] reports a pH-independent rate constant of 3.43×10^3 M^{-1} s^{-1} for the slow step in Scheme 3 at 30 °C. This yields a maximum in the observed rate at about pH 6, due to the protonation equilibria of both diimine (pK = 5.75) and diamine (pK = 6.44). The observed half-life for the formation of **41** at pH 5.7 for a 10^{-4} M solution of *p*-phenylenediamine, mixed with 10^{-4} M diimine is 35 s. In alkaline solution, substantial amounts of 4,4′-diaminoazobenzene are also observed[44]. Sakata and coworkers[47] obtained **41** in ethanol solution by combining the intermediate radical cation with *p*-phenylenediamine. About 6.5 radical species were required to form one molecule of **41** and ~12% 4,4′-diaminoazobenzene, independent of the amount of diamine present initially. Oxidation of diamine by Br_2 also produced **41** in ethanol.

Similar studies by Sakata and coworkers[47] were made using *N*,*N*-dimethyl-*p*-phenylenediamine radical and substrate. After 4 days, the hexamethylated Bandrowski's



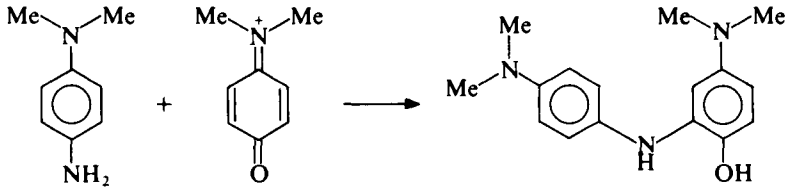
SCHEME 3. Mechanism for formation of Bandrowski's base[46]

base (**42**) was isolated, along with an equivalent amount of 4,4′-bis(dimethylamino)-azobenzene (**43**) and an unknown substance.

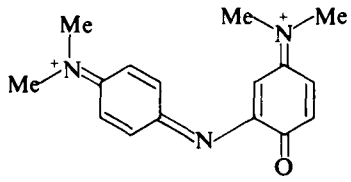


(**42**) (**43**)

Electrochemical oxidation of **44** in aqueous solution at pH 4 produces a violet solution (λ_{max} = 550) with the consumption of three electrons per mole of **44**, enough required to form **42**. The explanation given (without product isolation) is that some deamination occurs and only a coupling with the quinone immonium salt, similar to the first coupling reaction of Scheme 3, occurs[48]. Species **45** thus formed is then oxidized by the loss of four electrons to form the colored species **46** in solution. In alkali, the solution is blue (λ_{max} = 720), which compares with the alkaline ethanol solution color of **42** mixed with **43**



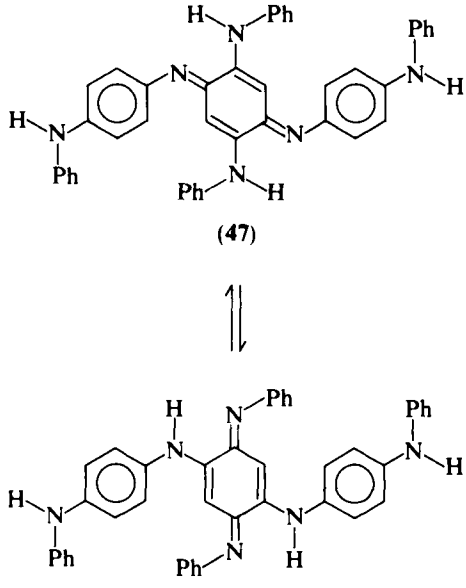
(44) (45)



(46)

(λ_{max} = 660 nm)[47]. Both Sakata and coworkers[47] and Lelievre and coworkers[30,48] refer to radical coupling as a possible mechanism to form these colored species.

Another electrochemical oxidation study of *N*-phenyl-*p*-phenylenediamine in aqueous acetate buffer also yielded three electrons per mole of substrate, which the authors[49] suggest is a result of the formation of the trimeric condensation product (**47**), shown in two tautomers. The relatively insoluble product is capable of undergoing a two-electron oxidation and a two-electron reduction, but no products were isolated. It is clear that N-substitution on *p*-phenylenediamines complicates the self-coupling chemistry of these



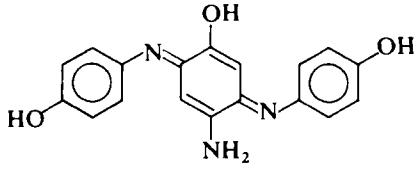
(47)

species, leading to a number of highly colored condensation products, which are difficult to isolate and characterize.

In an attempt to understand these self-coupling reactions in more detail, Bishop and Tong[50] studied the kinetics of azo dye formation from quinonediimines of *N,N*-diethyl-*p*-phenylenediamines. Only small amounts of dye are formed by coupling at the primary nitrogen group, in competition with deamination of the dialkyl amino group in the alkaline pH range studied. The amount of dye formed was independent of pH, and was at a maximum at half oxidation of the diamine. Thus, the mechanism has the same [OH^-] dependence as deamination, and involves both diamine and diimine. It is not possible to distinguish a mechanism involving coupling of these two species from a mechanism involving radical–radical coupling, since they have the same dependence on the initial concentration of diamine and diimine. In addition, the radical would be the neutral radical, which accounts for the hydroxide dependence, and this species does not exist in measurable concentrations[50].

The amount of azo dye increases with the substitution of electron-withdrawing groups on the aromatic ring, changing from ~ 1.8% for no substitution to 24% for a single chlorine atom. Complete chloro substitution of simple *p*-phenylenediamine shows essentially complete azo dye formation (77–84%), when oxidized by chlorine or bromine in anhydrous methanol[51]. The reaction also requires the presence of acid, and presumably involves direct coupling of the diimine with its protonated form because only the diimine salts are initially present.

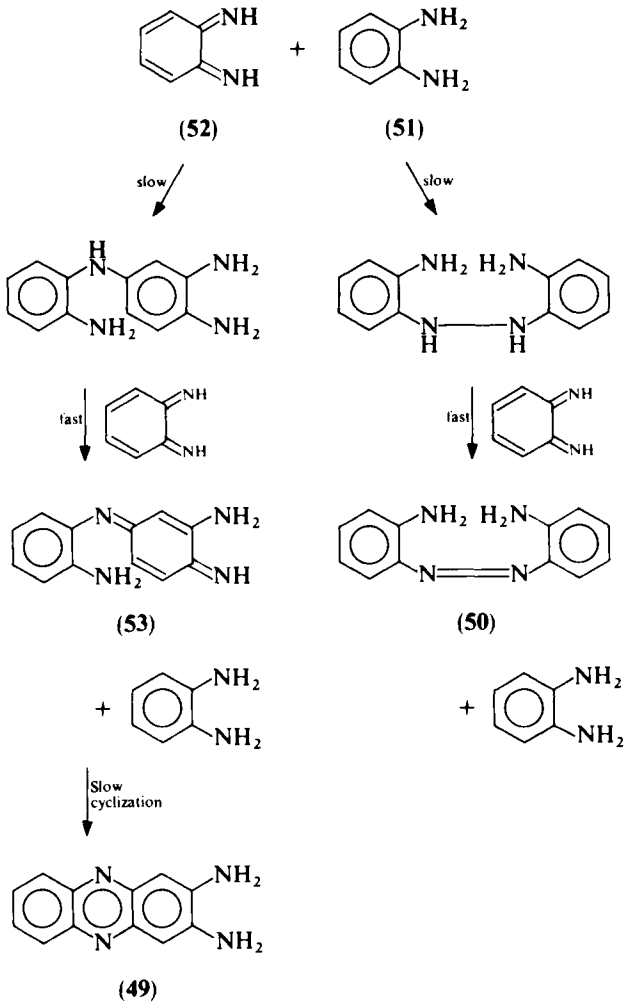
Brown and Corbett[52] extended earlier mechanistic studies of *p*-quinonediimine self-coupling to the same reaction by *p*-quinonemonoimine in the presence of its parent, *p*-aminophenol. The reaction mechanism is essentially the same as outlined in Scheme 3 to form the product trimer (**48**), but it is kinetically complicated due to the various ionic forms of monoimine and aminophenol which exist from pH 7 to 12. The rate-determining



(**48**)

step is the first coupling reaction between monoimine and aminophenol. The rate constant between protonated monoimine and parent aminophenol is 1.9×10^4 $M^{-1} s^{-1}$, which is about six times faster than for diimine coupling with its parent phenylenediamine. The rate constant for coupling of the protonated monoimine with the aminophenolate anion is 130 times faster than with the neutral aminophenol. Reaction between neutral monoimine and aminophenolate anion is very slow, and it is complicated by another reaction at high pH, as indicated by the lowered yield of **48** formed. Between pH 7 and 11.5 **48** forms in 100% yield due to slow deamination of the monoimine, which is the only other known competing reaction.

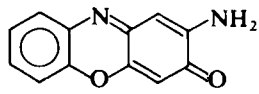
o-Quinonediimines and *o*-quinonemonoimines also undergo self-condensation reactions to form dimeric products. In the case of the diimine, the two major products are 2,3-diaminophenazine (**49**) and 2,2′-diaminoazobenzene (**50**)[15]. The ratio of these products depends on solvent and pH. In aqueous buffer the product is almost entirely **49**, and in diethyl ether, it is exclusively **50**[53, 54]. The products form by partial oxidation of the *o*-diamine to the *o*-diimine (**52**), which couples slowly with the parent in two parallel pathways[53, 54]. The coupling of diimine with diamine is assumed by analogy with



(49)

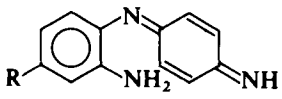
Corbett's work on *p*-diimines[44,46] and by the observation that the formation of **50** is accelerated in diethyl ether by addition of diamine to a diimine solution[54].

o-Quinonemonoimine couples with its parent aminophenol slowly in aqueous solution at pH 4.5–10 to form 2-aminophenoxazin-3-one (**54**), along with some *o*-benzoquinone[53]. The reaction mechanism is probably similar to that proposed for the formation of **49** involving coupling of *o*-quinoneimine and subsequent cyclization[53].

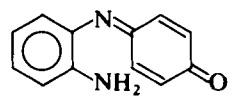


(54)

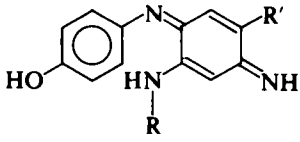
The cyclization reaction involving formation of phenazines from several *N*-(2'-aminophenyl)quinoneimines has been studied in aqueous solution as a function of pH[55]. In examples **55–58**, the cyclization reaction occurs only at pH 6–10. For compounds **56**, **57**



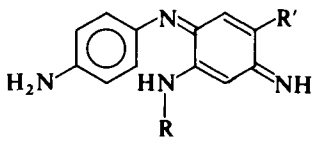
(**55**) **a**: R = H
b: R = Me
c: R = Cl



(**56**)

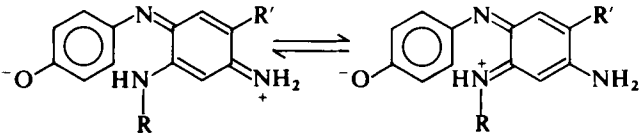


(**57**) **a**: R = R' = H
b: R = H, R' = Me
c: R = R' = Me
d: R = Ph, R' = Me



(**58**) **a**: R = R' = H
b: R = H, R' = Me
c: R = R' = Me
d: R = Ph, R' = Me

and **58**, the reaction clearly involves the protonated diimine, which, in the case of **57**, is a zwitterion[56]. The monoimine couples quantitatively from pH 5 to 12[55]. At low pH, hydrolysis at the azomethine bond competes with cyclization, forming *o*-phenylenediamine and quinoneimine from **55** and *p*-aminophenol or *p*-phenylenediamine



reactive form of **57**

and *p*-quinoneimine from **57** and **58**, respectively. At high pH, the competing reaction is the hydrolysis of the primary imine group. These reactions are in contrast to those of *N*,*N*-dialkyl-*p*-quinonediimines (described earlier), where the primary imine is preferentially cleaved in acid solution and the substituted imine is cleaved in alkaline solution.

The cyclization rate constants, expressed in terms of the reactive species, vary widely depending on substituents. For **55**, the observed rate constant decreases by a factor of 10 per pH unit from pH 6 to 9, which is above the p*K* for ionization of the protonated diimine. Rate constants and p*K* values are summarized in Table 8, which also includes data for **56** for comparison. Interestingly, **56** reacts slowly in acid to form 2,3-diaminophenazine **49** in high yield. The cleavage products, benzoquinone and *o*-phenylenediamine, apparently cross-oxidize to form **49** according to Nogami and coworkers[54].

TABLE 8. Rate constants for cyclization of **55** at 30 °C[a]

Structure	k_c (s^{-1})[b]	p$K^{a,c}$
55a	27.6	4.3
55b	13.1	4.2
55c	443.0	4.2
56	0.0013	—

[a] Ref. 55.
[b] Rate constant calculated for protonated form.
[c] Measured spectrally for protonated diimines.

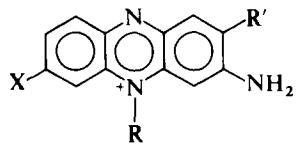
Cyclization of **57** is quantitative between pH 7 and 10 to form **59b** or **60b**, but the rate constants are quite different[56]. As R goes from H, to Me, to phenyl, the rate constant, expressed in terms of the diimine cation concentration, increases significantly as shown in Table 9. The same rate constants for structure **58**, forming **59a** or **60a**, are 10–100 times

TABLE 9. Rate constants for cyclization to phenazine[a]

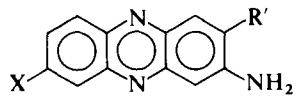
R	R′	Structure	k(s^{-1})[b]	Structure	k(s^{-1})[b]
H	H	**57a**	8.4×10^{-5}	**58a**	6.1×10^{-6}
H	Me	**57b**	7.0×10^{-5}	**58b**	2.7×10^{-6}
Me	Me	**57c**	1.36×10^{-3}	**58c**	1.4×10^{-5}
Ph	Me	**57d**	2.30×10^{-2}	**58d**	2.2×10^{-3}

[a] Measured at 30 °C; Ref. 56.
[b] Based on protonated form of reactant.

lower ($t_{1/2} \sim 5$ h at 30 °C), and may well be closer to the rate constant for formation of diaminophenazine (**49**), from *o*-phenylenediamine and *o*-quinonediimine.



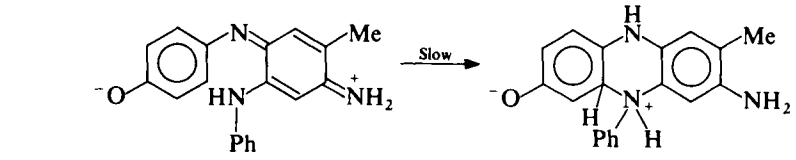
(**59**) **a**: X = NH_2
b: X = OH



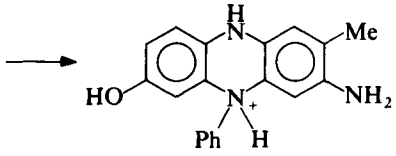
(**60**) **a**: X = NH_2
b: X = OH

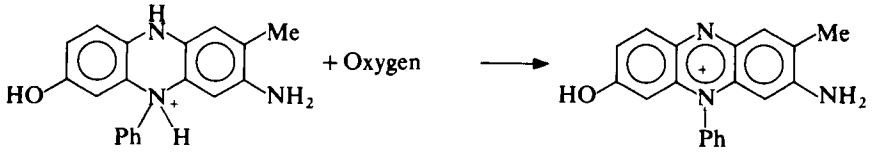
In some compounds, such as **57d**, reactant loss rate is faster than the rate of appearance of the phenazine (**59b**), due to slow oxidation of the intermediate dehydrophenazine[56]. Most experimental studies[55-57] rely on oxygen dissolved in solution to bring about the oxidation to form **59** and **60**. Ferricyanide, added to the solution, rapidly increases the phenazine product formation, even when added after initial mixing of **57d** with pH 8 buffer.

The self-coupling of N-substituted *o*-quinoneimines has received little study. Berkenkotter and Neison[58] studied the oxidative coupling of *N*,*N*′,*N*′-triphenyl-*o*-phenylenediamine (**61**) in acetonitrile at a platinum electrode. The product, in 88 % yield, is



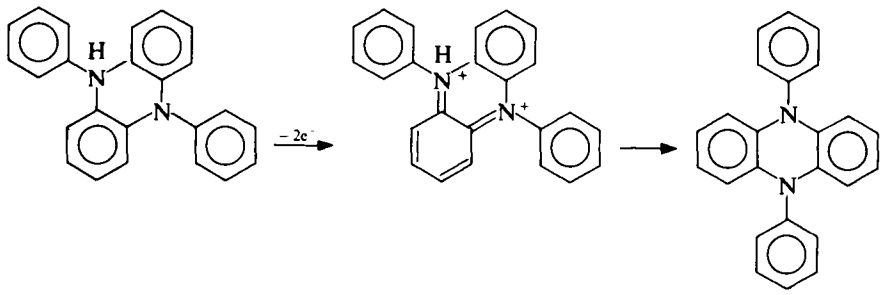
(57d)





(59b)

the corresponding 5,10-diphenyldihydrophenazine (**62**). The mechanism is presumed to occur by cyclization of the two-electron oxidation product, but contribution by the radical intermediate could not be ruled out. Similar complex coupling schemes were postulated by



(61) (62)

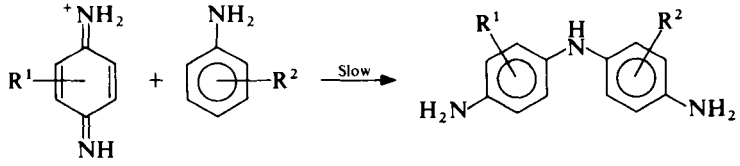
Haynes and Hewgill[59] to account for formation of N-substituted phenazines isolated from the chemical oxidation of methoxy-substituted anilines.

B. Coupling with Amines

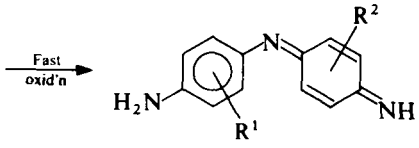
Although oxidative coupling of substituted *p*-phenylenediamines and *p*-aminophenols with the parent anilines yields highly colored solutions containing a mixture of products as

discussed earlier, Corbett and coworkers[60-63], in a series of papers, studied the initial coupling step in aqueous solution.

In the case of *p*-quinonediimines, the initial coupling kinetics indicate that anilines couple with the protonated diimine (**63**) in the rate-limiting step. The fast-oxidation step,



(**63**)

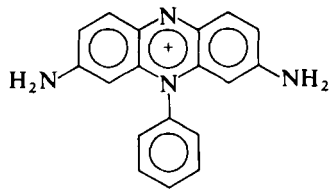


(**64**)

which produces indamine dye (**64**) occurs with excess diimine or ferricyanide in solution. In alkaline solution, above the pK_a of **63**, log k_{obs} decreases linearly as pH increases. The reaction is complicated by hydrolysis of the product dye, forming *p*-quinonemonoimine and *p*-phenylenediamine. Because the coupling reaction is slow, large excesses of aniline are necessary to form significant amout of dye.

A careful study[60] of substituent effects on both aniline and **63** with 21 compound combinations, involving three substituents, –Me, –OMe and –Cl, was carried out at 30 °C at pH 9. Electron-donating groups on aniline increase the rate constant, whereas the same group on **63** decreases the rate constant. The substituent effect on the diimine also includes the effect on pK_a of the protonated species, which was not measured separately. The results are summarized in Table 10. The second-order rate constant for coupling of the unsubstituted aniline with unsubstituted **63** (factor = 1.0) is 165 $M^{-1}\,s^{-1}$ at 30 °C[60]. The rate constant for substituted species is obtained by multiplying this value by the factors in Table 10.

An additional complication to the formation of indamine dye is the additional coupling of diimine and the cyclization of the product to form phenosafranine dyes (**65**)[61].



(**65**)

Substituents on aniline block this reaction, resulting in almost quantitative indamine dye formation.

Corbett[62] also studied the coupling kinetics of *p*-quinonediimines with *m*-aminoanilines. Again, the rate-limiting step in alkaline solution is the reaction of the

TABLE 10. Mean effect of substituents on coupling of **63** with aniline and *m*-aminoaniline at 30 °C

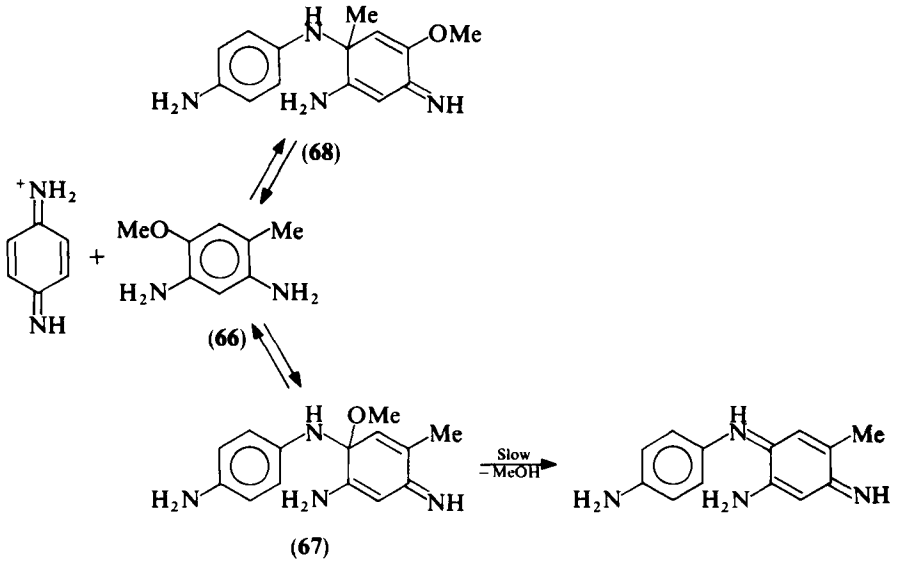
Diimine		Aniline[a]		*m*-Aminoaniline[b]	
Substituent	Factor	Substituent	Factor	Substituent	Factor
Me	0.234	2-Me	4.84	2-Me	5.33
Cl	1.98	3-Me	8.94	4-Me	3.03
		2-OMe	7.5	2,4-$(Me)_2$	14.3
		3-OMe	35	4-OMe	25
		3-Cl	0.37	4,6-$(OMe)_2$	800
		2-NH_2	1210		

[a] Ref. 60.
[b] Ref. 63.

protonated diimine with neutral *m*-aminoaniline. The second-order rate constant for coupling *m*-aminoaniline to *p*-quinonediimine is 2×10^5 M^{-1} s^{-1} at 30 °C[63], which is three orders of magnitude faster than the reaction of aniline with the same diimine. This increase is a result of the strong electron-donating effect of the second amino group on aniline.

The effect of methyl substituents in both reactants was also studied in alkaline solution. A methyl group on protonated diimine **63** yields a relative rate factor of 0.28 for coupling to *m*-aminoaniline, compared to a factor of 0.234 for coupling to aniline (Table 10). Surprisingly, addition of a second methyl group in either the 5- or 6-position of **63** had almost no additional effect on the rate constant. In the addition of methyl groups to *m*-aminoaniline, the effect is additive when two methyl groups are present (Table 10). A methoxy group accelerates the reaction even more and is additive, even when it is in the coupling position[63]. The rate-limiting step is still the initial coupling reaction; elimination of methanol is rapid.

The situation is more complex with 2,4-diamino-5-methoxytoluene (**66**), as shown in the scheme below. Initial coupling proceeds at two positions, but only the leuco-dye adduct

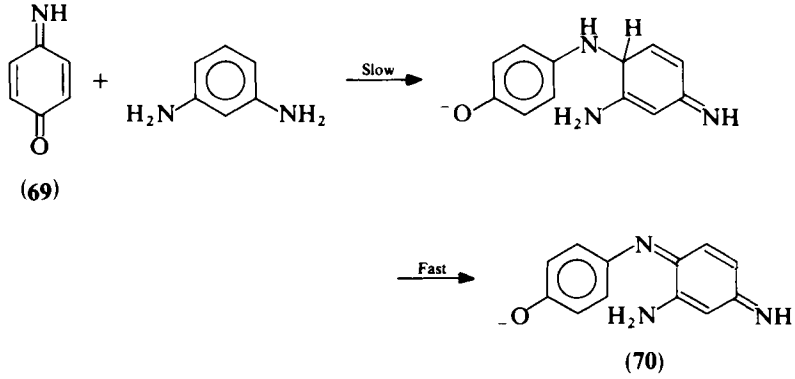


(67)

(**67**), formed by coupling at the *ipso* position to the methoxy group can eliminate methanol to form dye. The rate-limiting step now is the elimination reaction. The reaction proceeds in several steps. The fast process is through formation of adduct **67** and elimination. More slowly, adduct **68**, which is formed competitively with **67**, dissociates and dye is formed via **67**. Similar complicated coupling kinetics were also observed when diimine coupling with methyl-substituted aminophenols was studied, where methyl groups existed at the coupling position, *para* to OH or to NH_2[64].

Monoquinoneimines (**69**) also couple to aniline, although the observed reactions are slow. Competing reactions such as deamination and self-coupling can interfere. Corbett[63, 65] studied monoimine coupling with the more reactive *m*-aminoanilines, using excess aminoaniline to assure that coupling is the predominant reaction. The pH dependence of the kinetics suggests that, at high pH, significant contribution to the reaction occurs through reaction of the neutral monoimine **69**.

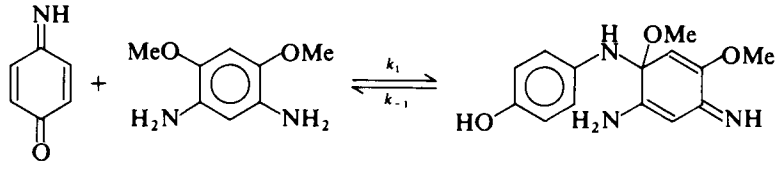
The reaction is controlled by the coupling step; the intermediate leuco dye is oxidized rapidly to the indophenol (**70**) either by the monoimine or by other oxidants in the system.



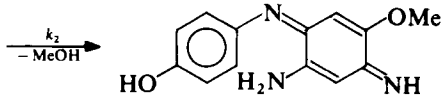
The rate constant for the conjugate acid of **69** is 3.53×10^4 M^{-1} s^{-1}, about six times lower than the rate constant for diimine (**63**; R^1 = H) conjugate acid. The rate constant for **69** coupling is only 11 M^{-1} s^{-1}, but the corresponding reaction of neutral diimine is not observed. Experimentally, the observed rate constants for monoimine coupling are almost 10^3 slower at all pH values than for diimine, because the conjugate acid pK is more than two pH units lower. This lowers the concentration of the active species by more than 100-fold, and it is six times less reactive anyway.

The effect of substituents on the reactivity of **69** are as expected. The contributions of methyl substitution on *m*-aminoaniline are additive, the rate constants being a factor of 4.8-fold higher for 2-Me, 3.7-fold higher for 4-Me, and 12-fold higher for 2,4-dimethyl substitution. Substitution of a methyl group on **69** decreases the rate by $\sim$ 20 in either the 2- or 3-position. One methoxy substituent on *m*-aminoaniline increases the rate constant by a factor of 17.3, and two groups increase it by a factor of 300[63].

The reaction of 1,5-dimethoxy-2,4-diaminobenzene (**71**) with **69** is somewhat more complicated than observed for other substituted anilines. Dye formation occurs through methanol elimination, which is faster than the forward coupling step at millimolar concentrations, but not fast at all pH values compared with reversal of the leuco-dye adduct (**72**) back to reactants, k_{-1}. The result is a complex pH dependence of the apparent rate constants, but the rate constant k_1 can be obtained[63].



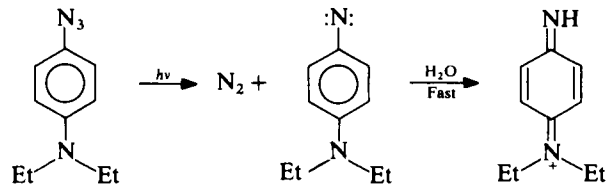
(69) (71) (72)



(73)

C. Coupling with Phenols and Naphthols

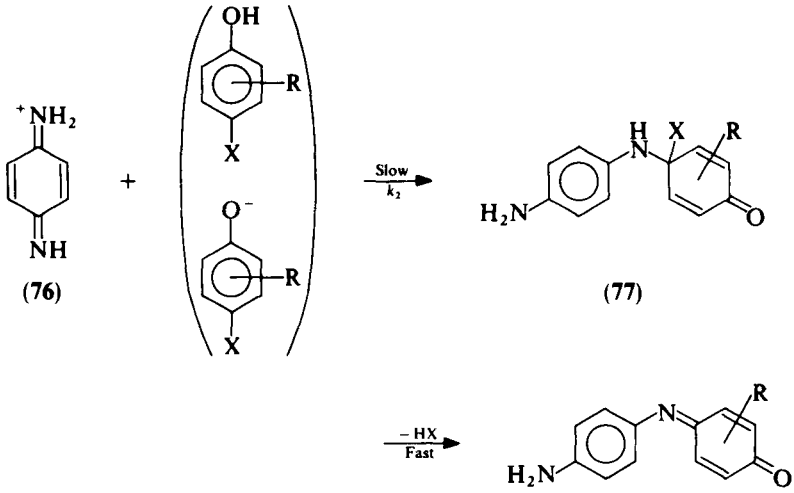
The interest in coupling reactions of diimines and monoimines with phenols has been extensive, due to the importance of the resulting dyes in color photography. Mechanistic studies of the reactions in alkaline and acid solution began with Tong and Glesmann[16, 66, 67] using ferricyanide to rapidly produce *N,N*-dialkylquinonediimines from the corresponding *p*-phenylenediamines. Later, work by Corbett[63, 68], using simple quinonediimine and phenols, confirmed the coupling mechanism postulated earlier. More recently, Pelizzetti and Saini[69] reproduced much of the earlier work and extended their studies to several other phenols and naphthols. Mann and coworkers[70, 71], and Baetzold and Tong[72] extended the experimental techniques of forming reactive diimine **75** by using flash photolysis of an azide precursor (**74**) in solution with the naphthol coupler. In this way, dye formation was studied in octanol, a solvent in which **75** is not very soluble[72].



(74) (75)

In aqueous solution, the rate-limiting step for dye formation is the initial coupling reaction of the conjugate acid of quinonediimine (**76**) with either phenol or the phenolate anion, depending on the pH[63, 68]. An exception to this mechanism is when X is Me, and no elimination reaction occurs. If X is H, the dye forms by oxidation of the leuco-dye adduct **77** with either another molecule of **76**, or with ferricyanide. This reaction is not rate limiting.

Because **76** reacts with both ionic forms of the phenol, the pH dependence of log k_2 has the form shown in Figure 7[68]. The dotted lines show the contribution to the reaction by each ionic form. In the approximately pH-independent region, the concentration of **76** is decreasing at the same time that the concentration of the phenolate anion is increasing.



Above the phenolate pK_a, the anion concentration is constant, but **76** is still decreasing and the observed rate constant decreases as pH increases.

The effect of substituents on both **76** and phenol has been studied for several phenols and diimines. Electron-donating substituents on phenol increase the reactivity and the effect is additive, but the position is also important[68, 69]. For example, the second-order rate constant of **76** with phenolate ion is 8.43×10^4 M^{-1} s^{-1} at 30 °C. Substitution of a methoxy group in the 2-, 3-, or 4-position increases the rate constant by a factor of 37.0, 7.9 and 13.0, respectively[63, 68]. Similarly a methyl group in the 2- or 3-position increases the rate constant by a factor of 28.1 and 8.7, while 2,5-dimethyl substitution yields a factor of 243 ($28.1 \times 8.7 = 244$). The positional difference is not steric because the 2,3-dimethyl

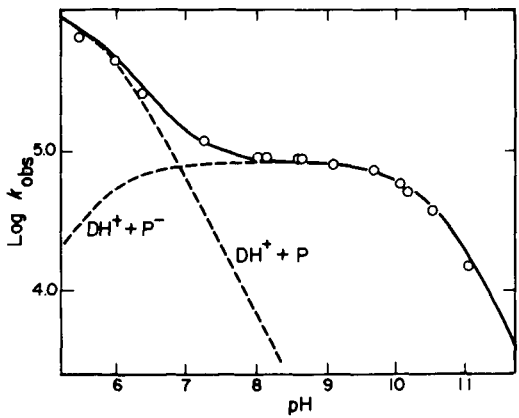


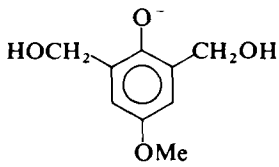
FIGURE 7. The effect of pH on coupling of *p*-benzoquinonediimine with 2,6-dimethylphenol (P) at 30 °C[68]. Full line calculated from equation below; dotted lines, contribution from each ionic form of phenol; $k_{obs} = k_1 f_{DH^+} f_p + k_2 f_{DH^+} f_p$; f, fraction of each species existing in solution; $k_1 = 1.56 \times 10^4$ M^{-1}s^{-1}; and $k_2 = 8.0 \times 10^4$ M^{-1} (Table 11)

substitution, in which a buttressing effect might be expected, yields a more reactive phenol than 2,5-dimethyl substitution. When naphthol replaces phenol, the coupling rate constant increases by a factor of 4500 with **76** and 1500 with **75**[69].

When extensive substitution occurs on either the phenol or the diimine adjacent to the coupling site, significant steric inhibition has been observed. For example, 3-*t*-butyl substitution lowers the reactivity by a factor of 6.6 compared with 3-methyl substitution[69]. Similarly, 2,3,5,6-tetramethylphenol couples seven times slower than predicted from the additivity of one methyl[68, 69]. Electron-withdrawing substituents on phenol decrease the reactivity, and this effect is additive also, although only chloro substitution has been studied in detail[68, 69].

Substitution on quinonediimine has the opposite effect. Electron-donating groups, such as methyl, decrease the rate constant by a factor of 4–9, depending on position while a chloro group increases the rate constant by a factor of 4[68]. These effects include the change in pK_a of the diimine conjugate acid **76** which was not factored out of the rate studies. A 3-Me group on *N*,*N*-diethylquinoneimine decreases the rate constant by a factor of 26 with three different phenols[69].

Tong and Glesmann[67] also observed significant steric effects due to ring substituents on *N*,*N*-diethylquinonediimines when a coupling-off group other than hydrogen is involved and substitution occurs adjacent to the imino coupling site. With 2,6-bishydroxymethyl-4-methoxyphenolate ion (**78**), where a methoxy group occupies the coupling site, a 3-chloro



(78)

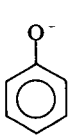
group on the diimine has no effect on the rate constant, even though it should accelerate the reaction. Substitution of 3-*i*-propyl or 3-*t*-butyl on the diimine decreases the rate constant by a factor of 3 and 3000 respectively, compared with 3-methyl substitution, even though there is no significant change in the inductive effect.

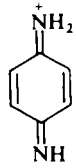
A summary of measured rate constants for the coupling of phenols and naphthols with several quinonediimines, the structures of the reactive species and the reaction conditions are given in Table 11. Of interest is how well the substituent effects of the phenols agree, independent of the diimine involved, unless steric effects are also present. Pelizzetti and Saini[69] showed that substituents on phenol had almost the same effect (rate factors compared with the parent) for the coupling of **81** as Corbett[68] observed for coupling with **79**.

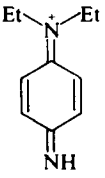
In all reactions except one considered so far, the rate-limiting step has been the addition of the phenol anion to positively charged diimine. Tong and Glesmann[66, 67] examined several reactions in which the inetrmediate leuco dye accumulated in the reaction, because elimination of a coupling-off group from the reaction site was rate limiting. They studied *N*,*N*-dialkylquinonediimines (**82**) coupling with 4-substituted naphthols (**83**), where the leaving group (X) was methoxy or chloro.

At low naphtholate concentrations or excess **82**, k_1 can be the rate-limiting step, and the observed rate increases with anion concentration. At excess anion concentrations, the intermediate **84** rapidly accumulates and dye formation through k_2 is independent of anion concentration. In addition, it was possible to add another nucleophile to compete with diimine **82** through the reversible formation of **84**, thus obtaining a measure of k_{-1}.

TABLE 11. Quinonediimine coupling rate constants with phenolate anions







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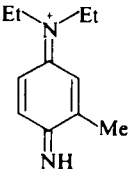

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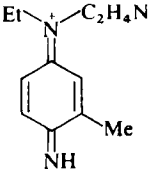


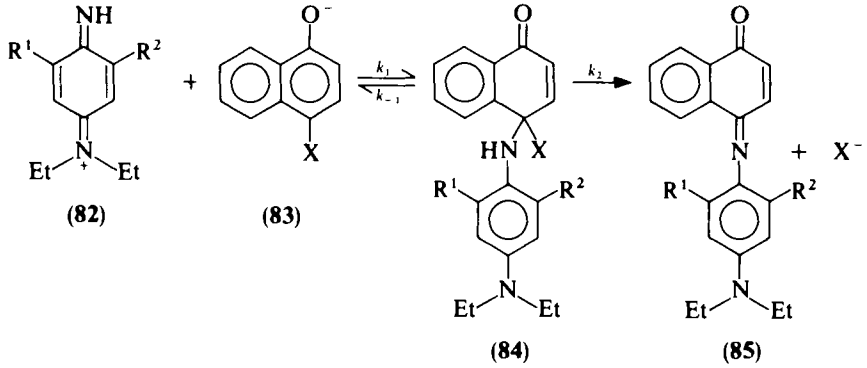
(81)

X	k_c^- (M^{-1} s^{-1})[a]	k_c^- (M^{-1} s^{-1})	k_c^- (M^{-1} s^{-1})	k_c^- (M^{-1} s^{-1})[b]
H	8.43×10^4	5.5×10^3	2.0×10^2	2.7×10^3
2-Me	2.37×10^6	1.8×10^5	—	1.0×10^5
2-Cl	No dye			7.94×10^2
2-Ph	—	—	—	2.2×10^4
2-CONHPh	—			4.0×10^2
2-OMe	3.12×10^6	—	—	—
2-*i*-Pr	2.71×10^6	—	—	—
2-*t*-Bu	3.15×10^6	—	—	—
3-Me	2.37×10^6			2.0×10^4
3-Cl	No dye			5.0×10^2
3-Et	—			1.3×10^4
3-*t*-Bu	—			3.0×10^3
3-NO_2	—			5.0×10^0
3-COMe	—			1.7×10^2
3-NH_2	1.73×10^7[c]			—
3-NEt_2	—			1.6×10^6
3-OMe	6.65×10^5	1.3×10^4	5.00×10^2	8.3×10^3
4-Cl	—			8.0×10^1
4-OMe	1.1×10^6[d]			1.0×10^4
2,3-Me_2	3.07×10^7			6.45×10^5
2,5-Me_2	2.05×10^7			—
2,6-Me_2	8.0×10^7[d]			4.0×10^6
2,5-Cl_2	—			2.45×10^2
2,6-Cl_2	—			1.7×10^2
2-Me, 4-Cl	—			5.5×10^3
2,5-Me_2, 4-Cl	—			6.9×10^5
2,6-Me_2, 4-Cl	2.2×10^6			—
Naphthol	3.8×10^8			4.46×10^6
2-COOH Naphthol	—	5.0×10^4	2.0×10^3	—

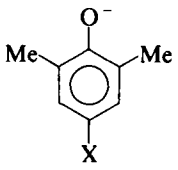
[a] 30 °C, phosphate buffer 0.1 M, Ref. 68.
[b] 25 °C, Borax buffer 0.125 M, Ref. 69.
[c] Ref. 64.
[d] Ref. 63.

The value of k_2 is ~ 100 times larger for the elimination of chloride ion than for the elimination of methoxide to form methanol.

When k_1 is the rate-limiting step, the effect of electron-donating substituents on naphthol increases the coupling rate constant, as described earlier. Such substituents also increase the pK_a for phenol ionization, so one might expect a good correlation between $\log k_1$ and pK_a. Such a correlation was found[67] for 4-substituted 2,6-dimethylphenolates (**86**) coupling with **79**, where the substituents (X) varied from SO_3^- to OMe. On the other



(82) (83) (84) (85)



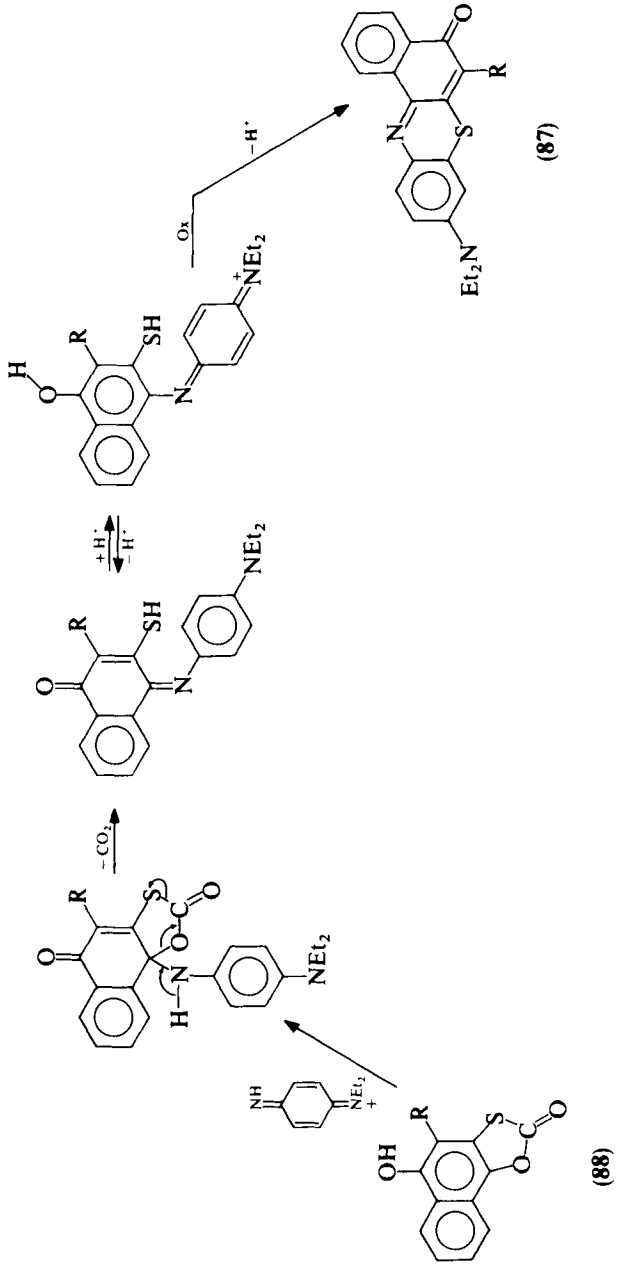
(86)

hand, Pelizzetti and Saini[69] said that no such correlation existed for the phenols they studied, many of which are shown in Table 11.

Corbett and coworkers[63, 73] studied the coupling kinetics of benzoquinonemonoimine with several substituted phenols to form indophenol dyes. The leuco-dye intermediate is rapidly oxidized by monoimine, making the initial step rate limiting. The reaction is fastest in alkaline solution, where the phenolate ion reacts with the neutral monoimine faster than with the conjugate acid. This is in contrast to the diimine reactivity, where there is no reported reactivity with the neutral diimine[68]. Effects of substituents on phenol are additive, although the observed rate constants are significantly lower. The neutral monoimine is $\sim 10^5$ less reactive than the corresponding diimine conjugate acid[73].

An interesting route to the formation of thiazine dyes (**87**) through coupling of *N*,*N*-diethylquinonediimine (**79**) with naphtho[2,1-*d*]-1,3-oxathiol-2-ones (**88**) has been reported by Mann and coworkers[74]. Essentially, the reaction involves coupling to a substituted naphthol, which rearranges to form the final phenothiazine dye (**87**), as outlined below.

Since the oxidative coupling products of *p*-phenylenediamines with phenols or anilines yield highly colored products, attempts have been made to use these reactions in the analytical methods of assay for low concentrations of such species. For example, Rao and Sastry[75] used metaperiodate, IO_4^-, to oxidize *N*,*N*-dimethyl-*p*-phenylenediamine at pH 7.8 in the presence of several phenols to measure the phenol concentration spectrophotometrically. Both *o*- and *p*-aminophenol can be determined by alkaline oxidation with hypochlorite in a self-coupling reaction[76]. Differential dye-forming kinetics have been used to analyze mixtures of anilines[77]. Additional studies have been evaluated by Corbett[78], who pointed out that some of these procedures do not adequately account for deamination reactions which compete with the dye formation step. He provided some guidelines for future attempts to use dye-forming reactions for quantitative analysis, which take into account the kinetics of both dye formation and deamination.

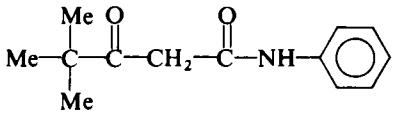

(88)
(87)
Ox
$-H^+$
$+H^+$
$-H^+$
$-CO_2$
NEt_2
Et_2N
SH
OH
R
S
N
O

At least a 25% excess of coupling reagent over the species to be determined, and at least five equivalents of oxidant (preferably ferricyanide) should be used.

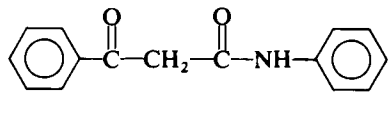
Some other interesting analytical coupling procedures have been developed to determine metal ions. For example, Cu(II) catalyzes the oxidation of *N,N*-dimethyl-*p*-phenylenediamine by H_2O_2 and the product quinonediimine forms a dye with *N,N*-dimethylaniline absorbing at 728 nm[79]. Concentrations of Cu(II) down to 10^{-9} M can be analyzed with few interfering metals. A similar method has been employed for Mn(II) and Ag(I) determinations, where the H_2O_2 catalyzed dye-forming reaction is used to detect the end point of a titration[80].

D. Other Coupling Reactions

Several other acidic methylene functions can ionize and couple with quinonediimines and monoimines to form photographically important dyes. Yellow dyes are formed by reaction with pivaloyl-[81] or benzoylacetanilides[82] (**89** and **90**). With 4-equivalent couplers

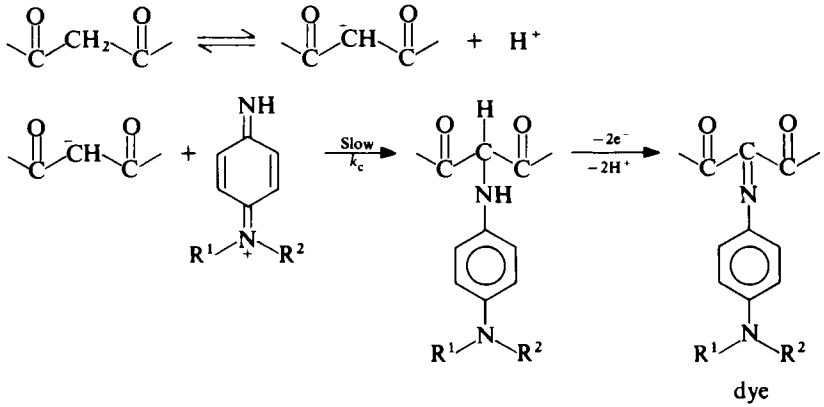


(**89**)



(**90**)

like **89** and **90**, the kinetics of dye formation are controlled by initial leuco-dye formation from the coupler anion and the diimine, which is followed by rapid oxidation to form the azomethine dye. The initial ionization of the coupler may be rate limiting, causing an induction period for dye formation[2], unless it is preionized[82].

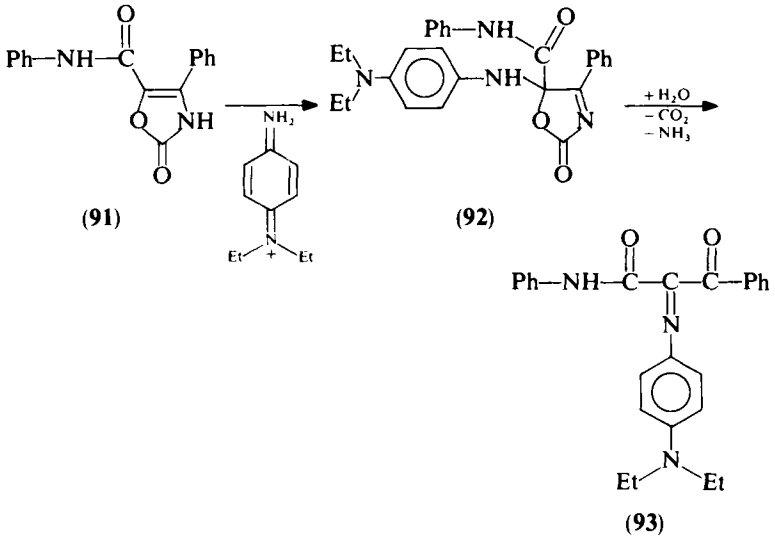


dye

Pelizzetti and Saini[82] studied the kinetics of dye formation as a function of substituent in both aromatic rings of **90**, using three different quinonediimines shown in Table 11 (**79**, **80** and **81**). Electron-donating substituents on the acetanilide (**90**), such as methyl and methoxy, increase the coupling rate constant, although they also increase the pK_a for coupler ionization. For a given substituent, the effect on $\log k_c$ is about twice as large as the effect on pK_a. The effect of a substituent in the benzoyl ring ($\rho = -1.3$) is ~ 9 times larger than the effect in the acetanilide ring ($\rho = -0.48$).

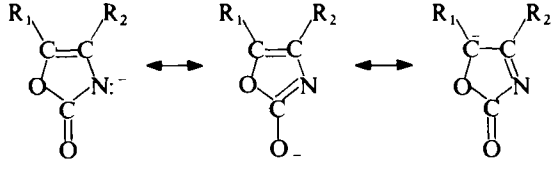
A methyl substituent on the quinonediimine decreases the rate constant by about a factor of six, compared with the factor of 25 decrease for coupling with phenolate ions[69]. The $C_2H_4NHSO_2Me$ group on **81** dissociates near pH 9.6[17], forming a zwitterion, which is also capable of coupling to form dye[66]. For each coupler, the rate constant for the zwitterion is slower than for the cationic diimine by a different amount ranging from 0.22 to 0.44. This compares with a rate of 0.05 for coupling with all substituted phenols[69].

The same yellow dyes can be formed by coupling oxidized *N,N*-diethyl-*p*-phenylenediamine with 2-oxo-4-oxazoline-5-carboxamide derivatives (**91**) of the benzoylacetanilides by ring-opening and CO_2 elimination, as shown below[83]. The oxazoline (**91**) ionizes in



(**91**) (**92**) (**93**)

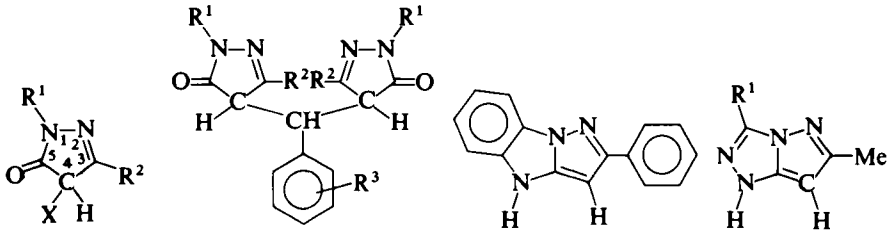
structures **95** and **96**. The leuco dye **92** formed in the initial coupling reaction undergoes acid hydrolysis with loss of CO_2 and NH_3 to form the stable azomethine dye **93**.



(**94**) (**95**) (**96**)

Magenta dyes (λ_{max} between 520 and 550 nm) are formed by coupling quinonediimines with nitrogen heterocycles containing an ionizable methylene group. Four classes of heterocycles studied are pyrazolin-5-ones (**97**)[70, 84], bis-pyrazolin-5-ones (**98**)[85], pyrazolo[1,5-*a*]imidazoles (**99**)[86] and pyrazolo[3,2-*c*]-*s*-triazoles[87] (**100**).

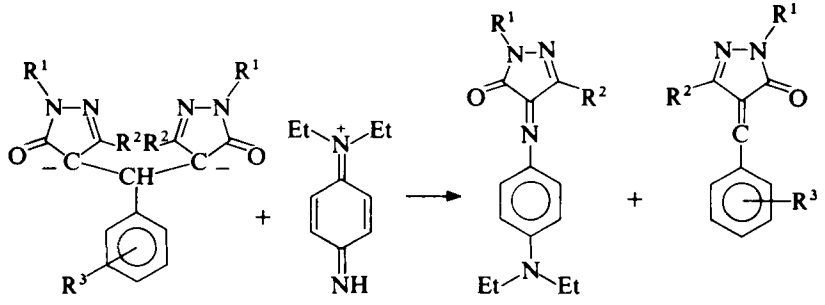
Pyrazolin-5-one coupling has received the most mechanistic study for both X = H (4-equivalent coupling) and for X equal to some other good anionic leaving group (2-equivalent coupling). When X = H, the coupling reaction proceeds to 100% dye yield with



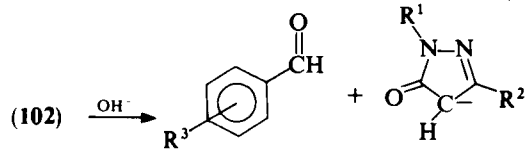
(97) (98) (99) (100)

N,*N*-diethylquinonediimine (**79**). The same is true when X = Br or Cl. Most other groups produce only small quantities of dye, due to side reactions of the leuco dye or coupler[2]. With R^1 = phenyl, the rate constant for coupling with R^2 = Me and X = H is 1×10^5 M^{-1} s^{-1}. When R^2 = NHCOMe, the rate constant is somewhat lower[84], 1.6×10^4 M^{-1} s^{-1} and the pK_a of the coupler is lower[70], 7.3 compared to 8.0. When X = Br, the rate constants are further decreased and < 100% dye is formed[84], particularly as the solution pH increases. No dye is formed when X = NHCOMe, COMe or Me. The reaction mechanism appears to be a rate-limiting formation of leuco dye, which can rapidly form dye or competitively react to form colorless products[2].

Bis-pyrazolin-5-ones (**98**) were reacted with quinonediimines **79** and **80** by flash photolysis of the azide precursor[70-72] in 30% *n*-propanol aqueous solution using phosphate buffers at pH 10 with an ionic strength of 0.18[86]. The reaction is monitored by following dye **101** formation and analyzed according to a second-order rate expression since the coupler is not in large excess. In studying the ionic strength dependence of the observed rate constant Fanghänel and coworkers[86] determined the rate-limiting step with the reaction of the quinonediimine cations **79** and **80**, with the dianion of the bis-pyrazoline-5-one. The intermediate (**102**) undergoes slow hydrolysis, forming a benzaldehyde and the simple pyrazolin-5-one (**97**; X = H) anion according to the following reactions.



(98) dianion (79) (101) (102)

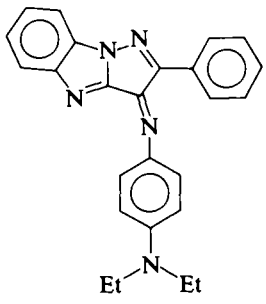


(97) X = H anion

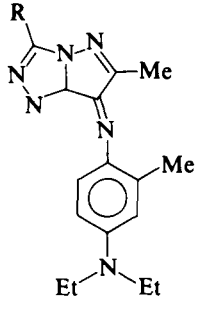
(97) + (79) → (101)

The hydrolysis rate of **102** is slow with second-order rate constants of 0.24 $M^{-1} s^{-1}$ for R^2 = Me and R^3 = 4-NMe_2 to 1400 $M^{-1} s^{-1}$ for R^2 = NHCOMe and R^3 = 4-OMe. Since these reactions are slower than hydrolysis of the quinonediimine (see k_4 in Table 2), only a small amount of dye forms in the second coupling step. For example, hydrolysis of **79** is 1×10^4 $M^{-1} s^{-1}$.

Couplers **99** and **100** react with **79** or **80**, formed by oxidation of the *p*-phenylenediamine with ferricyanide[86] or persulfate[87], to form the corresponding azomethine dyes. No mechanistic studies were made, but dyes **103** and **104** were isolated and characterized by analysis and by spectral comparison with dyes formed in an independent synthesis.



(103)

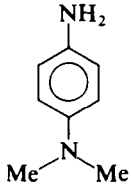


(104)

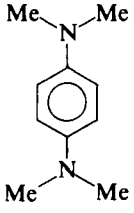
V. SULFONATION

A. Addition of Sulfites

Upon oxidation of *p*-phenylenediamine in the presence of sulfite at an electrode surface, the potential of oxidation shifts negative in proportion to the relative amount of sulfite added[88]. A second wave appears at a more positive potential. Similar studies with *N*,*N*-dimethyl-*p*-phenylenediamine[89] (**105**) and *N*,*N*,*N'*,*N'*-tetramethyl-*p*-phenylenediamine[90] (**106**) in acid solution showed that even when only one electron is added to form a cation



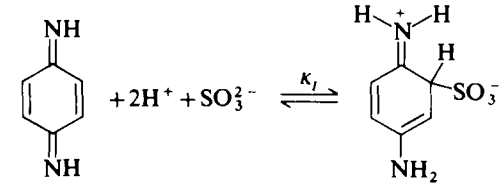
(105)



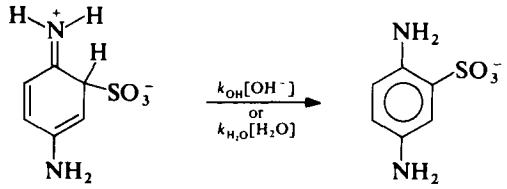
(106)

radical, rapid follow-up sulfonation occurs. Again, a second, more positive, oxidation wave occurs requiring two electrons. Both groups of workers explain their results by saying that sulfonation proceeds much more rapidly than oxidation, such that no intermediate sulfite–phenylenediamine complex can be observed. In excess sulfite, a second sulfite can add to the first product producing disulfonated *N*,*N*-dimethyl-*p*-phenylenediamine[89].

A careful kinetic study[91] of sulfonation using ferricyanide oxidation in phosphate buffer, showed definite accumulation of an intermediate, especially in an acid solution with a large excess of sulfite. For unsubstituted quinonediimine, the pH dependence of the rate indicates that the intermediate complex (**107**) must be protonated. This intermediate loses a proton in the rate-determining step. The reaction is independent of phosphate buffer



(6) **(107)**



(107)

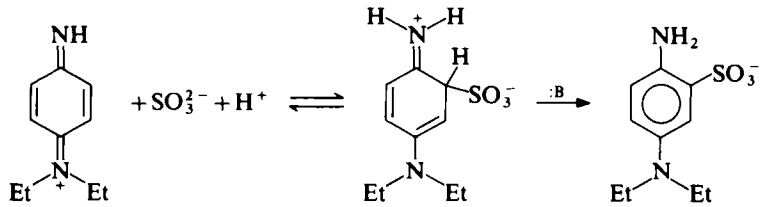
concentration, indicating no general catalysis to form the product. The reaction rate is given by equation 11.

$$\text{rate} = (k_{OH}[OH^-] + k_{H_2O})K_I[H^+]^2[SO_3^{2-}][\mathbf{6}] \tag{11}$$

Between pH 8 and 9.5, the observed second-order rate constant, $k_{SO_3^{2-}}$ in equation 12, is second order in $[H^+]$, but shifts to first order above pH 9.5. At lower pH, the reaction is complicated by incomplete oxidation and, above pH 11, deamination begins to compete. At pH 9, $k_{SO_3^{2-}} = 300\ M^{-1}\ s^{-1}$. A plot of log $k_{SO_3^{2-}}$ vs. pH is given in Figure 8.

$$k_{SO_3^{2-}} = K_I[H^+]^2(k_{OH}[OH^-] + k_{H_2O}) \tag{12}$$

In the case of *N*,*N*-diethylquinonediimine (**79**), the reaction is complicated by the catalysis of phosphate ions in the buffer. Extrapolation to zero phosphate concentration at constant ionic strength for several pH values between 8 and 10 yields a constant value for the decay of the intermediate due to the water reaction. There is no pH dependence and $k_{SO_3^{2-}} = 3.7 \times 10^4\ M^{-1}\ s^{-1}$. The phosphate effect is suggestive of general base catalysis



(79) **(108)**

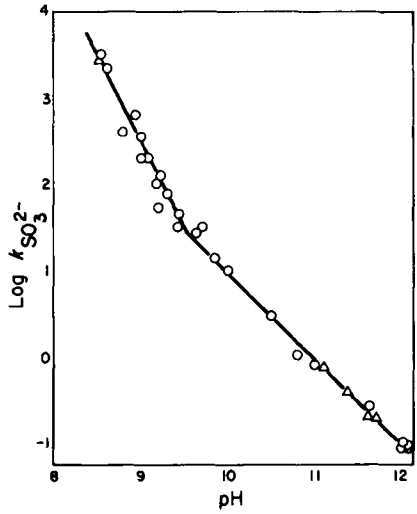
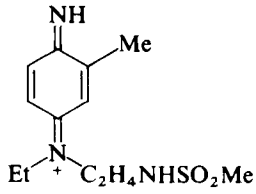


FIGURE 8. Effect of pH on the sulfonation of *p*-benzoquinonediimine in phosphate buffer (μ = 0.375)[91]. O Phosphate buffer only; Δ phosphate buffer diluted 1 : 4 with 0.375 M NaCl; and solid line calculated according to equation 12

assisting to break the C–H bond. The product of sulfonation (**108**) was confirmed by separate preparation[92].

Sulfonation of *N,N*-dimethylquinonediimine is more complicated, because extrapolation to zero phosphate concentrations as a function of pH yields different intercepts. The intercept value cannot be divided into a water rate and a hydroxide rate within experimental error, as done for unsubstituted quinonediimine. The diimine can also be sulfonated *ortho* to the alkylated imine due to reduced steric hindrance on going from ethyl to methyl. The observed rate constant in 0.375 M phosphate buffer is ~ 4 times larger than for *N,N*-diethylquinonediimine (**79**)[91].

A study[93] of the sulfonation of **81** was made by following the formation of the sulfonated product by stopped-flow fluorescence spectrometry. The observed pseudo-first-order observed rate constants were linear with sulfite only at low phosphate buffer



(81)

concentration and at high pH. The second-order rate constant, obtained when the observed rate constant is linear with sulfite, increases with phosphate concentration and with decreasing pH, but not in a linear way. The product mix varies with pH and includes at least three species, only two of which were identified. Unidentified product, based on the

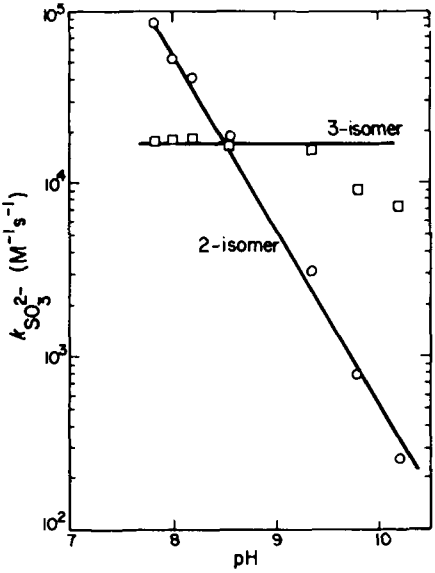
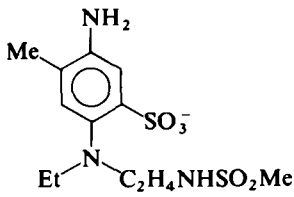


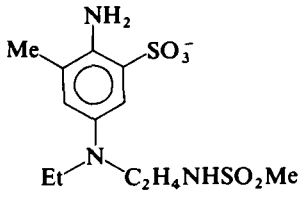
FIGURE 9. Effect of pH on sulfonation rate of **108** to form the 2-isomer (**109**) and the 3-isomer (**110**)[93] in 0.2 M phosphate buffer. O $k_{SO_3^{2-}}$ for 2-isomer; □ $k_{SO_3^{2-}}$ for 3-isomer

theoretical yield expected from **81**, amounted to 10–30 % of the reaction depending on pH. Multiplying the product yield by k_{obs} for total product formation (or **81** loss) and dividing by total sulfite concentration yields $k_{SO_3^{2-}}$ as a function of pH for the formation of the 2-isomer (**109**) and the 3-isomer (**110**). The result at total phosphate = 0.2 M is given in Figure 9.



(**109**)

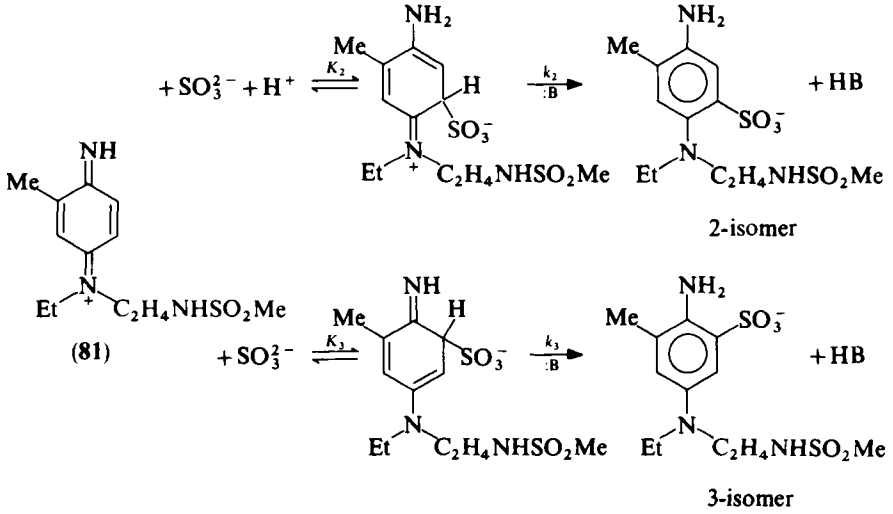
2-isomer



(**110**)

3-isomer

The results are consistent with a parallel reaction to form either the 2-isomer or the 3-isomer with no interconversion between the two paths, i.e. they are irreversible overall. The lack of sulfite dependence at low pH for formation of the 3-isomer is consistent with reversible formation of a sulfite complex, which rapidly builds up at high sulfite concentrations and decomposes in the rate-limiting, but sulfite-independent, step. The pH dependence for 2-isomer formation occurs because a proton must be added to the primary amine to prevent formation of a negative charge at that site, which would not be stabilized by resonance in the ring.



In addition to the above reaction, the drop in $k_{SO_3^{2-}}$ at high pH for formation of the 3-isomer in Figure 9 can be explained by ionization of the sulfamyl substituent on **81**, which apparently reacts more slowly, if at all[93].

Although phosphate increases the reaction rate, the effect is not linear. Possibly chloride ion, added to maintain $\mu = 0.75$, is acting as a weak base and has some effect on the irreversible, rate-limiting, base-catalyzed proton removal step. The overall expression for $k_{SO_3^{2-}}$ is given by equation 13, where k_2 and k_3 are dependent on phosphate and perhaps chloride. The value of pK_a for ionization of the sulfamyl group is 9.95 at $\mu = 0.75$[93], somewhat higher than the value of 9.5 obtained by Tong and coworkers[28] from deamination kinetics.

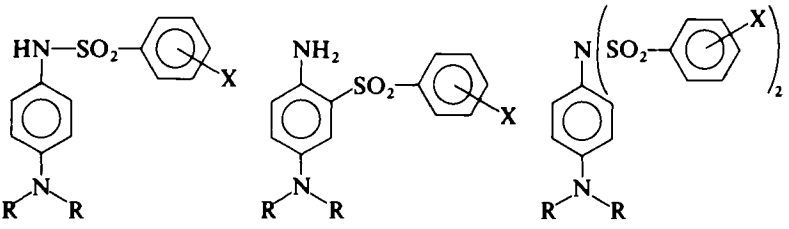
$$k_{SO_3^{2-}} = (k_2K_2[H^+] + k_3K_3)[H^+]/([H^+] + K_a) \quad (13)$$

Attempts to identify other products in the reaction mixture were inconclusive. No disulfonates were obtained, even with large excesses of sulfite. Deamination products should not form competitively, and were not observed below pH 12. Sulfamate formation from addition to N-, rather than C-, may occur in small amounts, based on product analysis using high performance liquid chromatography (HPLC)[93]. No other species in the product mix were identified.

B. Addition of Sulfinates

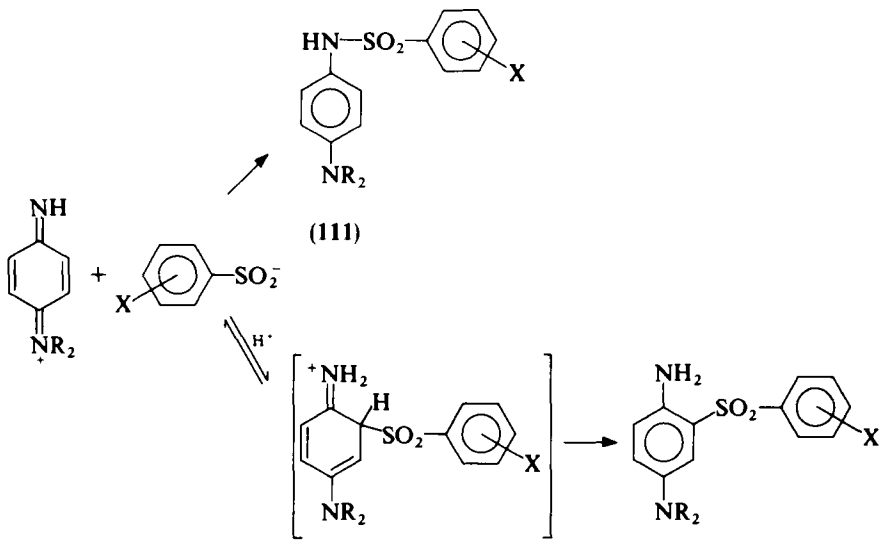
The reaction of arylsulfonic acid with *N,N*-dialkylbenzoquinonediimines in alkaline solution should be similar to the reaction of sulfite ion. Finley and coworkers[94] studied the addition reaction for both *N,N*-dimethyl- and *N,N*-diethylquinonediimines formed oxidatively from ferricyanide and the corresponding phenylenediamine. They observed three addition products, a sulfonamide (**111**), a sulfone (**112**) and a disulfonamide (**113**) in oxygen-free phosphate buffer.

The product distribution was obtained from a characteristic vector analysis of the UV spectrum of chloroform extracts of the reaction mixture diluted with ethanol. The major product above pH 7 was the sulfonamide (**111**) (> 80%), independent of whether R was methyl or ethyl, and almost independent of X.



(111) (112) (113)

At pH 5, ~ 40% of the sulfone (**112**) was observed, while essentially none was formed above pH 7. The disulfonamide (**113**) occurred only at 5% or less, along with a similarly small amount of the parent *p*-phenylenediamine. The products are apparently formed



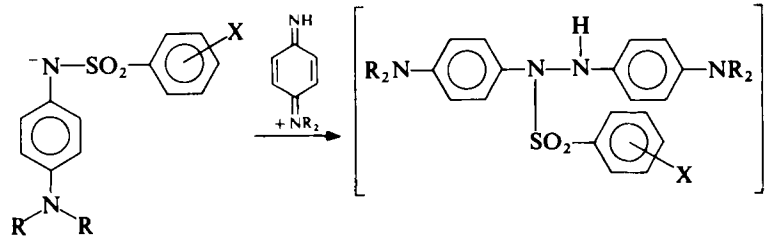
(111)

(112)

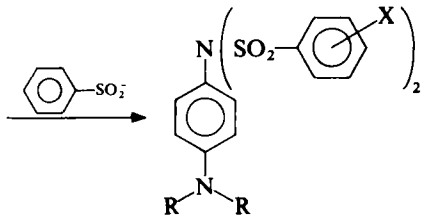
competitively, with the sulfone product requiring the addition of a proton to form the initial adduct as observed for sulfite. The disulfonamide apparently forms through further reaction of **111** anion with diimine[94].

Burmistrov and coworkers[95] studied the products of substituted benzenesulfinate addition to *N*-phenylquinonemonoimine (**114**). The single product identified (68–96% yield) was **115**, after oxidation with lead tetraacetate. When hydroxymethylsulfinic acid was used, a dimer was formed, which was oxidized to **116** with $Pb(OAc)_4$.

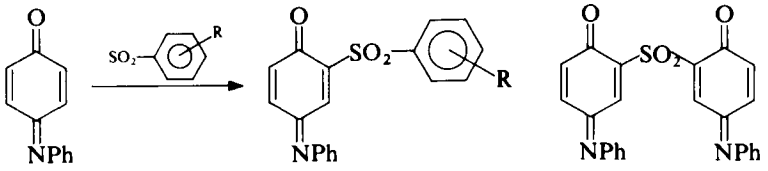
The reaction of benzenesulfinic acid with *N*-(thioaryl)quinonemonoimine (**117**) was studied by Kolesnikov and coworkers[96]. Two products were formed, the sulfone (**118**) and a thiosulfonate (**119**).



(111) anion

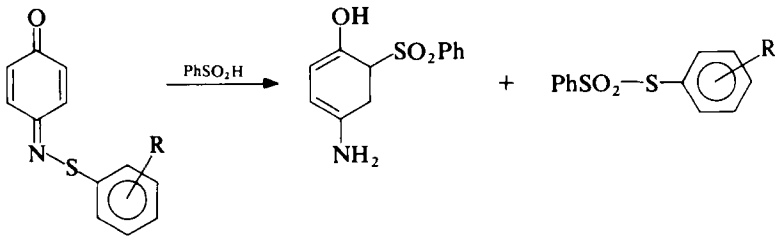


(113)



R = H
= 4-Me
= 4-Cl

(114) (115) (116)

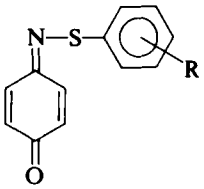


(117) (118) (119)

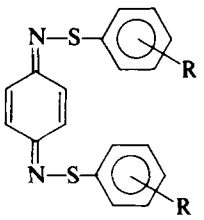
VI. OTHER QUINONEIMINE CHEMISTRY

A. *N*-(Arylthio)quinoneimines

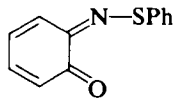
Compounds **120**–**123**, formed by several different reactions, have been described in the literature. For compound **120**, with R equal to H, 4-OMe, 4-Cl, 4-NO_2, or 2-NHCOMe



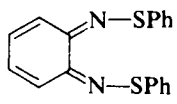
(120)



(121)

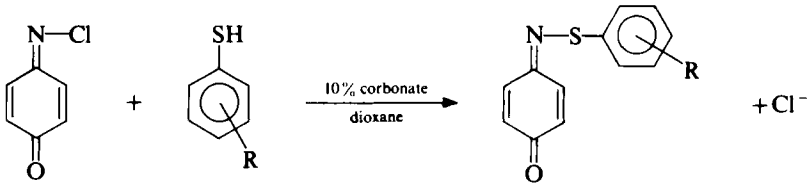


(122)



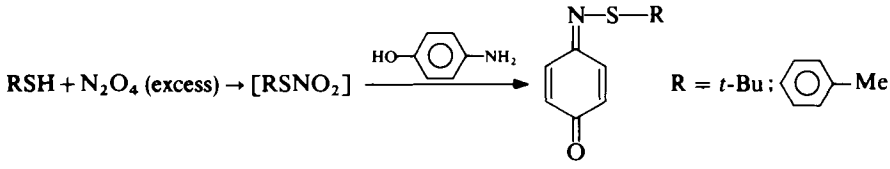
(123)

the following reaction was used[96, 97] in which the *N*-chloroquinoneimine in dioxane solution was added to the thiol in aqueous 10% sodium carbonate. The deep-red precipitate was filtered and identified by infrared and nuclear magnetic resonance spectroscopy.



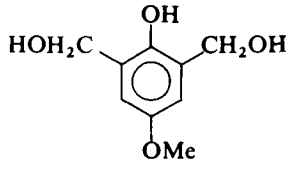
(120)

Both *N*-(aryl)- and *N*-(alkyl)thioquinoneimines can be prepared by reacting the appropriate thiol with N_2O_4 to produce the unisolated thionitrate, which oxidizes and adds to *p*-aminophenols[98]. The compounds were yellow, and were identified by IR, NMR and mass spectroscopy.

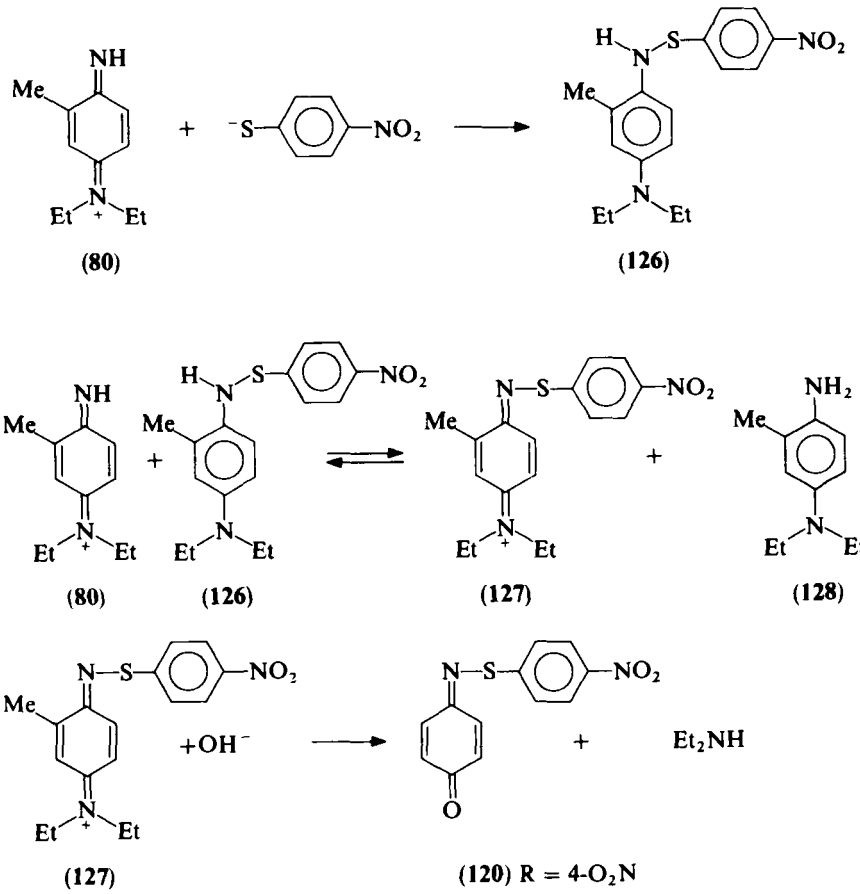


(124)

In a study of acylthiol addition to oxidized color developing agents, Wightman and colleagues[99] observed the formation of **120** with R = 4-NO_2. Their mechanistic work, using a competing dye-forming reaction with a substituted phenol (**125**), suggested the following scheme for the formation of **120**.



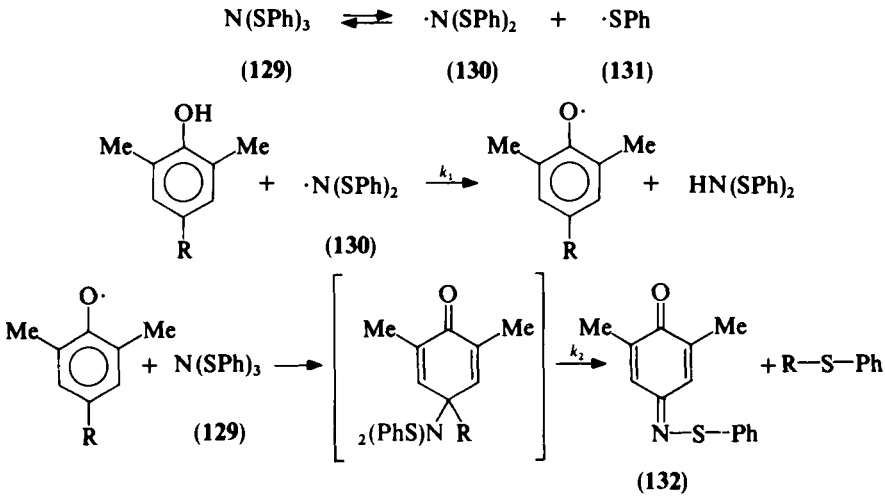
(125)



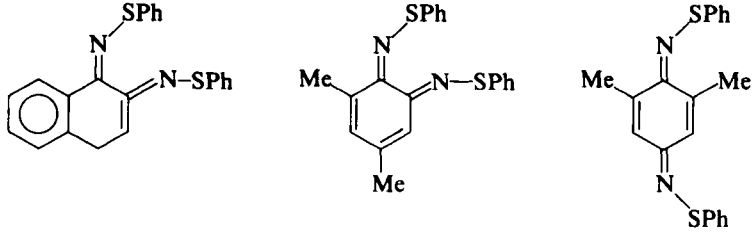
The initial product (**126**) is oxidized more easily than the starting *p*-phenylenediamine (**128**) and irreversible deamination of **127** drives the reversible redox reaction to form **120**. The oxidized intermediate (**127**) can also couple with **125** to form the same dye as formed from **125** and the diimine (**80**), but the reaction is much slower.

The initial rate of *p*-nitrothiophenolate addition to diimine **80** exceeds the rate of coupling with **125**. When R = 4-Me instead of 4-NO_2, the reaction is significantly faster, due to the enhanced nucleophilicity of the thiol. The reactions were studied at a pH well above the p*K* of the thiols.

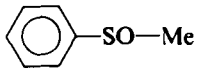
Another method for the formation of **120** and **122** is the reaction of trisulphenamides (**129**) with phenols and naphthols[100]. Thermal decomposition of **129** yields the free radical (**130**), which reacts with phenols in two steps to form the *N*-(arylthio)quinoneimines **120** and **122** in dichloromethane. The predominant products with unhindered phenols are *o*-*N*-(arylthio)quinoneimines (**122**), because the 2- and 6-positions have the highest electron density in the radical formed in the first step. The radical mechanism outlined above is corroborated, in part, by kinetic isotope studies in dichloromethane in the presence of either H_2O or D_2O. The presence of D_2O decreases the initial atom abstraction rate constant, k_1, when the atom is deuterium instead of hydrogen.



When the substrate is β-naphthylamine, the disubstituted species (**133**) is formed in 33–38% yield in dichloromethane. 2,4-Dimethylaniline yielded modest formation of **134**, but aniline and *N*-methylaniline gave only intractable mixtures. Compound **135** was isolated when 2,6-dimethylaniline was the substrate.



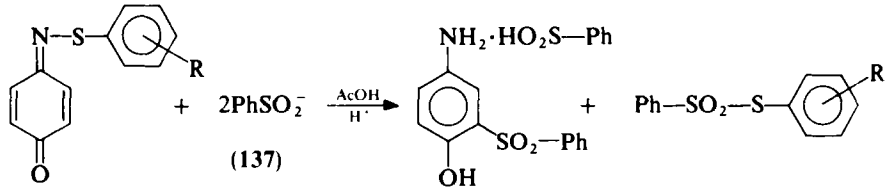
From liquid ammonia solutions of methyl phenyl sulfoxide **136**, Armitage and Clark[101] isolated **123**, which presumably forms by reaction of the phenylthiol radical **131** and



(136)

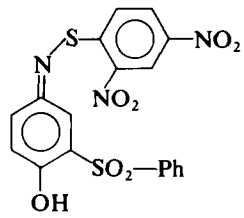
the dibenzenesulphenamide radical **130** in the reaction mixture. These species are also the same radicals suggested as forming from the thermal decomposition of tribenzenesulphenamide (**129**)[100].

The reactivity of *N*-(arylthio)quinonemonoimines has received very little study. The only study found in the literature[96] describes the reaction of benzenesulfinate (**137**) on **120** in acetic acid. The substrate (**137**) reacts at two sites of the molecule, both to cleave the



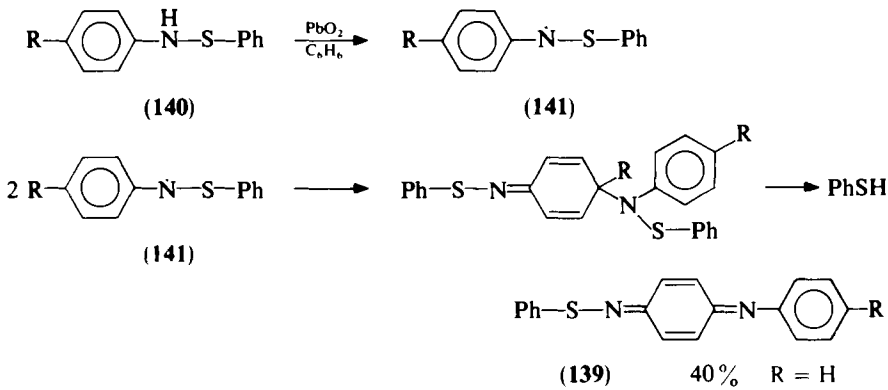
(120) R = 4-O_2N

arylthio group from nitrogen and to add to the ring. The intermediate species (**138**), where only one molecule of **137** reacts, was isolated only in the case of dinitro substitution[96].



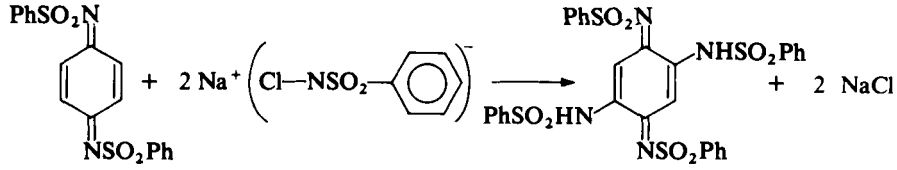
(138)

A series of *N*-(arylthio), *N'*-phenylbenzoquinonediimines (**139**) has been prepared by oxidation of benzenesulfenanilide (**140**) with PbO_2 in benzene[102]. The reaction apparently proceeds by a radical coupling mechanism involving **141**.



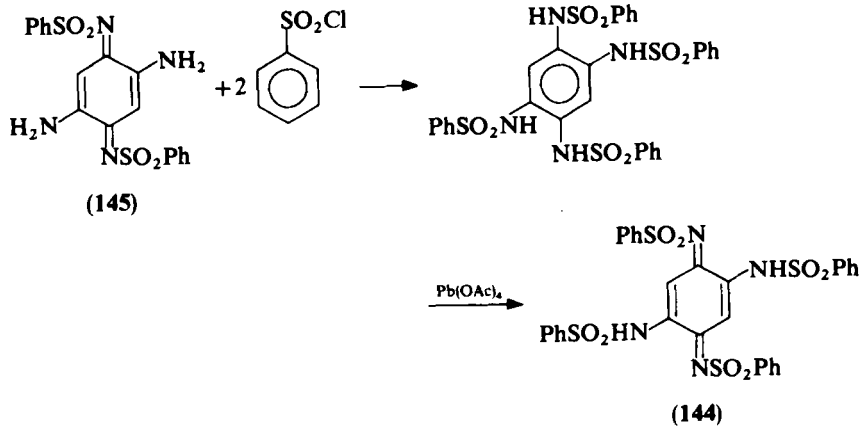
B. *N*-(Arylsulfonyl)quinoneimides

Many publications exist in the Russian literature describing the addition of many nucleophiles to both *o*- and *p*-*N*,*N'*-bisarylsulfonylquinonediimines and monoimides. Unfortunately, most of these papers are not readily available, so only a brief survey is possible from entries in *Chemical Abstracts*. For example, Kremlev and coworkers[103] studied the oxidative addition of *N*-chlorobenzenesulfonamide (**143**) to both *o*- and *p*-*N*,*N'*-bis(phenylsulfonyl)quinonediimide (**142**) to yield disubstituted oxidation products



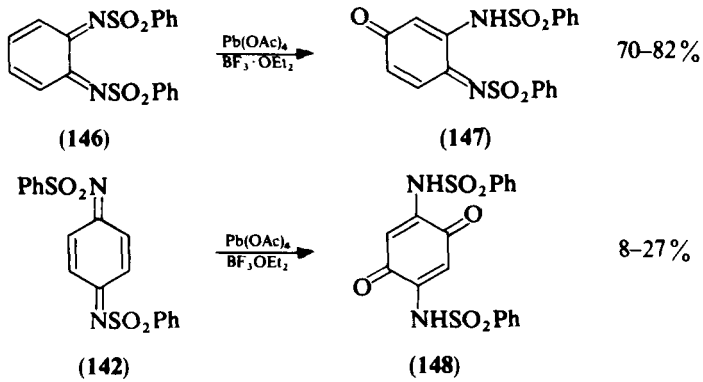
(142) (143) (144)

(144) in acetone. No monosubstituted product was isolated. The same product (144) was formed by addition of benzenesulfonyl chloride to 145, followed by oxidation by lead



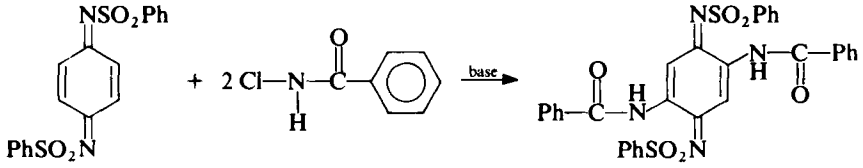
(145) (144)

tetraacetate. Treatment of 142 or 146 with $BF_3{\cdot}OEt_2$ and $Pb(OAc)_4$ in refluxing acetic acid yields significant amounts of 148 and 147[104] respectively. Addition of acylchloramide



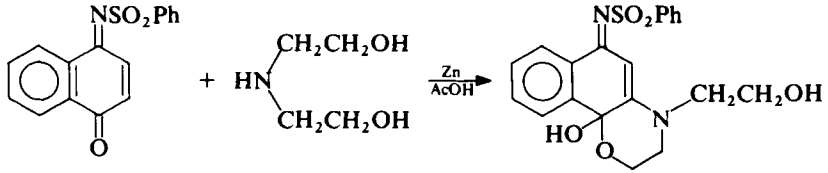
(146) (147) (142) (148)

(149) to 142 in the presence of base yields disubstitution on the ring, unless one ring position is blocked by chloro, methyl, or benzylamino[105].

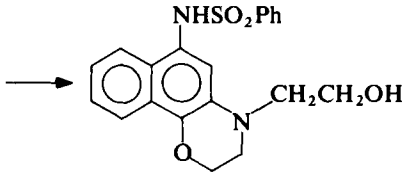


(142) (149)

The addition of several nucleophiles to monosulfonamides has been studied by Titov and coworkers[106-110], primarily by product isolation. *N,N*-Bis-hydroxyethylamine (**150**) adds to **151** to form a novel ring compound (**152**), which forms **153** by treatment with zinc in acetic acid[106]. A mechanism was proposed. Simpler amines, such as phenylethylamine,

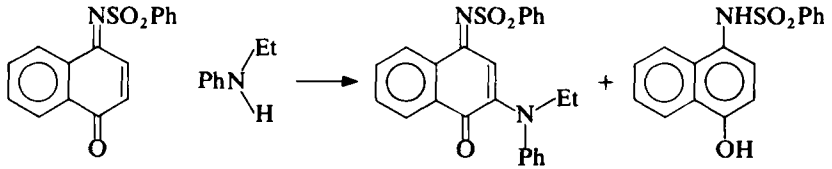


(151) (150) (152) 91%



(153) 84%

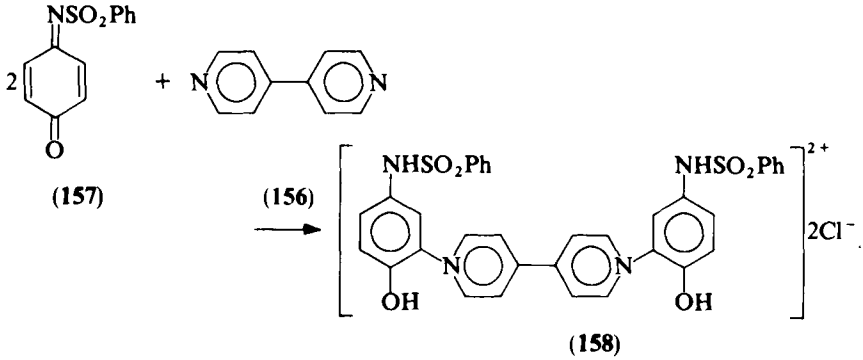
add once to **151**, forming the 1,4-addition product, which is oxidized by the starting material to yield **154** and the *p*-sulfonamidonaphthol (**155**)[107]. A similar reductive



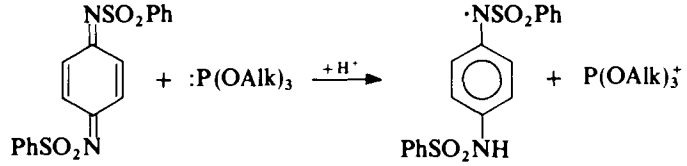
(151) (154) (155)

addition reaction of bipyridine **156** to **157** was reported, forming the bipyridinium dication salt **158**[108].

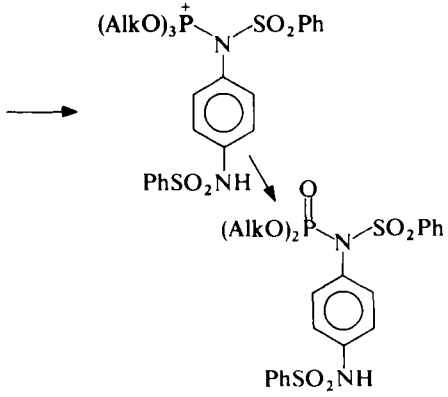
In contrast to the examples of ring-addition cited above, dialkyl and trialkyl phosphites add to the sulfonamide group, forming a P–N bond[109-111]. Adveenko and Koshechko[111] suggest that the reaction proceeds through a free radical mechanism, based on ESR studies of the reaction mixture. The reactions occur on addition of solid quinoneimine (**159**) to



(157) (156) (158)

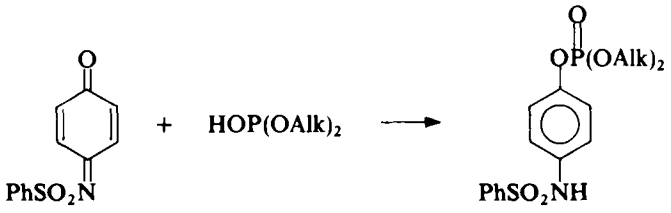


(159) (160)



(161)

liquid trialkyl phosphite (**160**) with heating. Alkyl groups ranged from methyl to ethyl, *i*-propyl and butyl. Both phenyl and *p*-tolyl aromatic sulfonamido groups react. When *N*-

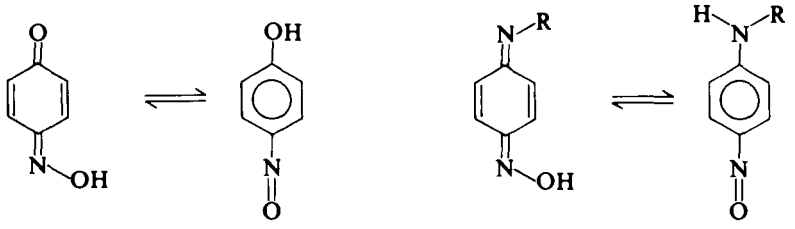


(157) (162)

(arylsulfonyl)-*p*-benzoquinonemonoimine (**157**) is the substrate, dialkyl phosphites form the corresponding phosphate ester (**162**)[109]. Alkyl groups studied were ethyl and *i*-propyl.

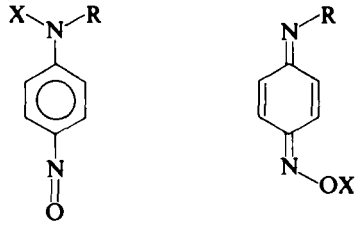
C. Quinone Oximes

The tautomeric equilibrium of quinone oximes (**163**) with nitrosophenol (**164**) is well established in the literature, and was reviewed in the earlier edition of this chapter[1]. This



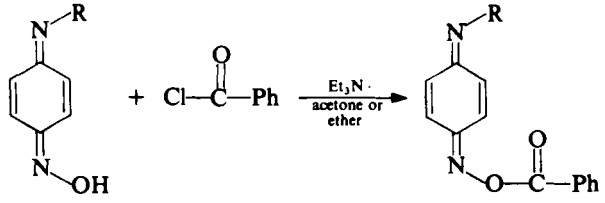
(**163**) (**164**) (**165**) (**166**)

equilibrium can complicate product identification when quinone oxime chemistry is studied. For example, addition of acid chlorides to quinoneimine oximes (**165**) could produce addition at either nitrogen, forming **167** or the oxime ester **168**, where X is the acid



(**167**) (**168**)

group C(= O)R or SO_2R[112]. Titov and coworkers[112–114] have carried out extensive studies of oxime ester formation using acid chlorides in both aqueous base and organic solvents, such as acetone or ether. Products were identified by chromatography, and by hydrolysis and reaction with phenol or naphthol to form indophenol or indoaniline dyes.

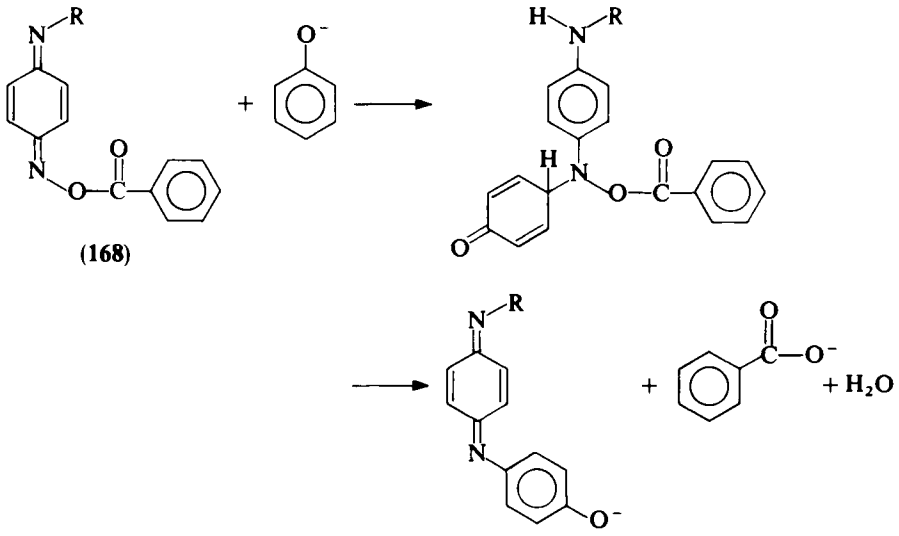


(**165**) (**168**)

When R is alkyl, such as ethyl or methyl, ether is the preferred solvent with the use of a strong base such as triethylamine. When R is phenyl, or substituted phenyl, acetone is the

solvent of choice and a weaker base, such as pyridine, can be used. The acid chloride of benzenesulfonic acid reacts cleanly in acetone at 0 °C to form the sulfonate ester, but the simple acetate ester required using excess acetic anhydride in benzene with heating. Esters have also been prepared when the R group is an aromatic acyl function, such as benzoyl or toluyl, using acetone–water mixtures and bicarbonate as the base[113].

When phenol or naphthol is added to an alkaline aqueous–alcohol solution of oxime ester (**168**), the blue indoaniline (**169**) is formed. If base is not added, the reaction proceeds

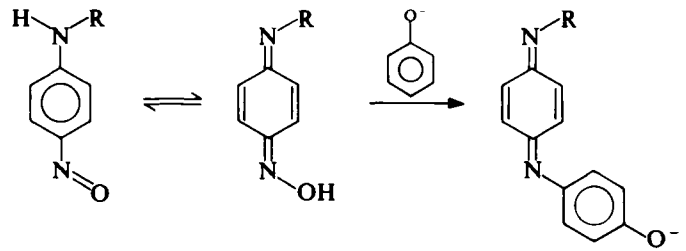


(**168**)

(**169**)

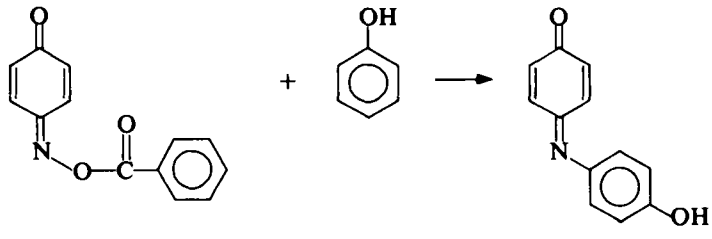
even faster, suggesting that the mechanism involves the phenoxide ion and the protonated imine oxime ester[114]. This is consistent with the dye formation mechanism from quinonediimines described earlier. The reactivity of the *N*-alkyl (acyl)quinoneimine oxime esters (**168**) parallels the p*K* values for protonation of the imine; i.e. alkyl groups increase the reactivity because they are more basic and the substrate is protonated at higher pH.

The same dyes formed from the oxime ester above are also formed by oxidation of *N*-alkyl (aryl)phenylenediamines in the presence of phenol and by reaction of *p*-nitroso-*N*-alkyl(acyl)anilines with phenol. The latter reaction is a consequence of the tautomeric



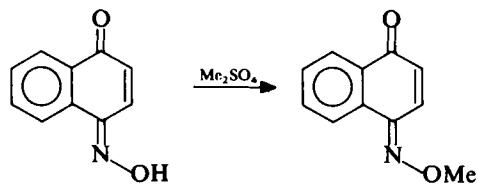
(**165**) (**169**)

equilibrium mentioned earlier. The same reaction with quinone oxime esters (**170**) produces an indophenol dye (**171**)[112].



(**170**) (**171**)

The formation of quinone oxime ethers has also been described briefly[115].



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The Chemistry of Quinonoid Compounds, Vol. II
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CHAPTER 22

Biochemistry of quinones

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I. INTRODUCTION

In *The Chemistry of the Quinonoid Compounds*, Part 2 of the present series, Bentley and Campbell presented the monograph 'Biological reactions of quinones'[1]. It was concerned with the development achieved up to 1973 in the research of the biochemistry of quinones including biosynthesis. The present chapter mainly deals with the results obtained in the field of the biosynthesis of quinones since then. Recent studies have clarified more detailed processes for many of the quinones whose basic biosynthetic pathway had been outlined by Bentley and Campbell. There are still many other quinones of different types, which were found before or even after 1973, and their biosynthetic pathways have meanwhile been made clear. Many of these new quinones are antibiotics, such as polyketide derived quinones and ansamycins.

Compounds labelled with stable isotopes such as ^{13}C, ^{2}H and ^{18}O have frequently been used in studies of biosynthesis since the 1970s, because the sensitivity of detection by NMR spectroscopy has markedly improved. One of the groups of natural products which benefited greatly from this technical advance is the group of microbial metabolites including quinones. In particular, the NMR studies of [$^{13}C_2$]acetate enriched metabolites provided the decisive information about the polyketide folding mode which had not been disclosed with [^{14}C]acetate feeding. Spectral analysis of metabolites enriched by doubly labelled precursor (^{13}C and ^{2}H or ^{18}O) also provided a lot of evidence about biosynthetic intermediates as will be seen later.

The number of experiments in which plant cell cultures were used to elucidate a biosynthetic pathway leading to quinones and other natural products of higher plants have dramatically increased. This method enables the observation of biosynthetic processes under defined and reproducible conditions and facilitates the use of stable isotopes because incorporation of labelled compounds can be high when compared to experiments in which intact plants are employed. It is impossible to cover all the results of recent intensive studies on the biosynthesis of quinonoid compounds in a limited number of pages, and so attention was given to some representative compounds of each group. Some quinones are biosynthesized by a simple polyketide-, shikimate-, or isoprenoid pathway, but many others are formed by mixed pathways, as can be observed in other groups of natural products. These quinones formed by mixed pathways were classified by the most characteristic feature of their biosynthetic pathway.

II. BIOSYNTHESIS OF QUINONES

A. Polyketide-derived Quinones

Representatives of this group of quinones are believed to be formed from varying numbers of coenzyme A esters of short chain aliphatic acids (such as acetyl coenzyme A, malonyl coenzyme A, methylmalonyl coenzyme A, butyryl coenzyme A etc.) giving rise to a hypothetical ketide (e.g. heptaketide, octaketide, polyketide, etc.) which folds and aromatizes. The prefix (e.g. hepta-, octa- or poly- etc.) corresponds to the amount of keto functions in the hypothetical ketide and the amount of acids involved in the biosynthesis of the resulting quinone. This type of quinone is found mainly in microorganisms and only a few were detected in plants. Major advances in studies of quinone biosynthesis over the last decade have been made in this group of quinones. Most of these quinones are of the hepta- to decaketide origin.

1. Penta- and hexaketide quinones

Experiments with ^{14}C-labelled acetate suggested that flaviolin (**1**) produced by *Aspergillus niger* and 2,7-dimethoxynaphthazarin (**2**) produced by *Streptomyces* sp. are probably of pentaketide origin although they lack the methyl- or carboxyl group which is a polyketide diagnostic feature[2]. Flaviolin (**1**) is also found to be produced by some other fungi such as *Philaphora lagerbergii*, often occurring together with a trihydroxytetralone, viz. scytalone (**3**). Scytalone (**3**) was shown to incorporate [^{13}C]acetates and especially [$^{13}C_2$]acetate with accompanying randomization of ^{13}C–^{13}C coupling[3–5]. This is the evidence demonstrating the intermediacy of a symmetrical compound such as 1,3,6,8-tetrahydroxynaphthalene (**4**) in the biosynthesis of scytalone (**3**). Feeding [2-^{13}C, 2-$^{2}H_3$]acetate and [$^{2}H_3$]acetate to *P. lagerbergii* revealed that ^{2}H is retained at C(4) and C(5), but not at C(2) and C(7) of **3**[6], while no acetate starter effect was found by NMR studies of **3** enriched by [2-^{13}C]malonate[7]. It seems, therefore, likely that scytalone (**3**), and hence the cometabolite flaviolin (**1**) may not originally be a pentaketide, but may be formed from a hexaketide chain via 2-acetyl-1,3,6,8-tetrahydroxynaphthalene (**5**) and tetrahydroxynaphthalene (**4**) as shown in Figure 1. This pathway could also be valid for the above-mentioned 2,7-dimethoxynaphthazarin (**2**) and mompain (**6**)[8], a metabolite of *Helicobasidium mompa*, although experimental proof is still missing. Studies using [$^{13}C_2$]acetate showed that 6-ethyl-5-hydroxy-2,7-dimethoxy-1,4-naphthoquinone (**7**), a metabolite of *Hendersonula toluroideae*, was formed by the acetate assembly pattern as depicted in Figure 1. It was also shown by further feeding studies with [2-^{13}C, 2-$^{2}H_3$]acetate that only two ^{2}H were retained in the 12-position of this quinone, suggesting that at the ethyl side chain of this quinone sequential reduction, dehydration and reduction would occur after cyclization[9].

2. Heptaketide quinones

This group of quinones is represented by dihydrofusarubin (**8**), javanicin (**9**), norjavanicin (**10**), and fusarubin (**11**), metabolites of *Fusarium solani*. Feeding of ^{13}C-labelled acetates and [2-^{13}C, 2-$^{2}H_3$]acetate to *F. solani* demonstrated that dihydrofusarubin (**8**) was formed by folding of the heptaketide chain as shown in Figure 2[10]. Fusarubin (**11**) and norjavanicin (**10**) were shown to be produced from dihydrofusarubin (**8**)[11]. The terminal carboxyl group is reduced to alcohol during conversion to **8** and **11**, and to the methyl group during conversion to **9**. The terminal alcohol group of **8** has been lost in **10** through a retroaldol reaction. Marticin (**12**), a phytotoxic metabolite of *Fusarium martii*, also belongs to this group. The acetate assembly pattern of **12**[12] is that shown for **11** in Figure 2. Marticin (**12**) appears to be formed by addition of a C_3 unit originating from an

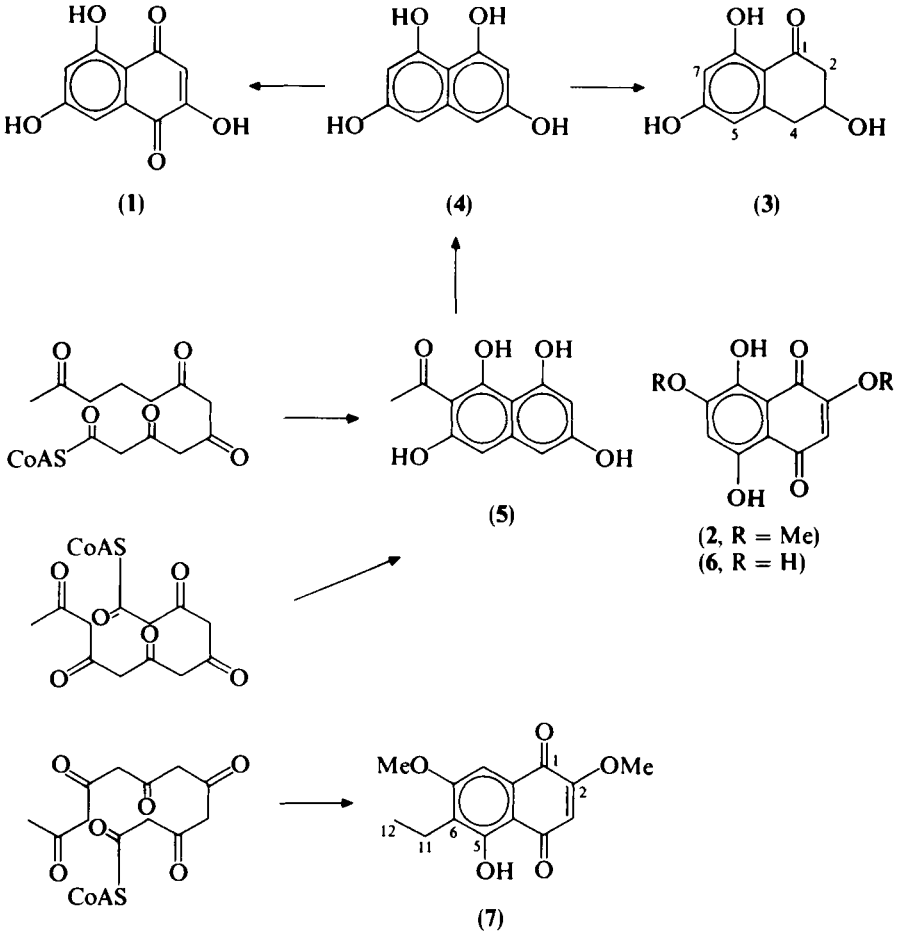


FIGURE 1

intermediate of the Krebs cycle such as succinate or oxaloacetate to the heptaketide skeleton of fusarubin (**11**) or one of its precursors.

Xanthomegnin (**13**) and viomellein (**14**) isolated from *Aspergillus sulphureus* and *A. melleus* are dimers of heptaketide quinones formed by the same acetate assembly pattern[13, 14]. The terminal carboxyl group remains in the form of a lactone in these molecules. Cercosporin (**15**)[15] and elsinochromes C (**16**) and D (**17**)[16], respectively, elaborated by plant pathogenic fungi *Cercospora kikuchii* and *Pyrenochaeta terrestris* are quinones of the same origin as above. These are probably biosynthesized by oxidative coupling of substituted naphthalenes which are formed by cyclization of the heptaketide chain, either before or after decarboxylation.

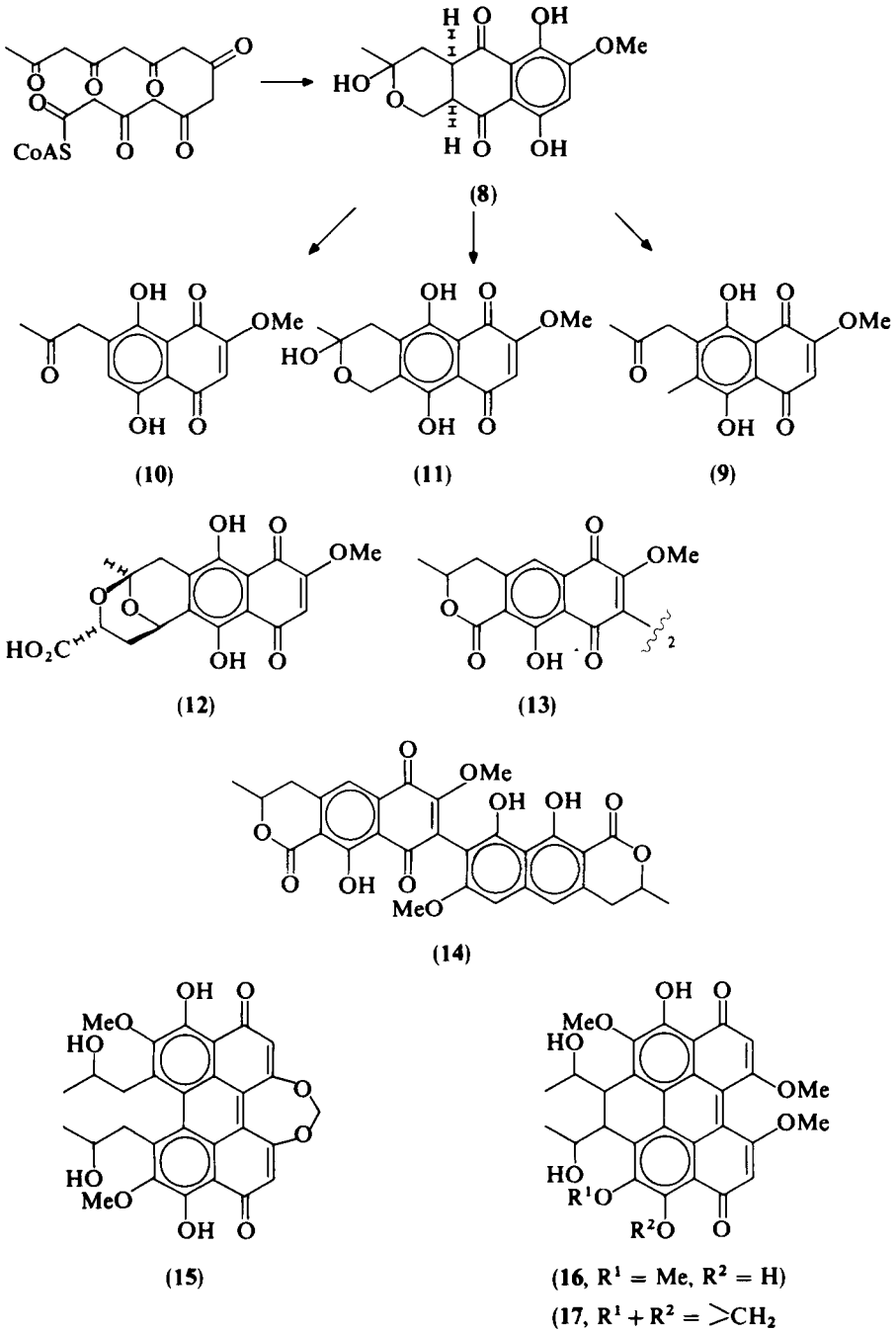
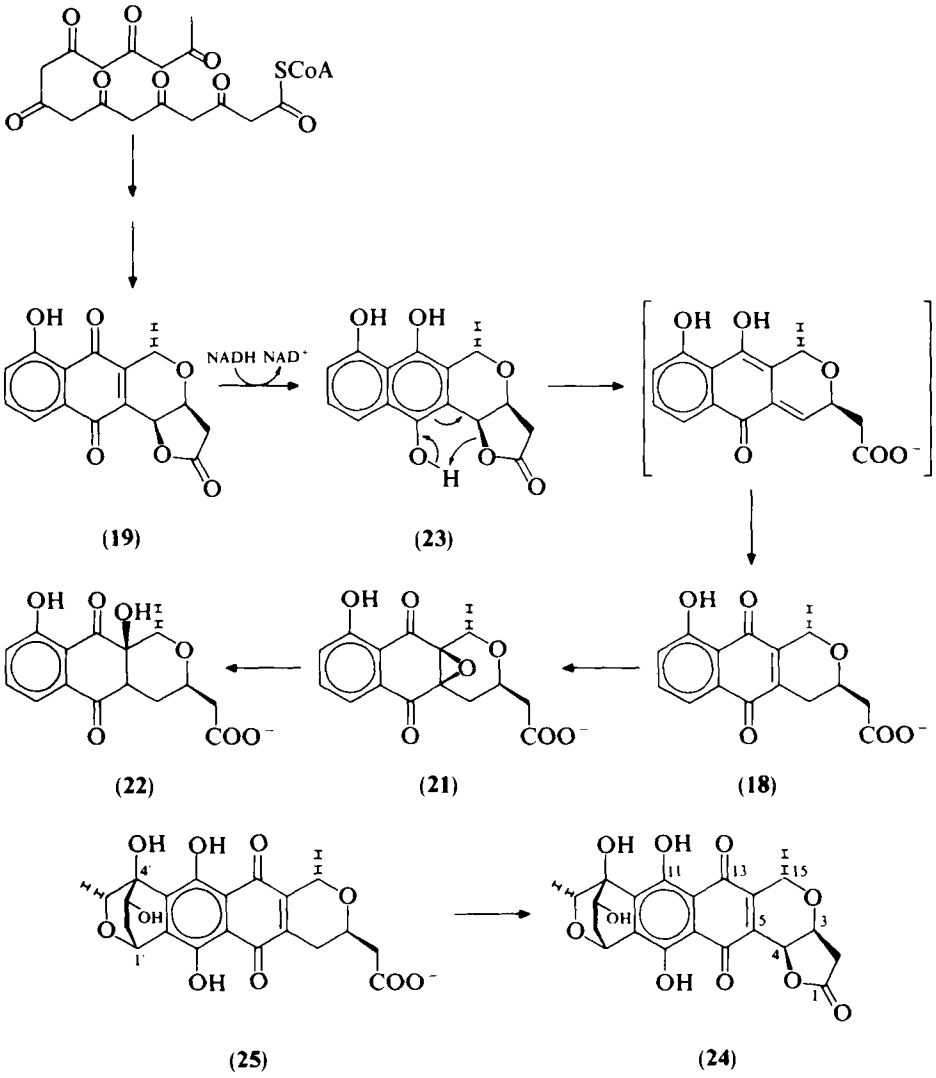


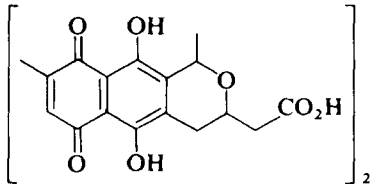
FIGURE 2

3. Octaketide quinones

a. Benzoisochromane quinones Antibiotics, such as nanaomycins A (**18**)–D (**19**) of *Streptomyces rosa*, granaticin of *S. olivaceous*, and *S. violaceoruber*, naphthocyclinones of *S. arenae*, and actinorhodin (**20**) of *S. coelicolor*, belong to this group (Figure 3).

Nanaomycins were shown to be formed by folding of the octaketide chain as depicted in Figure 3[17]. The biosynthetic relationship of the nanaomycins was studied by bioconversion experiments of **18**, **19**, etc., using *S. rosa* grown in the presence of cerulenin, a specific inhibitor of polyketide biosynthesis. Time-course studies revealed that the production of nanaomycin D (**19**), the first component formed from the hypothetical octaketide





(20)

FIGURE 3

intermediate, was followed by sequential conversion to nanaomycins A (**18**), E (**21**) and B (**22**)[18]. Nanaomycin D reductase was isolated from *S. rosa*. This enzyme is a NADH dehydrogenase, which reduces **19** to a hydroquinone intermediate (**23**) under anaerobic conditions. The resulting hydroquinone intermediate is then non-enzymatically converted to **18**[19].

The ketide folding pattern of granaticin (**24**) is the same as that of nanaomycins[20, 21]. Portions not derived from acetate originate from glucose, which was first converted to 2,6-dideoxyhexose, and then bound to the aromatic ring at the 1',4'-positions of the sugar. During these processes, protons at the 3,5-positions of glucose were lost, while the hydroxy group at the 6-position was substituted by the proton at the 4-position with inversion of configuration. ^{13}C-NMR spectral studies of **24**, which was obtained by feeding [1-^{13}C, $^{18}O_2$]acetate to *S. violaceoruber*, demonstrated that acetate-derived oxygen was retained on C(1), C(3) and C(11) and probably on C(13)[20]. An isotope shift was found on C(3) and not on C(15), indicating the retention of a C–O bond on C(3) during formation of the dihydropyran ring. The cell-free extract of *S. violaceoruber* was found to catalyse the conversion of dihydrogranaticin (**25**) to granaticin (**24**) (Figure 3) without incorporation of ^{18}O from $^{18}O_2$. This suggests that the final step of granaticin (**24**) formation is not hydroxylation at C(4) and lactonization, but the direct cyclization of the carboxyl group onto the 4–5 bond. This reaction is the reverse of the conversion of nanaomycin D (**19**) to A (**18**).

There are seven homologues of naphthocyclinones including α-(**26**), β-(**27**), γ-(**28**), and δ-compounds (**29**) and all these are unsymmetrical dimers of isochromane quinones. Feeding experiments of biosynthetically prepared naphthocyclinones including the monomer (**30**) to *S. arenae* demonstrated the biosynthetic relationships shown in Figure 4[22], which parallels those of nanaomycins D (**19**), A (**18**) and E (**20**) (epoxide). β-Naphthocyclinone epoxide (**31**) corresponding to **19** was further converted to α-naphthocyclinone (**26**) through epoxide ring-opening followed by extrusion of a two-carbon unit.

Actinorhodin (**20**) is a symmetrical dimer of a benzoisochromane quinone[23] (Figure 3). The genes for actinorhodin biosynthesis have been mapped and since they are located in a short segment on the chromosome it was suggested that they form an uninterrupted cluster[24]. Indeed a large continuous segment of *Streptomyces coelicolor* DNA was isolated which contains the complete information required for the synthesis of **20** from simple primary metabolites. This DNA fragment was introduced into a vector which enabled expression of actinorhodin (**20**) biosynthesis after transformation into protoplasts of *Streptomyces parvulus*, an organism which usually does not produce **20**[25].

A series of 76 mutants of *Streptomyces coelicolor* unable to produce **20** were isolated[26]. These mutants were grouped together according to their ability to carry out cosynthesis. Cosynthesis is the ability of two mutant strains placed in close neighbourhood on a single agar plate to carry out antibiotic formation. This joint production of actinorhodin (**20**) is

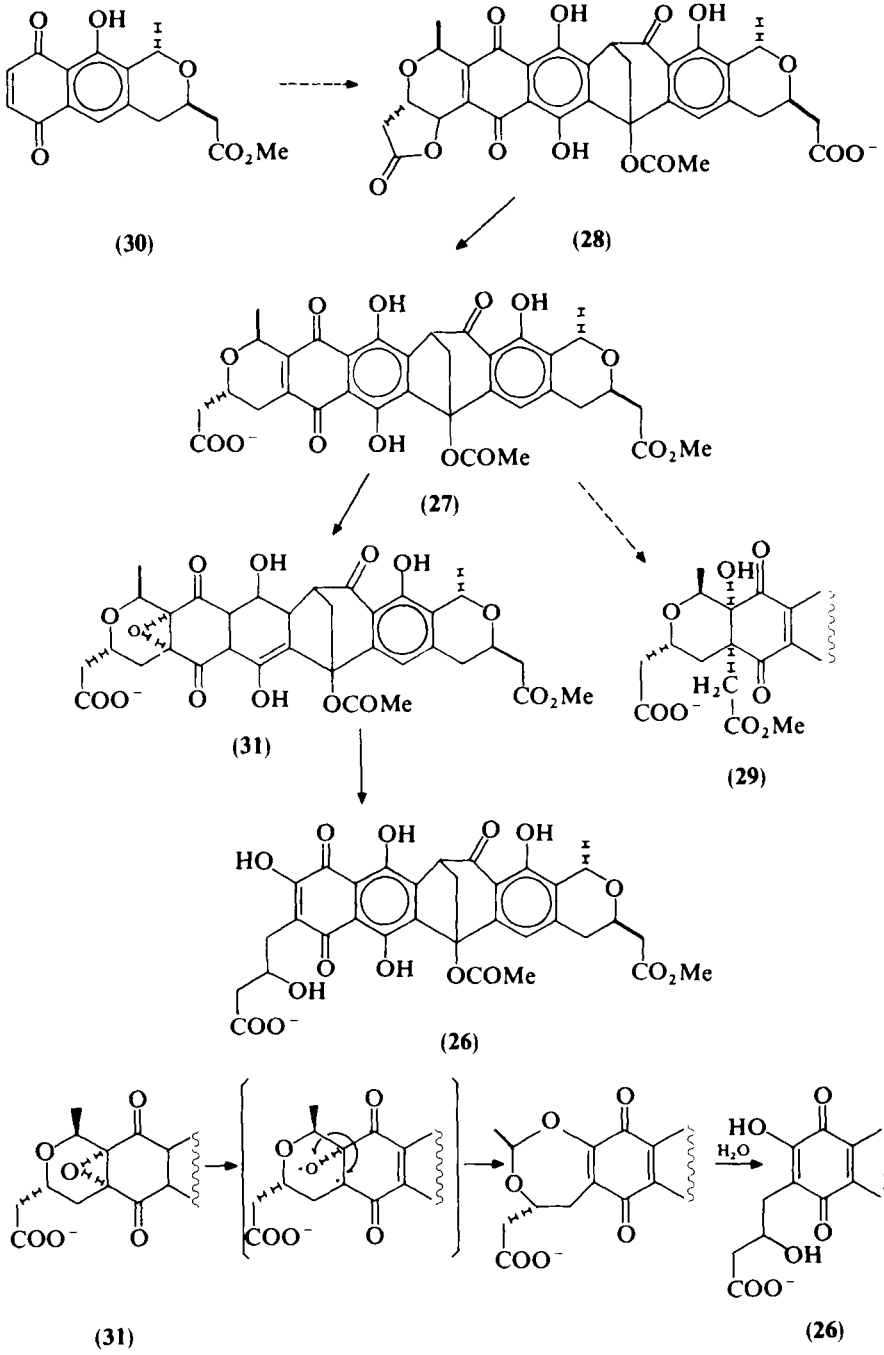


FIGURE 4

possible because one mutant excretes an intermediate which is converted by the second mutant to the product (actinorhodin). Isolation and identification of the intermediates made it possible to elucidate late steps in the biosynthetic sequence leading to **20**[26, 27].

The regulatory phenomena involved in actinorhodin (**20**) biosynthesis are also highly interesting because they reveal a close relationship between the biosynthesis of **20**, formation of a so-called autoregulator (also called 'A-factor', i.e. 25-isocapryloyl-3S-hydroxymethyl-γ-butyrolactone)[28] and morphological changes of the *Streptomyces* strain such as sporulation and formation of aerial mycelium[29].

Benzoisochromane quinones are found not only in microorganisms, but also in higher plants. Eleutherin (**32**) and isoeleutherin of *Eleutherine bulbosa* and ventiloquinones A (**33**)–K[30] and ventilatones A (**34**) and B[31] which have recently been isolated from *Ventilago* species are included in this group. Besides the acetate assembly mode (a) depicted in Figure 5, mode (b) is also feasible for these plant quinones. But, it is not possible to predict the mode of folding without biosynthetic experiments, because the terminal carboxyl group seems to be lost in these quinones.

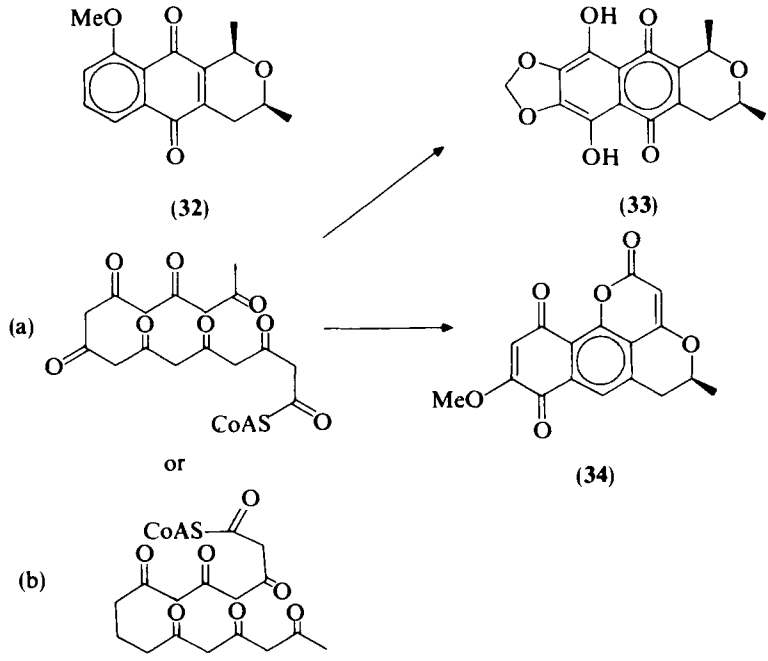


FIGURE 5

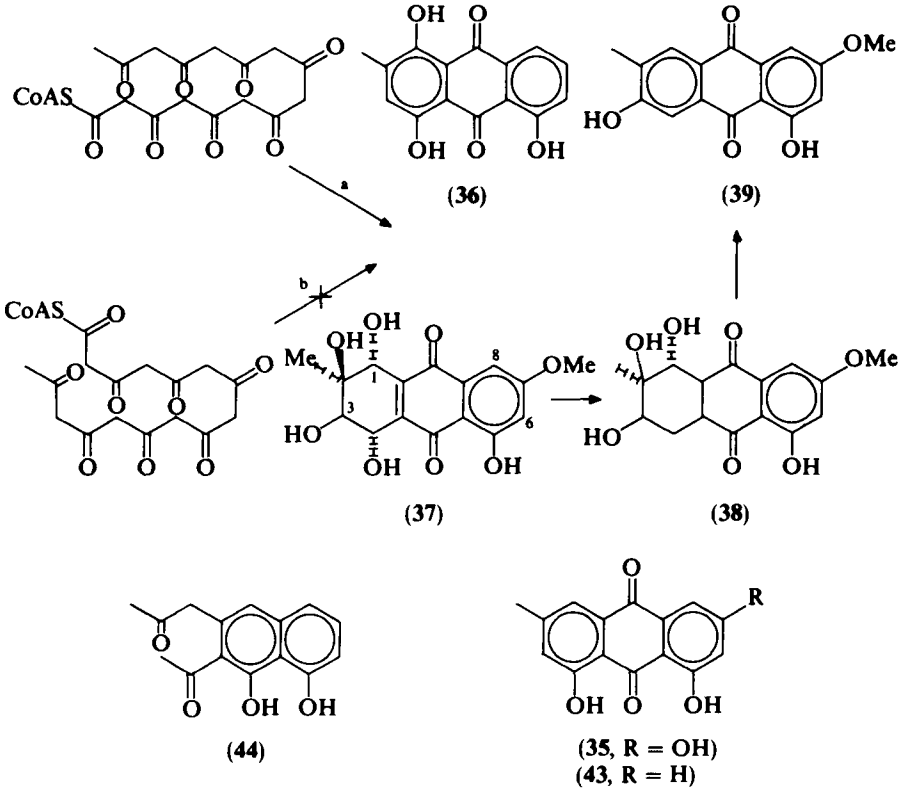
b. Anthraquinones It has been known for a long time that some anthraquinones are formed from an octaketide chain. It was believed that emodin (**35**), for instance, is biosynthesized by folding mode (a) shown in Figure 6. This assumption was based on results of [^{14}C]acetate feeding experiments. But, there was no definite evidence indicating that quinones of this type are not formed by folding pattern (b). However, [$^{13}C_2$]acetate feeding experiments demonstrated that islandicin (**36**)[32, 33] produced by *Penicillium islandicum*, and altersolanol A (**37**), dactylariol (**38**) and macrosporin (**39**)[34, 35] elaborated

by *Alternaria solani*, a pathogenic fungus of tomatoes and potatoes, were all formed by route (a). Application of **37** to *A. solani* suggested that this metabolite would be converted to **39** via **38**. NMR studies of **37** and **39** enriched by [^{13}C, $^{2}H_3$]acetate showed that ^{2}H was retained in the C-methyl groups and at the 1-, 6- and 8-positions of both compounds, but did not remain at the 3-position of altersolanol A (**37**). The absence of ^{2}H at the 3-position of **37** seems to be of biosynthetic significance with respect to the introduction of an OH group in this position.

Aloesaponol (**40**), laccaic acid D methyl ester (**41**) and aloesaponarin (**42**) isolated from *Aloe saponaria* are also octaketide anthraquinones, but these compounds are evidently formed by a different folding mode of the ketide chain, which is delineated in Figure 6. The metabolic relationship[36] between these natural products is also depicted.

Interesting results on the biosynthesis of chrysophanol (**43**) (Figure 6) have been obtained recently. Structurally this metabolite differs from emodin (**35**) in that the OH group in position 6 of the anthraquinone skeleton is missing. The assumption that in the biosynthesis of chrysophanol removal of the oxygen function would occur at a non-aromatic stage seemed to be obvious. A cell-free system from *Pyrenochaeta terrestris* has been obtained, however, that dehydroxylates emodin (**35**)[37]. The dehydroxylation is stimulated in the presence of $NADPH_2$, Fe(II), ATP and under anaerobic conditions (N_2). The role of ATP in this reaction is unexplained. To the authors' knowledge this is the first case that enzymatic dehydroxylation of an aromatic compound has been demonstrated.

It is noteworthy that *P. islandicum* converted a ^{14}C-labelled naphthol derivative (**44**) to islandicin (**36**) and its dimer, viz. skyrin (**45**)[38].



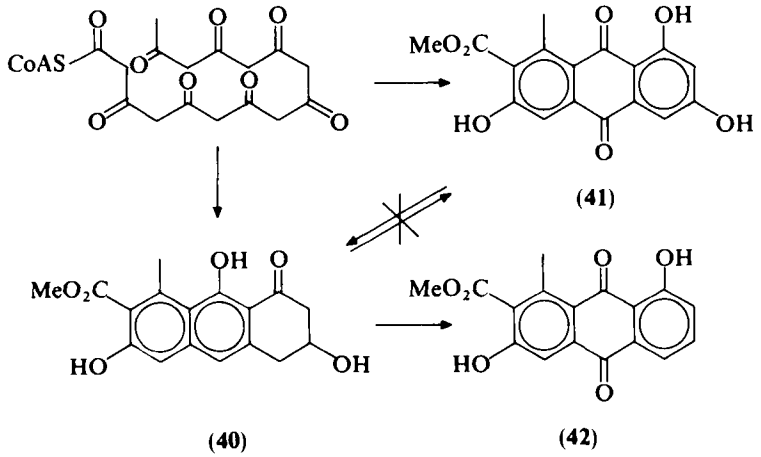


FIGURE 6

c. Dimerization of octaketide anthraquinones *P. islandicum* and *P. brunneum* also produce several anthraquinone dimers, such as skyrin (**45**), iridoskyrin (**46**), rubroskyrin (**47**), flavoskyrin (**48**) and rugulosin (**49**) (Figure 7). These dimers are certainly formed by dimerization of monomeric anthraquinones or monomeric anthrones. However, there is evidence that labelled emodinanthrone (**50**) was incorporated into skyrin (**45**) and iridoskyrin (**46**) in a higher ratio than labelled emodin (**35**)[39]. The formation of flavoskyrin produced by *P. islandicum* is rationally explained by Diels–Alder type 4S + 2S cycloaddition of an enolic form (**51**) of tetrahydroemodin[40]. (−)-Regulosin (**49**) is produced from flavoskyrin (**48**). Diels–Alder type cycloaddition is often found in natural products other than quinones[41,42].

4. Nonaketide quinones

There are only two nonaketide quinones, i.e. bikaverin (**52**)[43], an antiprotozoal metabolite of *Fusarium oxysporum* and phomazarin (**53**)[44], an azaanthraquinone of *Pyrenochaeta terrestris*. Several experiments using labelled acetates, particularly those using [$^{13}C_2$] acetate, demonstrated that these quinones were biosynthesized by the acetate assembly modes shown in Figure 8. But, as regards phomazarin, the assembly mode by two ketide chains such as mode (c) could not be ruled out by acetate feeding experiments only. This quinone enriched by ^{14}C- or ^{13}C-labelled malonate showed only a low level of labelling at C(15), but a normal level at C(11). These results disaffirm the possibility of the two chain assembly. It seems very likely that the ring system which was formed by mode (a) underwent oxidative fission at the stage of biquinone and then a nitrogen function was introduced to form phomazarin (**53**).

5. Decaketide quinones

a. Anthracyclins Anthracyclins are produced by species of the genus *Streptomyces*. Anthracyclins are glycosides with a 7,8,9,10-tetrahydro-5,12-naphthacenequinone skeleton (anthracyclinones). All anthracyclinones are decaketides. In some of them, the starter unit is the acetyl group as usual, while in others it is the propionyl-, isobutyryl-, butyryl or acetoacetyl group[45].

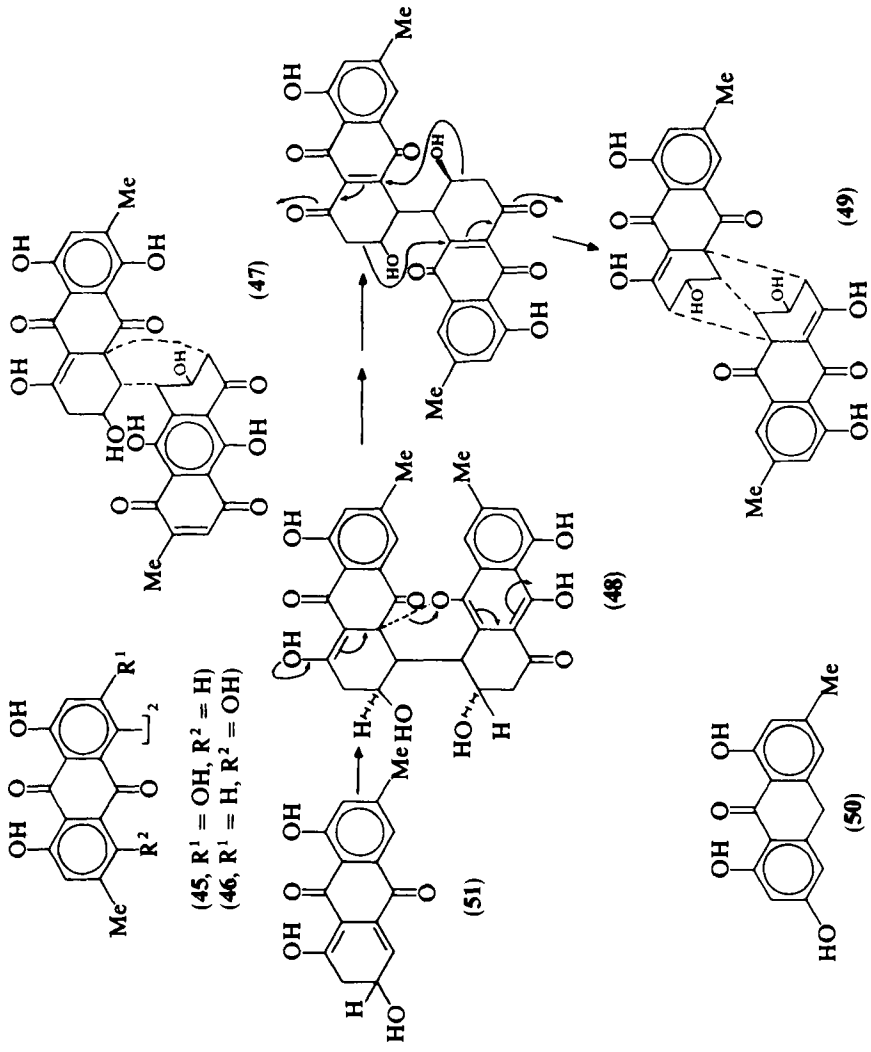


FIGURE 7

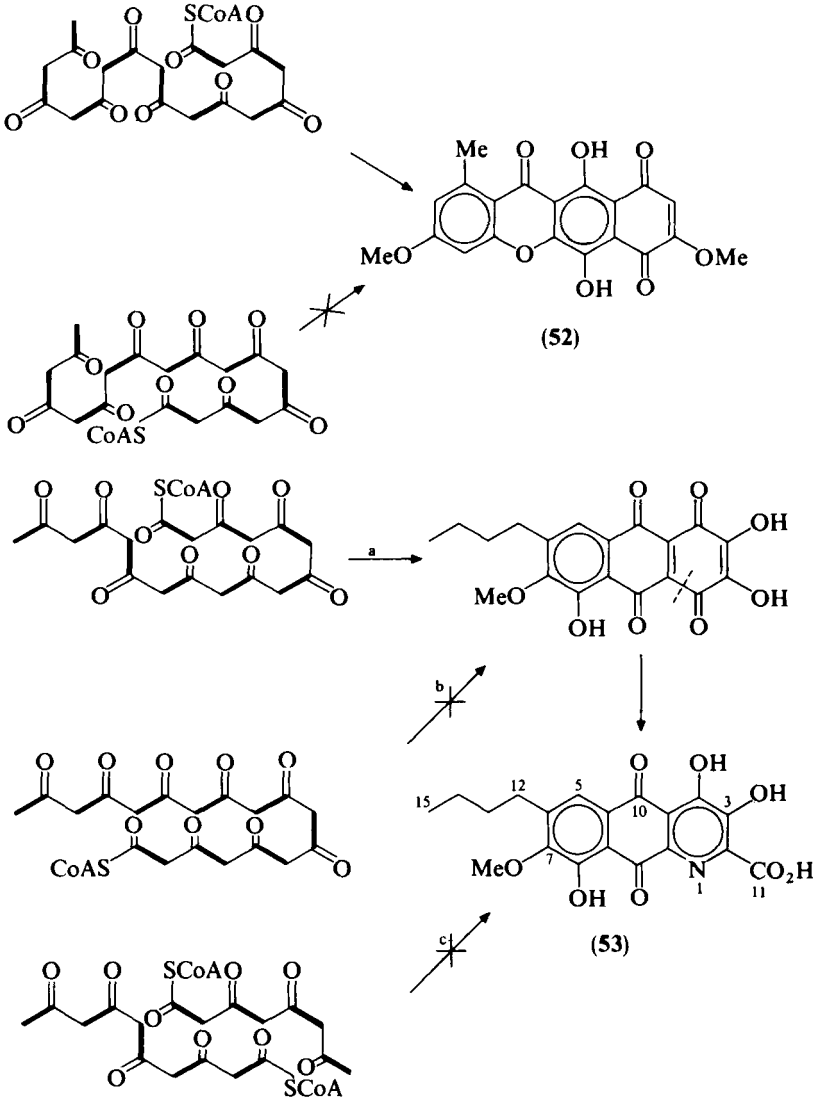


FIGURE 8

The biosynthesis of daunomycinone (**54**), the aglycone of a representative anthracyclin, daunomycin (**55**), was studied by feeding [^{13}C]acetates to *S. peucetius*. The results showed that the acetate assembly pattern of this compound was as shown in Figure 9[46]. It was recently demonstrated that alkanoate (**56**) isolated from *S.* sp. ZIMET or its methyl ester (**57**) was converted to ε-rhodomycinone (**58**), daunomycinone (**54**), or other anthracyclinones when fed to the fermentation broth of mutant strains of *S. griseus*[46,47]. This result suggests the likely intermediacy of alkanoate **56** or its methyl ester (**57**) in the biosynthesis

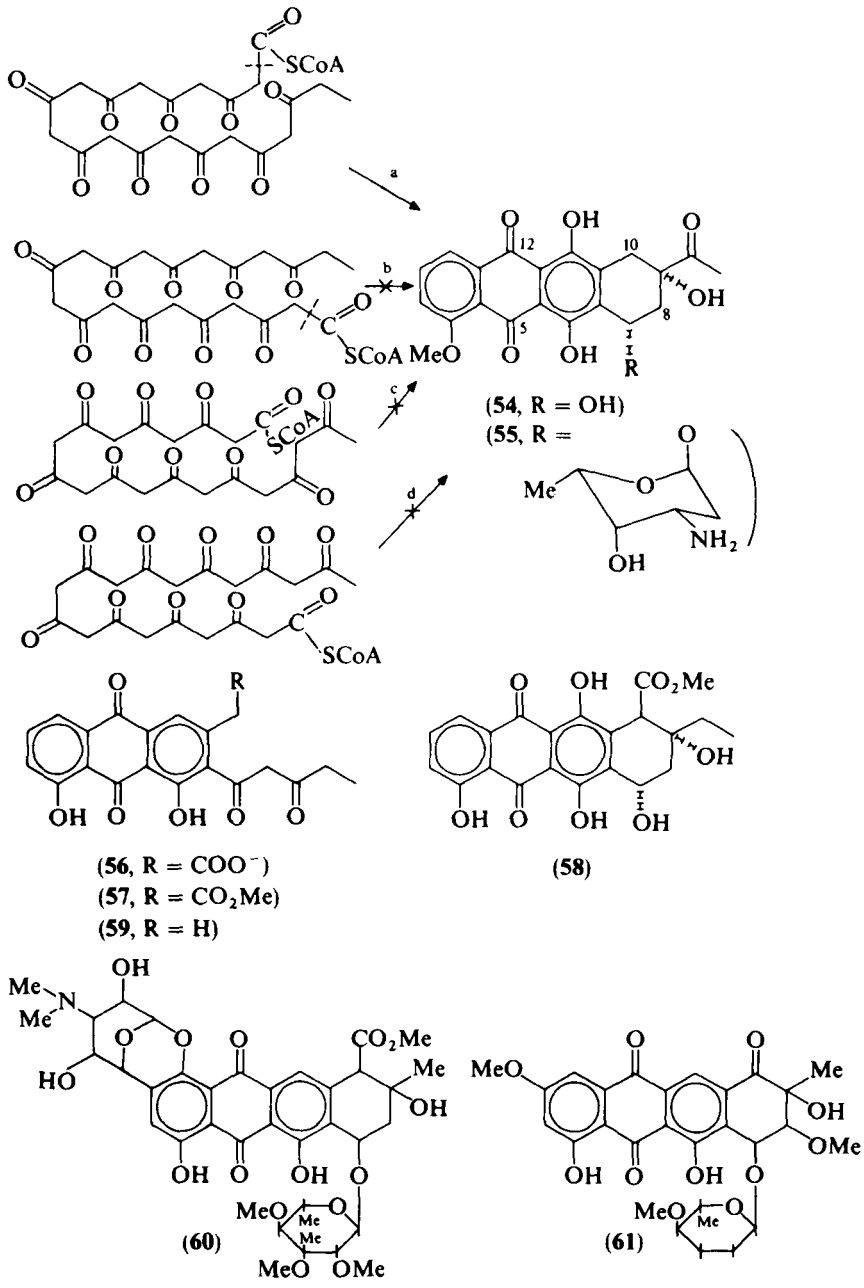


FIGURE 9

of daunomycinone (**54**) or other congeneric products formed from the decaketide chain. In accordance with the decaketide hypothesis alkanone (**59**), a decarboxylation product of alkanoate (**56**), does not undergo this conversion.

Application to *S. nogalata* and *S. elegreteus* of ^{13}C-labelled acetate disclosed decaketide assembly patterns for nogalamycin (**60**) and steffimycin B (**61**) similar to that of daunomycin (**55**). In the former compounds an acetyl group is the starter unit. The sugar moieties of both **60** and **61** are derived from D-glucose, and the methyl groups of MeO and MeN are derived from methionine[48].

The sequence of hydroxylation, methylation, decarboxylation and glycosidation in the anthracyclinone skeleton was also studied using various mutant strains of *Streptomyces* sp.[49-51]

b. Other decaketide quinones Vineomycin A_1 (**62**) and vineomycin B_2 (**63**), antibacterial and antitumour metabolites produced by *Streptomyces matensis*, have a unique benzanthraquinone skeleton. The chromophore portion of these compounds is biosynthesized by the acetate assembly mode shown in Figure 10[52]. Vineomycin B_2 is formed

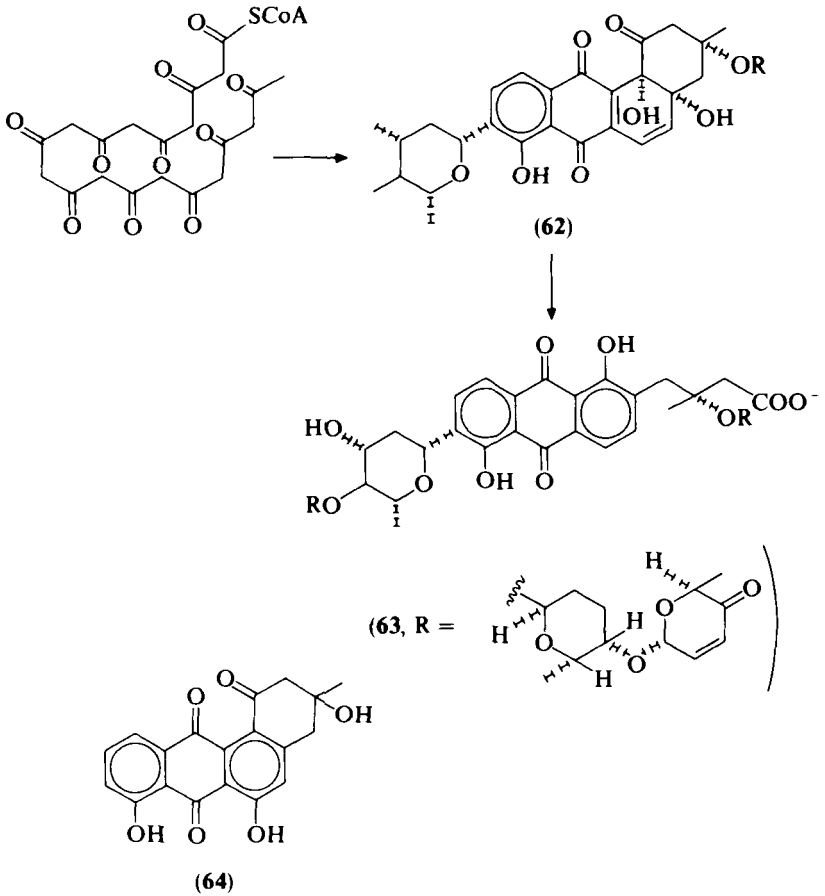


FIGURE 10

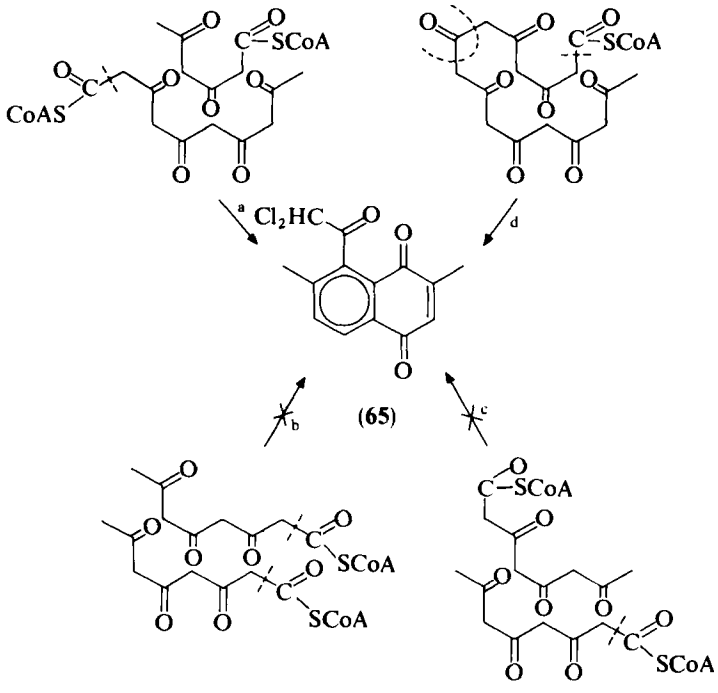
by ring fission of vineomycin A_1 at the site shown by a dotted line. Along with these two compounds, a congeneric metabolite, rabelomycin (**64**), is also produced by the same fungus.

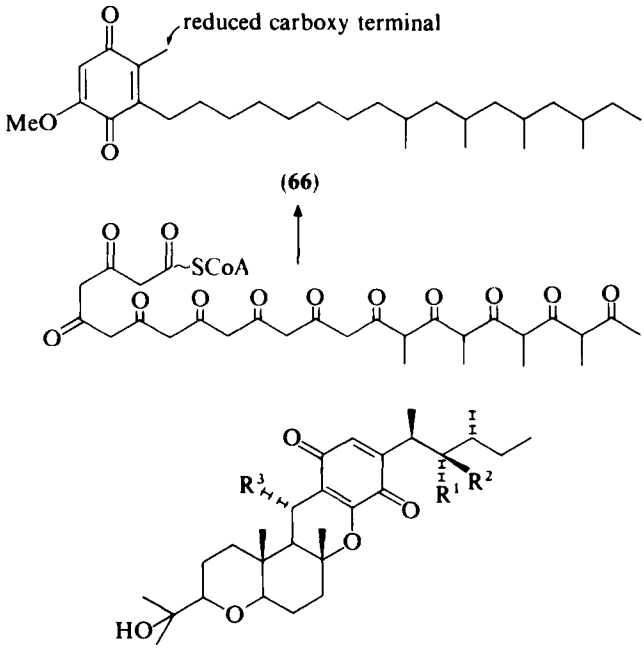
6. *Other polyketide-derived quinones*

a. Mollisin Mollisin (**65**), a naphthoquinone produced by *Mollisia caesia*, has a peculiar structure from the biosynthetic point of view, and seems to be formed from a triketide and a pentaketide chain. Although three modes of acetate assembly, a, b, and c, were presumed, the results of [$^{13}C_2$]acetate feeding experiments were consistent with mode a[53,54]. Another possibility is route d, in which the compound is formed by cleavage of a single octaketide chain[54].

b. Mavioquinone Mavioquinone (**66**) is a benzoquinone with a long alkyl side chain isolated from the lipid extract of *Mycobacterium avium*[55]. It is a dodecaketide biosynthesized from the acetate starter unit, four propionates and seven further acetates. The Me group attached to the oxygen is derived from methionine[56].

c. Cochlioquinones Cochlioquinones A (**67**) and B (**68**), metabolites of *Cochliobolus miyabeanus*, consist of a bis-C-methylated hexaketide and a sesquiterpene portion. The studies of the mass spectra of the degradation products of **67** and **68** obtained by incubation of the fungus in an atmosphere of $^{18}O_2$ and $^{16}O_2$ demonstrated that two oxygen atoms in this uncommon 2-(2-hydroxypropyl)tetrahydropyran structure were introduced at separate stages during the biosynthetic processes[57].





(**67**, R^1 = OAc, R^2 = H, R^3 = OH)
(**68**, R^1 R^2 = O, R^3 = H)

FIGURE 11

B. Shikimate-derived Quinones

There are as many quinones in this group as there are in the polyketide group. However, most of the quinones dealt with in this section are of mixed origin, and are biosynthesized, not only by the shikimate pathway, but also have a mevalonate and/or polyketide moiety.

1. p-Hydroxybenzoate-derived quinones

This group of compounds is represented by ubiquinones which are present in almost all organisms. Several quinones, which are biosynthesized via geranylhydroquinone (**69**) (Figure 12) and are found in boraginaceous plants, are also included in this group.

a. Ubiquinones Ubiquinones (**70**) play a role as lipid-soluble electron carriers in the membrane-bound respiratory chain. The structure of ubiquinones is shown in Figure 12. The number of isoprene units usually varies from 6 to 10. Biosynthetic studies on bacterial ubiquinones have already been outlined by Bentley and Campbell[1]. The present review includes the eucaryotic pathway. It has already been demonstrated in the 1960s that 4-hydroxybenzoate (**71**) formed by the shikimate pathway is the pivotal precursor in the biosynthesis of ubiquinones[58-61]. Up to the early 1970s evidence was obtained that in prokaryotes such as *Rhodospirillum rubrum*[62,63] and *E. coli*[64-68] ubiquinone-10 (or ubiquinone-8) (**70**) is biosynthesized from 4-hydroxy-3-deca-(or octa)prenylbenzoate

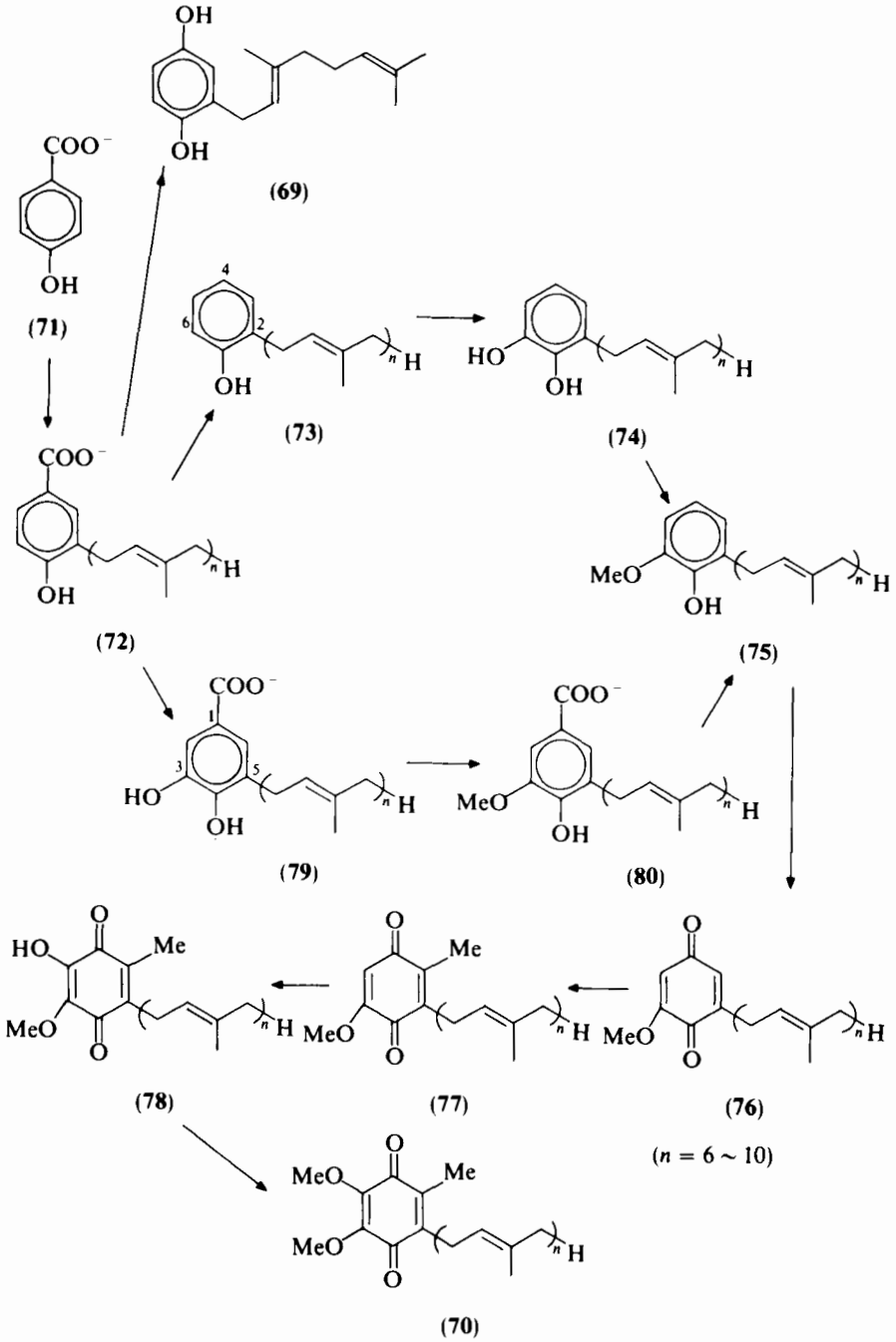
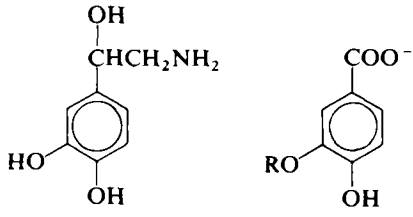

OH
OH
(69)
COO⁻
OH
(71)
4
6
2
n H
OH
(73)
HO
OH
(74)
COO⁻
n H
OH
(72)
MeO
OH
(75)
COO⁻
1
3
5
HO
n H
OH
(79)
COO⁻
MeO
n H
OH
(80)
O
HO
Me
MeO
n H
O
(78)
O
Me
MeO
n H
O
(77)
O
MeO
n H
O
(76)
(n = 6 ~ 10)
O
MeO
Me
MeO
n H
O
(70)

FIGURE 12

(**72**) via 2-prenylphenol (**73**), 3-prenyl catechol (**74**), 6-methoxy-2-prenylphenol (**75**), 6-methoxy-2-prenyl-1,4-benzoquinone (**76**), 6-methoxy-3-methyl-2-prenyl-1,4-benzoquinone (**77**), and 5-hydroxy-6-methoxy-3-methyl-2-prenyl-1,4-benzoquinone (**78**) as shown in Figure 12. As regards the pathway in eukaryotes (**75**, $n=9$), 5-demethoxy-ubiquinone-9 (**77**, $n=9$), and 5-demethyl-ubiquinone-9 (**78**, $n=9$) were shown to be intermediates in ubiquinone-9 biosynthesis in rats[69-71]. The corresponding $n=6$ compounds are involved in ubiquinone-6 (**70**, $n=6$) biosynthesis in yeast[72]. The later stages of ubiquinone biosynthesis in eukaryotes, therefore, are identical to those in prokaryotes.

It was also shown that nonaprenylphenol (**73**, $n=9$), an intermediate in the biosynthesis of ubiquinone-9 (**70**, $n=9$) in prokaryotes, cannot be an intermediate in rats[73]. Thus, it was recognized that the biosynthesis of ubiquinones (**70**) in eukaryotes and prokaryotes differs significantly in the middle stage, though both groups of organisms share certain portions of the ubiquinone biosynthetic pathway. A new intermediate, **79** ($n=7$), was recently isolated from the ubiquinone-deficient strain E3-24 of *Saccharomyces cerevisiae*[74]. This new intermediate accumulates in a yeast mutant impaired in methionine biosynthesis. Radioactivity from this product was incorporated into ubiquinone-6 (70, $n=6$) when growth of the auxotrophic yeast mutant was supported by methionine[75]. In the ubiquinone-deficient strain 26*H*,3-methoxy-4-hydroxy-5-hexaprenylbenzoate (**80**, $n=6$) accumulates. This compound was found to be converted to **70** by mitochondria isolated from wild-type yeast or rat liver[76,77]. All this evidence shows that 3,4-dihydroxy-5-polyprenyl benzoate (**79**) and 3-methoxy-4-hydroxy-5-polyprenylbenzoate (**80**) are intermediates between 4-hydroxy-3-polyprenylbenzoate (**72**) and 6-methoxy-2-polyprenylphenol (**75**) in eukaryotes.

Besides the biosynthetic pathways leading to ubiquinones as stated above, there seem to be alternate pathways in animal cells. For example, when norepinephrine (**81**), which is derivable from tyrosine, was incubated together with rat liver mitochondria, it was metabolized not only to vanillate (**82**) and protocatechuate (**83**), but also to their prenylated products[78]. If rat heart slices are used, 4-hydroxybenzoate (**71**) can be converted to **82** and **83**[79]. Thus in animals there may be variations in the metabolic route to 2-polyprenyl-6-methoxyphenol (**75**) depending on the substrates employed.



(**81**) (**82**, R = Me) (**83**, R = H)

FIGURE 13

b. Geranylhydroquinone-derived quinones in boraginaceous plants It has already been shown in 1971 that the carbon skeleton of alkannin (**84**), a naphthoquinone occurring in some boraginaceous plants, is formed from *p*-hydroxybenzoate (**71**), and two molecules of mevalonate (MVA). In these experiments labelled precursors were fed to *Plagiobothrys arizonicus*[80]. Recent administration experiments of **71**, *m*-geranyl-*p*-hydroxybenzoate (**85**) and geranylhydroquinone (**69**) to shikonin producing tissue cultures of *Lithospermum*

erythrorhizon demonstrated that shikonin (**86**), the enantiomer of **84**, is formed via **71**, **85** and **69**. Furthermore, in a quinone non-producing strain and in callus tissue which was impaired in pigment production by addition of 2,4-D to the medium or by blue light illumination, it was shown that the biosynthetic pathway was blocked at a step between **85** and **69**. These results were obtained by isotope dilution experiments in which [5-^{3}H]shikimate (**87**) was employed[81]. It is possible that blue light exerts its effect on pigment production via FMN[82].

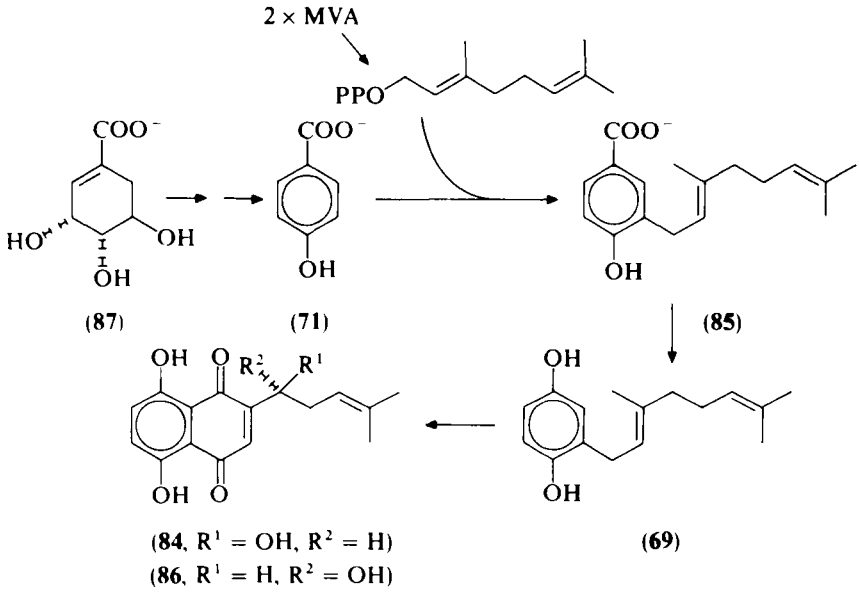


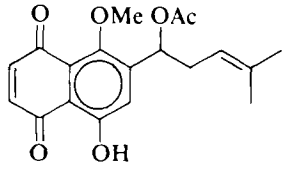
FIGURE 14

It is evident from the above results that **69** is the pivotal intermediate in the biosynthesis of shikonin (**86**) and alkannin (**84**). **69** also seems to be a precursor of many phenols including quinones in boraginaceous plants. For example, echinone (**88**) and echinofuran (**89**)[83] produced by tissue cultures of *Echium lycopsis* and cordiachromes A (**90**), B (**91**) and C (**92**)[84] (Figure 15) isolated from *Cordia alliodora* are likely to be biogenetically related.

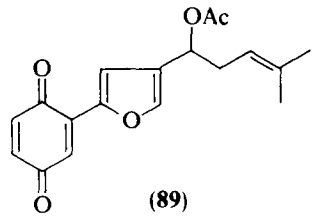
2. *Homogentisate-derived quinones*

a. Plastoquinones and tocopherols Plastoquinones (**93**) and tocopherols (**98–101**) belong to this group. They have the general structure shown in Figures 16 and 17. Phytylplastoquinone (**94**) (with a phytyl side chain) is structurally closely related to tocopherols. Bentley and Campbell[1] also outlined the work on the biosynthesis of these quinones. The pathway postulated up to 1973 was verified by recent studies.

The common precursor of the aromatic portion of these compounds is homogentisate (**95**) derived from shikimate (**87**)[85]. Experiments using labelled **95** and lettuce chloroplasts indicated that both plastoquinone-9 (**93**) and phytylplastoquinone (**94**) are biosynthesized from **95** via 2-demethylprenylplastoquinol (**96**) and prenylplastoquinol (**97**)



(88)



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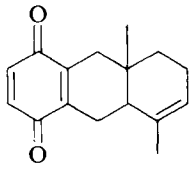

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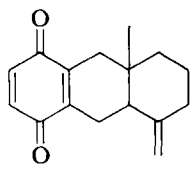

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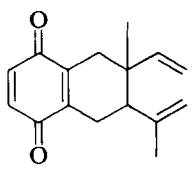

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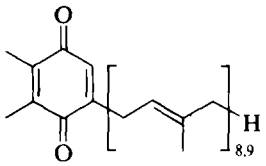
FIGURE 15



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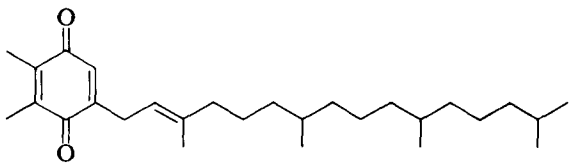


(94)

FIGURE 16

(prenyl = nonaprenyl or phytyl)[86] (Figure 17). While **95** is known as the precursor of α-(**98**), β-(**99**), γ-(**100**) and δ-tocopherols (**101**), recent experiments showed that **95** was also converted to α-(**98**) and δ-tocopherols (**101**) by lettuce chloroplasts[87]. The methyl group in the above series of compounds, which is not derived from *S*-adenosylmethionine, originates from **95** by decarboxylation.

The stereochemistry of this decarboxylation reaction was investigated after feeding homogentisate (**95**), chirally labelled in the methylene group, to *Raphanus sativus* seedling[88]. The chirally labelled homogentisate (**95**) was prepared as follows. Chemical and enzymatic exchange reactions were carried out with 4'-hydroxyphenyl pyruvate in the presence of base or 4'-hydroxyphenylpyruvate tautomerase, HTO or D_2O. The enantiotopically labelled products were converted to correspondingly labelled homogentisate (**95**) samples using 4'-hydroxyphenylpyruvate dioxygenase. After application to *Raphanus* of the homogentisate (**95**) so obtained, tocopherol and plastoquinone (**93**) were isolated and submitted to a mild Kuhn–Roth oxidation. The chirally labelled acetate samples carrying the desired methyl groups of the quinones were enzymically analyzed with known procedures[89]. The chirality of the acetate samples indicated stereochemical retention of the decarboxylation of homogentisate (**95**) during tocopherol and plastoquinone biosynthesis.

It is assumed that a decarboxylation reaction as outlined in Figure 18 takes place in which a quinone intermediate occurs and that the same group of the enzyme which deprotonates the carboxyl group also serves as a proton donor for an intermediate enolate.

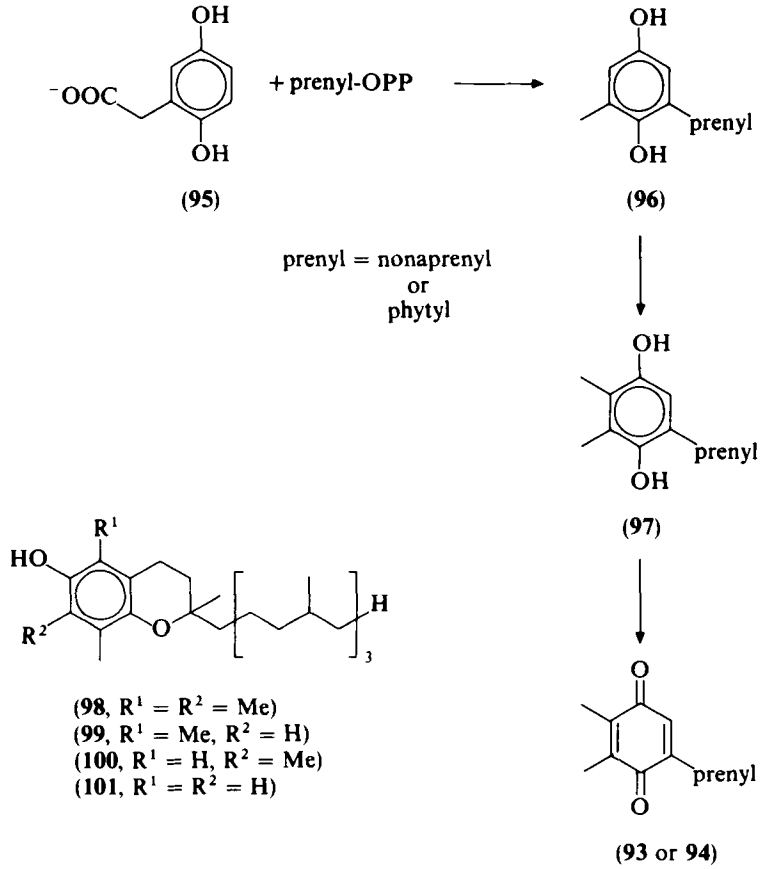


FIGURE 17

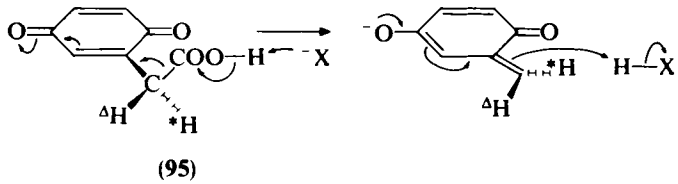


FIGURE 18

This would ensure removal of CO_2 and introduction of a proton from the same side and consequently stereochemical retention during decarboxylation.

Tocopherols (**98**–**101**) and plastoquinone (**93**) belong to the so-called lipoquinones. They are localized in chloroplasts and thus are assumed to be implicated in photosynthesis and the functioning of the chloroplasts. The steps of the biosynthesis of lipoquinones have been outlined (*vide supra*). The compartmentalization of the single steps has been

extensively investigated by plant physiologists[90]. The distribution of lipoquinones within the chloroplast has also been investigated[91,92]. Thus plastoquinone (**93**) which is associated with the light reaction of photosynthesis is contained mainly in the thylakoids, whereas **98** is contained mainly in the envelope of the chloroplast.

The aromatic precursors of lipoquinones are supplied by the shikimate pathway which is mainly localized in chloroplasts (rather than the cytosol)[93]. Homogentisate (**95**), the precursor of tocopherols and plastoquinone (*vide supra*), is formed in the stroma of the chloroplasts from 4′-hydroxyphenylpyruvate. The enzyme involved is 4′-hydroxyphenylpyruvate dioxygenase. Part of the enzyme, however, seems to be associated with the envelope membrane facing the stroma. The prenyl side chain introduced into homogentisate (**95**) on the way to tocopherols is phytylpyrophosphate. This introduction is catalysed by homogentisate-phytylpyrophosphate prenyltransferase which is localized in the inner membrane of the envelope. Subsequent methylation steps also proceed in this membrane.

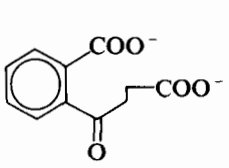
Since the inner membrane of the chloroplast is the main site of lipoquinone synthesis a transport of lipoquinones from the inner envelope membrane to the thylakoids must occur. Vesicles may be involved in such a transport.

3. *o*-Succinylbenzoate-derived quinones

o-Succinylbenzoate (OSB, **102**)-derived quinones are widely distributed in higher plants. The naphthoquinones of this group include phylloquinone (vitamin K_1, **103**), which is located in chloroplasts of green plants. Many other quinones such as prenylnaphthoquinones, lawsone (**104**) and juglone (**105**), as well as anthraquinones such as alizarin (**106**), tectoquinone (**107**) (Figure 19) and congeneric quinones contained in Rubiaceae, Bignoniaceae, Verbenaceae, etc. belong to this group of biogenetically related natural products. In microorganisms, menaquinones (vitamin K_2, **108**) are biosynthesized by the OSB pathway.

a. Pathway from shikimate to o-succinylbenzoate Details of the work in the early 1970s, which disclosed the precursorship of shikimate (**87**) and OSB (**102**) for the biosynthesis of some of these quinones, have already been reviewed by Bentley and Campbell[1]. These results are summarized as follows. It was first shown that shikimate (**87**) is the precursor of menaquinone (**108**), lawsone (**104**), juglone (**105**), etc. and that all seven carbons of shikimate (**87**) are involved in the biosynthesis of these quinones. The remaining three carbons in the naphthoquinone skeleton then proved to be derived from glutamate or 2-oxoglutarate (**109**). Therefore, the first aromatic ring was assumed to be formed by Michael-type addition of the succinylsemialdehyde thiamine pyrophosphate complex (**110**) to shikimate (**87**). The key intermediacy of OSB (**102**) was thus postulated and actually confirmed. It was also suggested that OSB (**102**) might be formed by condensation of chorismate (**111**) rather than shikimate (**87**) with **110**. Furthermore it was demonstrated that prenylation in menaquinone (**108**) biosynthesis and hydroxylation in lawsone (**104**) biosynthesis occur on an unsymmetrical intermediate. In contrast, in juglone (**105**) biosynthesis a symmetrical precursor is involved.

Until recently, it was believed that chorismate (**111**) links the shikimate pathway to OSB (**102**) because cell-free preparations of various strains of menaquinone-producing *Escherichia coli* were found to catalyse the conversion of chorismate and 2-oxoglutarate (**109**) to OSB (**102**) in the presence of thiamine pyrophosphate [94,95]. This is at variance with the observation that isochorismate (**112**) is converted to OSB (**102**) in a yield of about 90% by cell-free extracts of *E. coli* strains which are free of 2-oxoglutarate dehydrogenase[96]. (Both OSB synthase and 2-oxoglutarate dehydrogenase decarboxylate oxoglutarate in the presence of thiamine pyrophosphate, generating a carbanion which in



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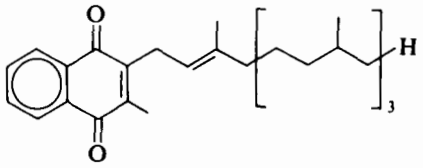

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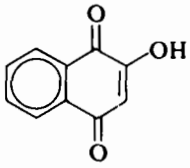

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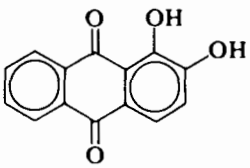

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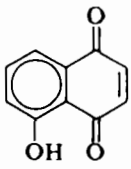

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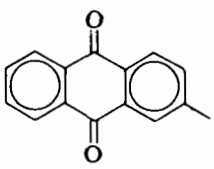

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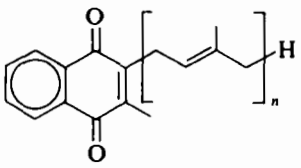


(108)

FIGURE 19

the case of the former enzyme reduces lipoic acid, whereas in the case of the latter attacks isochorismate.) Thus, it is concluded that the immediate precursor of OSB (**102**) is not chorismate, but rather isochorismate (**112**). The precursorship of **112** has also been previously suggested from a mechanistic point of view[97]. The reason for the mistaken belief that **111** was the immediate precursor of **102** could be accounted for by the fact that crude enzyme preparations which are able to convert **111** to **112** were employed. In addition the presence of a trace amount of **112** in the commercial preparations of **111** was overlooked[95].

The finding that **112** is the immediate precursor of OSB is at variance with genetic experiments[98] in which the formation of vitamin K_2 (**108**) was observed in *E. coli* mutants unable to convert **111** to **112**. Meanwhile it became evident, however, that the mutants used (*E. coli* AN 154[94,95] and *E. coli* AN 191[98]) are leaky[99].

An intermediate in the biosynthetic reaction from isochorismate (**112**) to OSB was recently detected[100]. The structure of this intermediate also strongly suggests isochorismate (**112**) as the starting material for OSB (**102**) biosynthesis. The intermediate is 2-succinyl-6-hydroxy-2,4-cyclohexadiene-1-carboxylate (**113**) (Figure 20). The structure of this intermediate shows that in the process of the conversion of **112** to **102** elimination of the pyruvate residue precedes removal of the hydroxyl function and aromatization.

Precisely speaking, the intermediacy of isochorismate (**112**) was proved only in the menaquinone biosynthesis of *E. coli*. However, it probably plays a similar role in the biosynthesis of other OSB-derived quinones.

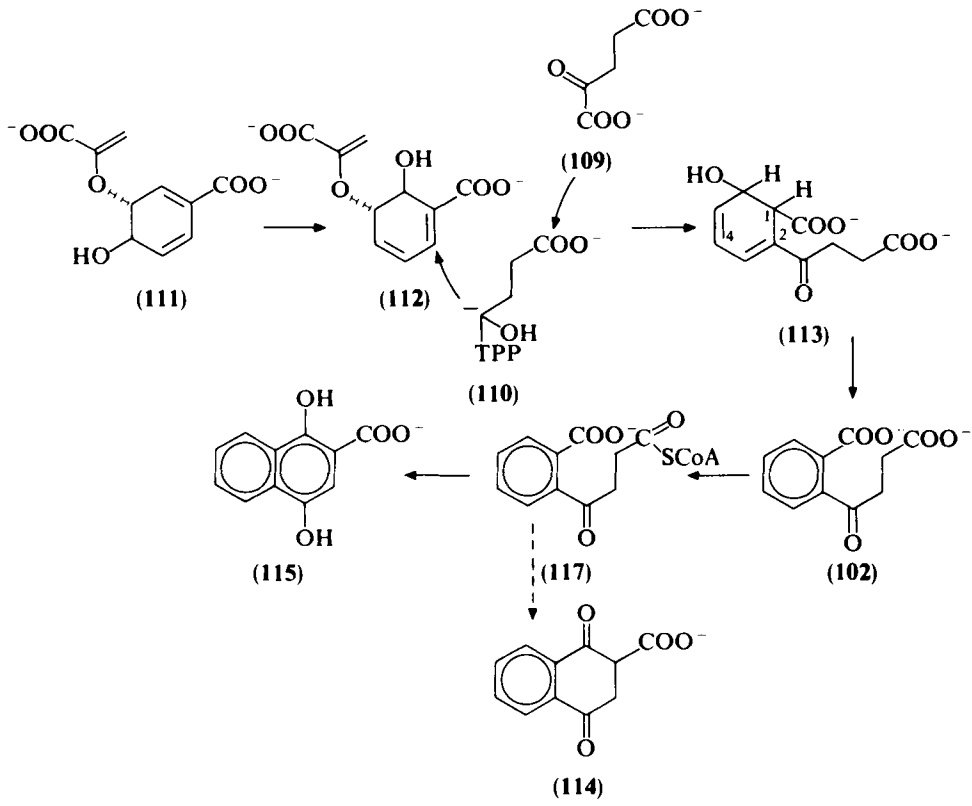


FIGURE 20

b. Formation of the naphthoquinone skeleton from o-succinylbenzoate One of the likely intermediates following OSB is 2-carboxy-4-oxotetralone (COT, **114**) formed by Dieckmann-type condensation and/or 1,4-dihydroxy-2-naphthoate (DHNA, **115**), an enol form of COT. As will be shown later, DHNA (**115**) proved to be a precursor of menaquinones (**108**) and phylloquinone (**103**). DHNA was efficiently and specifically incorporated into **108** in *E. coli* under anaerobic conditions[101]. It was also found that production of menaquinones (**108**) and demethylmenaquinones (**116**) increased by addition of **102** or **115** in some mutants of *E. coli*, while **115** accumulated after feeding **102**

to other mutants[98]. Partially purified naphthoate synthase which converts OSB (**102**) to DHNA (**115**) was obtained from cell-free extracts of *E. coli*, *Mycobacterium phlei* and *Micrococcus luteus*. This enzyme system needs ATP, CoA and Mg^{2+} as cofactors, and consists of OSB CoA synthetase which converts OSB to OSB CoA ester (**117**) and DHNA synthase which catalyses cyclization of the OSB CoA ester (**117**) to DHNA (**115**)[102-105]. Conversion of **102** to **115** proceeds through a highly labile OSB monocoenzyme A ester **117**[105] in which the 'aliphatic' rather than 'aromatic' carboxyl group of **102** is activated[106].

In addition to menaquinones (**108**), lawsone (**104**) in *Impatiens balsamina* and juglone (**105**) in *Juglans regia* were shown to be formed via DHNA (**115**) (*vide infra*). However, it is not yet known if the quinones and quinone congeners of *Catalpa ovata* are formed via the OSB CoA ester (**117**).

c. Pathway after formation of 1,4-dihydroxynaphthoate (DHNA) or 2-carboxy-4-oxo tetralone (COT) DHNA (**115**) or COT (**114**) formed from OSB (**102**) undergoes decarboxylation, hydroxylation and prenylation. Naphthoquinones and anthraquinones formed via **102** are similar in structure, but their biosynthetic pathways subsequent to DHNA or COT are different. They will be explained for each group of quinones.

Precise degradation studies of menaquinone isolated after administration of [7-^{14}C]shikimate (**87**) to *Mycobacterium phlei* revealed that the radiolabel was specifically incorporated into C(4)[107] (Figure 21). This means that prenylation occurs on the carbon next to the carbonyl group which was derived from the carboxy group of shikimate (**87**). In the cell-free extract of *E. Coli*, DHNA-octaprenyltransferase, which catalyses the conversion of DHNA (**115**) to demethyl menaquinone (**116**), was detected[108]. It is thus established that menaquinones (**108**) are formed by *ipso* attack of the prenyl group at the C(2) position of DHNA, followed by decarboxylation and methylation.

Structurally phylloquinone (**103**) differs from menaquinone (**108**) in that the polyprenyl side chain is replaced by the phytyl residue. The quinonoid chromophore of both types of compounds, however, is identical. Therefore, the biosynthetic pathway of the chromophore is likely to be identical in both cases. It was demonstrated that OSB was incorporated into phylloquinone (**103**) in maize shoots and that the mode of incorporation was the same as that demonstrated for menaquinones (**108**)[109]. Prenylation of DHNA by phytol was also found to occur in the presence of ATP in spinach chloroplasts[110].

The resulting demethylphylloquinone is eventually methylated at the thylakoid membrane with *S*-adenosylmethionine being the methyl donor. *In vitro* this reaction requires the presence of a fraction of the stroma[111].

As stated above, lawsone (**104**) is formed via an unsymmetrical intermediate, while juglone (**105**) is derived from a symmetrical intermediate. The results of feeding experiments of [1,4-^{14}C]-DHNA (**115**) to *Impatiens balsamina* showed that **104** is biosynthesized through oxidation at C(2) of DHNA (**115**) with accompanying decarboxylation[112]. It was also proved that, in *Juglans regia*, juglone (**105**) is biosynthesized via **115** and its decarboxylation product, naphthohydroquinone (**118**)[112]. It seems likely that hydroxylation of the naphthalene nucleus occurs at the stage of 1,4-naphthoquinone (**119**) or 4-oxotetralone (**120**) (a decarboxylation product of **114**)[113]. These compounds have a symmetrical structure.

Catalpa ovata (Bignoniaceae) contains four α-lapachones (**121**), catalponol (**122**) and catalpalactone (**123**). In addition callus tissue of this plant produces four dehydro-iso-α-lapachones (**124**), menaquinone-1 (**125**) (with one prenyl unit), and 1-hydroxy-2-methylanthraquinone (**126**). When [1-carboxy-^{14}C] OSB (**102**) was administered to the plant, it was incorporated into **121**, **122**, and **123**. In particular, ^{14}C was specifically incorporated into the phthalide alcohol carbon of **123** (Figure 22). Examination of the ^{3}H/^{14}C ratio in **122** isolated after administration of [1-carboxy-^{14}C, 2'-$^{3}H_2$] OSB (**102**) to the plant revealed that the two protons at the 2'-position of **102** were both retained in the 3-

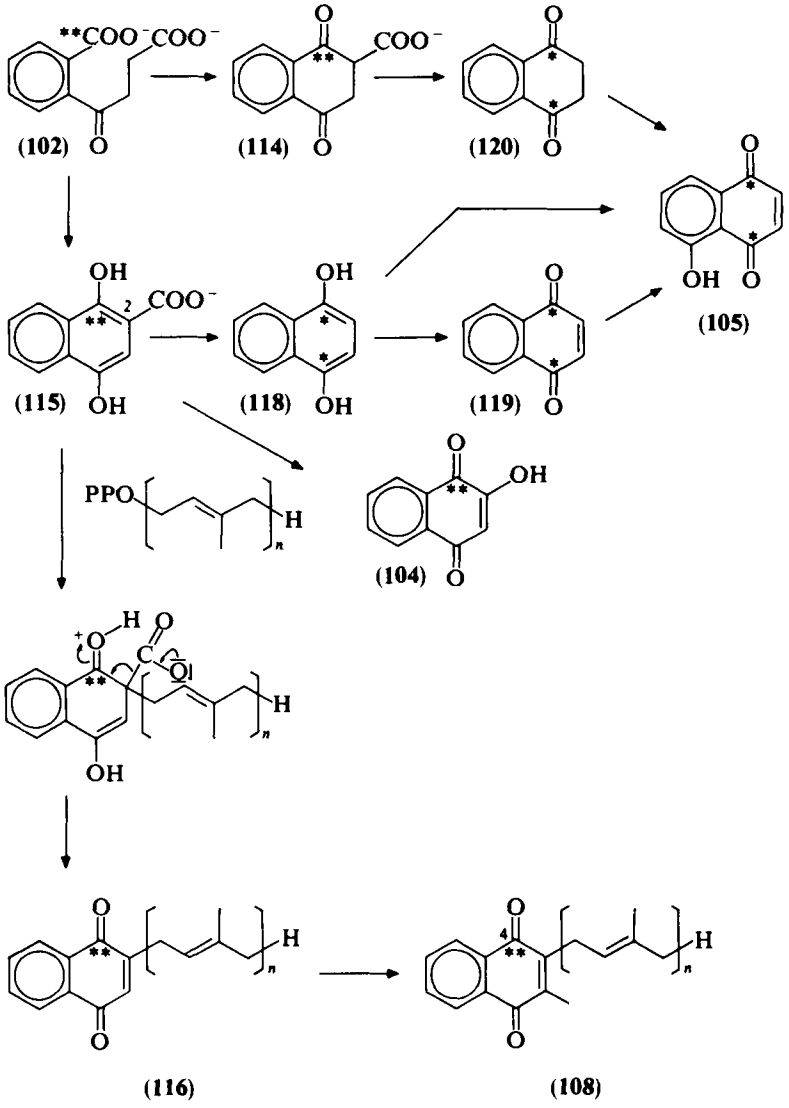


FIGURE 21

position of **122**. It is therefore concluded that, in the biosynthesis of these compounds, prenylation occurs at the same site as in microbial menaquinone (**108**) biosynthesis. Moreover, prenylation does not occur at an aromatic compound such as DHNA (**115**), but at a non-aromatic stage with COT (**114**) being a possible acceptor for the isoprene unit. Considering the structure of catalponol (**122**), it also seems possible that prenylation occurs at the state of 2-carboxy-4-hydroxy-1-tetralone (CHT) (**127**). Catalpalactone (**123**)

is biosynthesized by cleavage of the quinone ring of a prenylnaphthoquinone congener which was formed in the above-mentioned way[114-116].

The intermediacy of COT (**114**) and CHT (**127**) was supported by administration experiments in which ^{3}H-labelled **127** and its methyl ester were applied to the *Catalpa* plant. **114** and its methyl ester are likely to be too unstable to be synthetically accessible[117]. Prenyl-COT (**128**) and prenyl-CHT (**129**) were then shown to be the next intermediates[118]. They were trapped after application to the callus tissue of [1-carboxy-^{14}C]OSB (**102**). The cold extract of the plant cells were treated with diazomethane, resulting in the isolation of methylated prenyl-CHT and prenyl-COT. Incorporation of [^{14}C]OSB (**102**) into prenyl-COT (**128**) was higher when compared to prenyl-CHT (**129**). All these results demonstrated that a series of quinone congeners of *C. ovata* are biosynthesized through OSB (**102**), COT (**114**), prenyl-COT (**128**) and catalponone (**130**). The chirality of **128** and **130** was examined by dilution analyses carried out with both enantiomers of both substances. The results showed that (2*S*)-prenyl-COT (**128**) and (2*R*)-catalponone (**130**) are the intermediates. It was also found that **102** was incorporated into dehydro-iso-α-lapachones (**124**), menaquinone-1 (**125**) and 1-hydroxy-2-methylanthraquinone (**126**) in tissue cultures, indicating that these compounds are also formed by the pathway shown in Figure 22. The most important feature of this pathway is that prenylation occurs at the 2-position of COT (**114**) or CHT (**127**).

Anthraquinones are often found to coexist with naphthol derivatives such as 2,2-dimethylnaphthochromane in rubiaceous plants, suggesting that these anthraquinones are biogenetically closely related to prenylnaphthoquinones. This relationship of both groups was actually verified by the observation that shikimate (**87**), OSB (**102**) and mevalonate (MVA) were incorporated into alizarin (**106**) of *Rubia tinctorum*[119] and shikimate (**87**) and OSB (**102**) into morindone (**131**) and alizarin (**106**) of intact plants or cell suspension cultures of *Morinda citrifolia*[120]. Furthermore, specific incorporation of ^{14}C from [7-^{14}C]shikimate (**87**) into the 9-position of anthraquinone provided evidence that prenylation occurs at the position corresponding to C(3′) of OSB (**102**) in the biosynthesis of these anthraquinones[119]. These results coupled with the co-occurrence of mollugin (**132**)[121] and 2-methoxycarbonyl-3-prenyl-1,4-naphthoquinone (**133**)[122] in *Galium mollugo* (this plant belongs also to the family Rubiaceae) led to the assumption that prenylation occurs at the 3-position of DHNA (**115**) in the biosynthesis of these quinones (Figure 23).

This was recently verified by administration of [1-carboxy-^{13}C]OSB (**102**) to cell cultures of *G. mollugo*[123, 124]. Incorporation of ^{13}C into the 9-position of lucidin (**134**) at a rate of about 80% and a significant increase in the formation of a diglucoside (**135**) from 3-prenyl-DHNA (**136**) was observed. ^{13}C was incorporated into **135** at a rate of higher than 90%. Thus, it is very likely that DHNA (**115**) also is an intermediate in the biosynthesis of anthraquinones in rubiaceous plants. Prenylation, however, takes place at the 3-position of **115** during the biosynthesis of these quinones, differing from what is known about menaquinone biosynthesis.

Intact plants and cell cultures of *S. dunnii* (Gesneriaceae) are found to contain several 1,2-naphthoquinones with a reversed prenyl side chain as seen in dunnione (**137**). 1-Hydroxy-2-methylanthraquinone (**126**) and 1-hydroxy-2-(hydroxymethyl) anthraquinone (**138**) were also isolated from this tissue. Administration of [1-carboxy-^{13}C]OSB (**102**) to these cultures revealed that ^{13}C was incorporated into the 1-position of dunnione (**137**) and the 10-position of anthraquinones. Administration of OSB triggered formation of tectoquinone (**107**). These results together with those of feeding experiments in which [7-^{2}H]lawsone (**104**) and its 2-prenyl ether (**139**) were applied suggested that **137** was formed by a Claisen-type rearrangement of lawsone 2-prenyl ether (**139**) whereas anthraquinones were formed by prenylation at the 2-position of COT (**114**) or DHNA (**115**)[125, 126]. Whether **114** or **115** is the intermediate in the biosynthesis of **104** and this type of anthraquinones is still not known. However, data available to date suggest that **114**

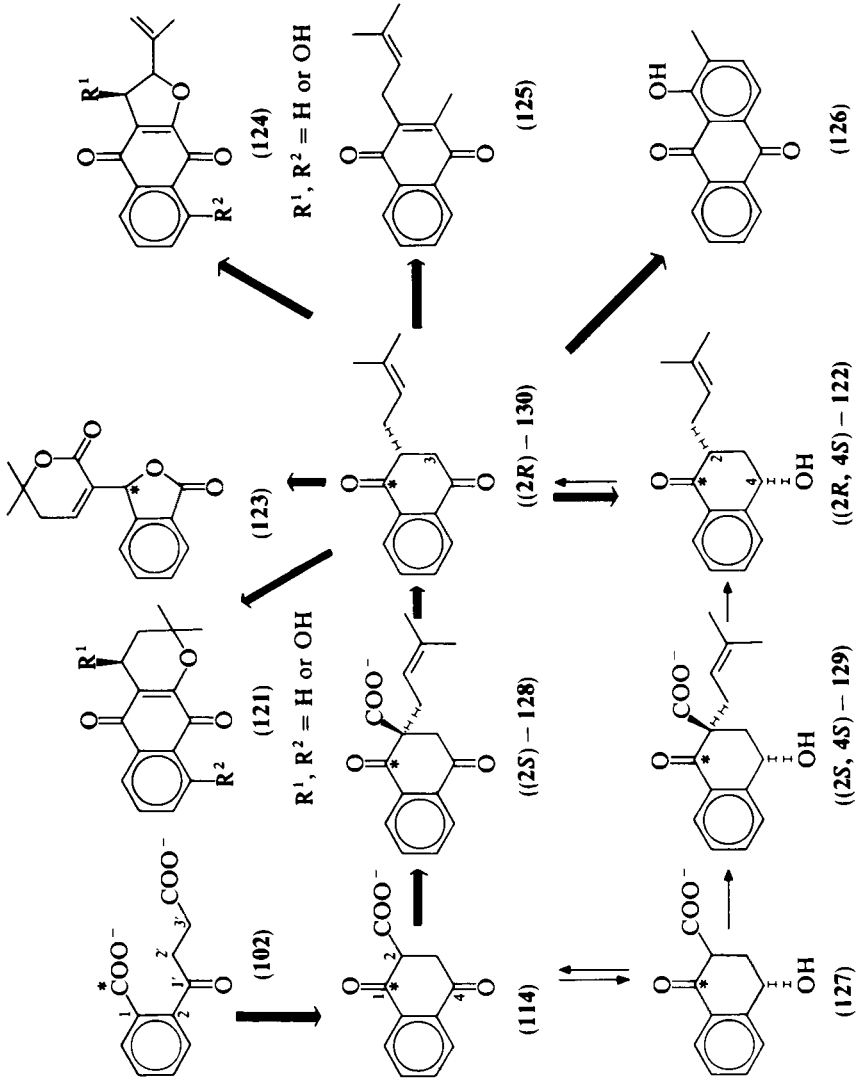

(102)
(121)
R¹, R² = H or OH
(123)
(124)
R¹, R² = H or OH
(114)
((2S) – 128)
((2R) – 130)
(125)
(127)
((2S, 4S) – 129)
((2R, 4S) – 122)
(126)

FIGURE 22

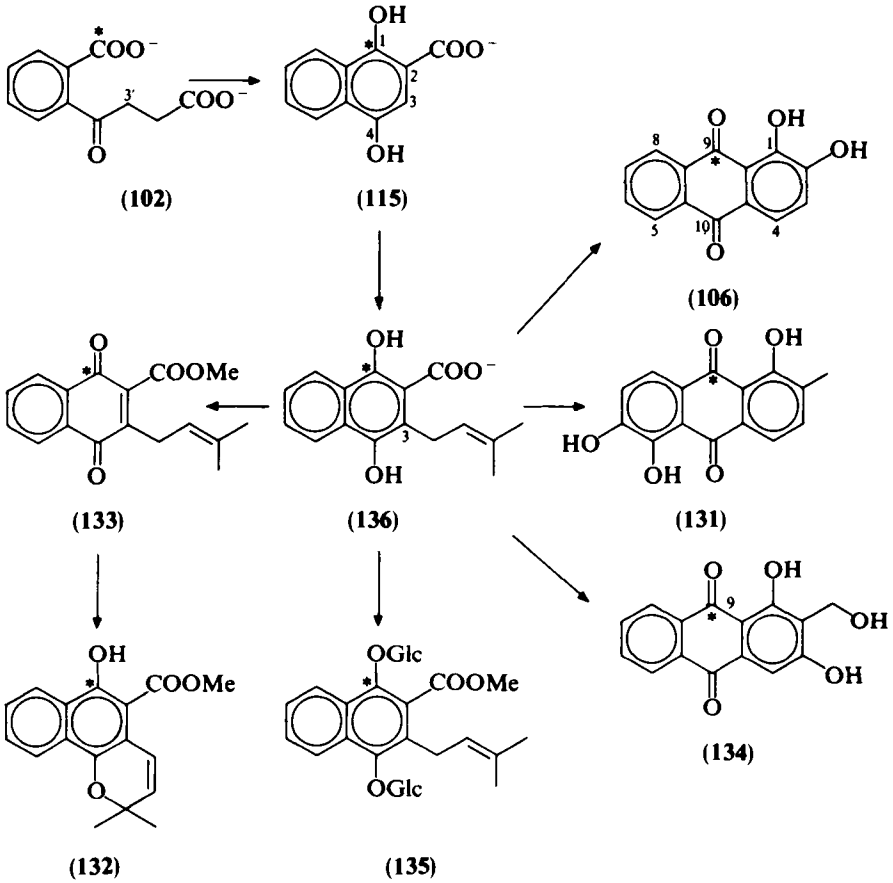


FIGURE 23

is the more likely candidate[127]. On the basis of the above results the biosynthetic pathway of quinones in *S. dunnii* is proposed as shown in Figure 24.

In spite of the fact that quinones are all formed from the same key intermediate, viz OSB (**102**), prenylation is different in the biosynthesis of menaquinones (**108**) produced by microorganisms, menaquinone-1 (**125**) produced by tissue culture of *C. ovata*, anthraquinones in rubiaceous plants or in tissue cultures of *C. ovata* as well as cell cultures of *S. dunnii*.

4. Quinones belonging to C_7N-antibiotics

Ansamycins are antibiotics with a so-called 'C_7N-ring system'. Many ansamycins are quinones. Ansamycins consist of an aromatic portion and a long aliphatic chain (*ansa* bridge) which connects non-adjacent sites of the aromatic portion. The aromatic portion is naphthalenoid or benzenoid. Quinones of the former type include rifamycins, damavaricins, streptovaricins and actamycins, while those of the latter type include geldanamycins,

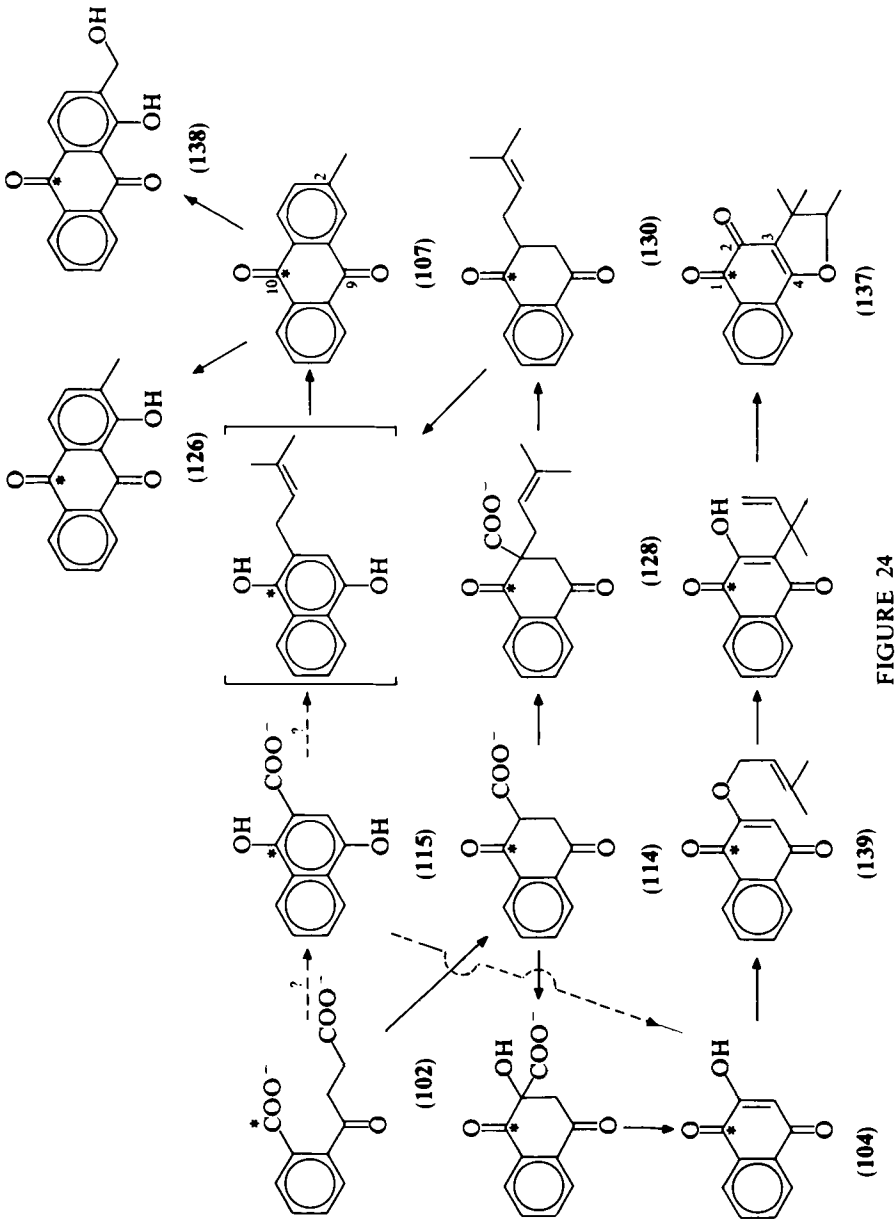


FIGURE 24

macbesin and so on. This section is mainly concerned with the biosynthesis of rifamycins including rifamycin S (**140**). Some related compounds are also mentioned.

Studies on the biosynthesis of rifamycins began with feeding ^{14}C- or ^{13}C-labelled precursors to *Nocardia mediterranei*[128-130]. The results showed that rifamycins are formed from a C_7N starter unit and a polyketide chain derived from acetate, propionate and methionine. There are various homologues of rifamycins. For example, rifamycin W (**141**)[131] produced by a mutant of *N. mediterranei*. Rifamycin W is known as an intermediate in the biosynthesis of rifamycins S (**140**) and B (**142**). C-atom 34a which originates from propionate is retained in rifamycin W (**141**), whereas it is lost in rifamycin S (**140**). Furthermore, C(12) and C(29) are directly linked together in rifamycin W (**141**), while they are separated by the introduction of an oxygen atom in rifamycin S (**140**)[132].

The C_7N-unit was presumed to be derived from an intermediate of the shikimate pathway because D-[1-^{13}C]glucose and D-[1-^{13}C]glycerate were incorporated into rifamycin[129, 133]. However, [U-^{14}C]shikimate (**87**) was not incorporated into rifamycin, and it was later found that shikimate does not permeate the cellular membrane of *N. mediterranei*[134]. Genetic experiments gave a clue as to the branch point of the C_7N-unit from the shikimate pathway. Two aromatic amino acid-deficient mutants of *N. mediterranei* were isolated and characterized. Of these two, the mutant strain A8 which was auxotrophic for aromatic amino acids was free from transketolase activity and produced much less rifamycin than the parent[135]. The other mutant strain A10 was devoid of shikimate kinase activity, but produced rifamycin[136]. 3-Deoxy-D-arabino-heptulosonic acid-7P(DAHP, **143**) cannot be formed without transketolase activity and products subsequent to shikimate-3P are formed without shikimate kinase. Therefore, the precursor of the C_7N-unit was assumed to be a compound of the shikimate pathway derived from metabolites between DAHP (**143**) and shikimate (**87**).

From this information and the structural features of ansamycins and their congeners such as maytansinoids it was assumed that the C_7N-unit would be 3-amino-5-hydroxybenzoate (AHBA) (**144**). This assumption was verified by the fact that AHBA (**144**) was incorporated into actamycin (**145**), an ansamycin produced by *Streptomyces* sp. E/784[137]. About at the same time additional evidence was obtained indicating that the C_7N-unit of rifamycins is actually AHBA (**144**). A number of mutants of *N. mediterranei* were found to accumulate a very early precursor of rifamycins, viz. product P8/1-OG (**146**) which consisted of **144** and the first propionate–acetate–propionate units of the *ansa* chain[138]. The isolation of this compound indicates that the starter for the biosynthesis of rifamycins certainly is 3-amino-5-hydroxybenzoyl CoA. Supplementation with AHBA (**144**) of the culture of the above-mentioned mutant A8 lacking transketolase activity strongly stimulated rifamycin production[139].

Supplementation of the culture of the mutant A8 with several 4-substituted AHBA derivatives demonstrated, however, that they were not able to substitute for the C_7N-unit, suggesting that C(3) substitutents are introduced in a later biosynthetic step leading to 3-substituted rifamycins[140]. The same results were also obtained in similar experiments using actamycin producing *Streptomyces* species[141]. The nitrogen function of **144** is derived from the amide nitrogen of glutamine[142].

The next problem to be solved was the mutual relationship among rifamycins. Protorifamycin I (**147**)[138] isolated from a mutant strain F1/24 of *N. mediterranei* is the earliest so far known precursor in the rifamycin group, while protostreptovaricin I (**148**)[143] isolated from *S. spectabilis* is the earliest occurring in the damavaricin and streptovaricin biosynthesis.

Two common hypothetical precursors, proansamycins A (**149**) and B (**150**), have been proposed for these compounds[144]. From proansamycin B (**150**) protorifamycin I (**147**) would be formed by oxidation at C(34a) while protostreptovaricin I (**148**) by methylation at C(3). From proansamycin A (**149**) protorifamycin I (**147**) and protostreptovaricin I

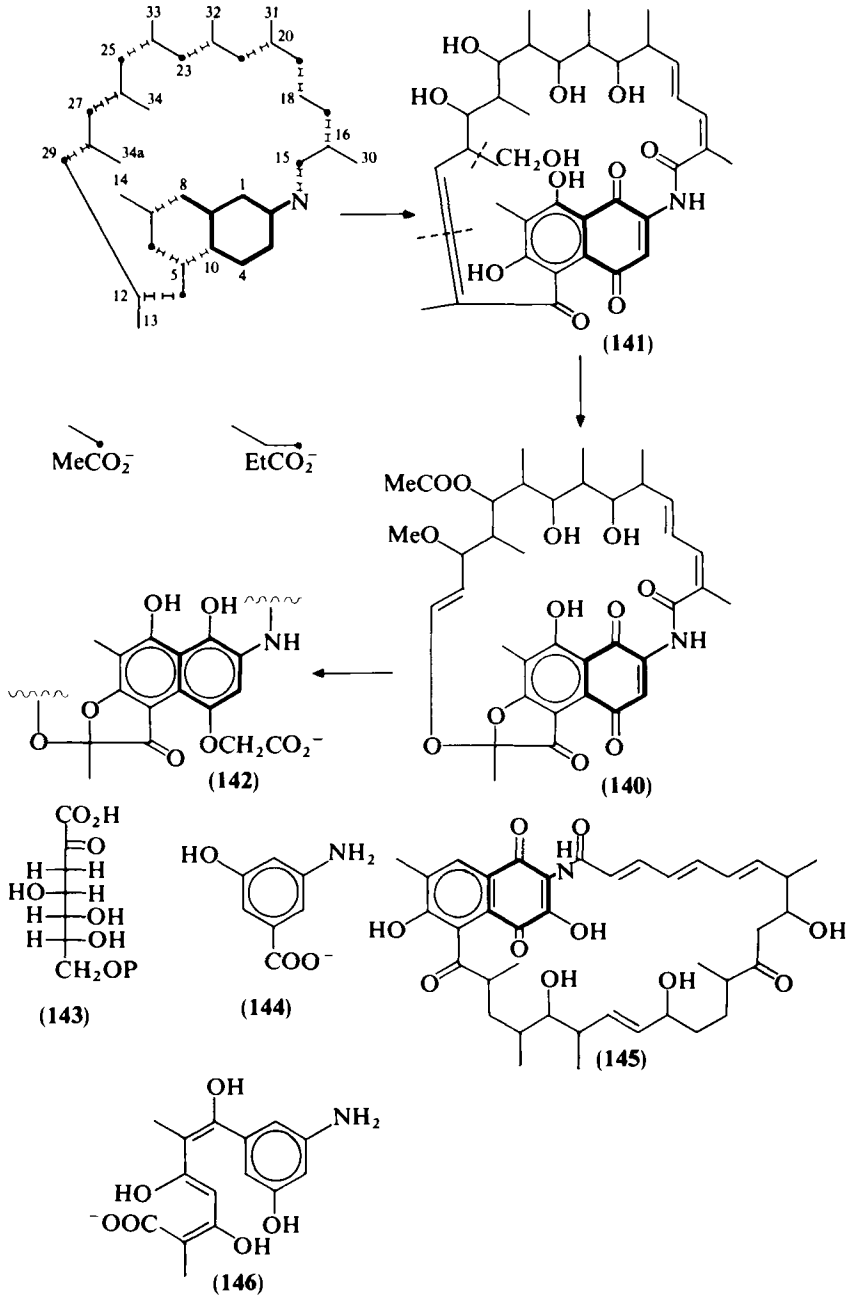


FIGURE 25

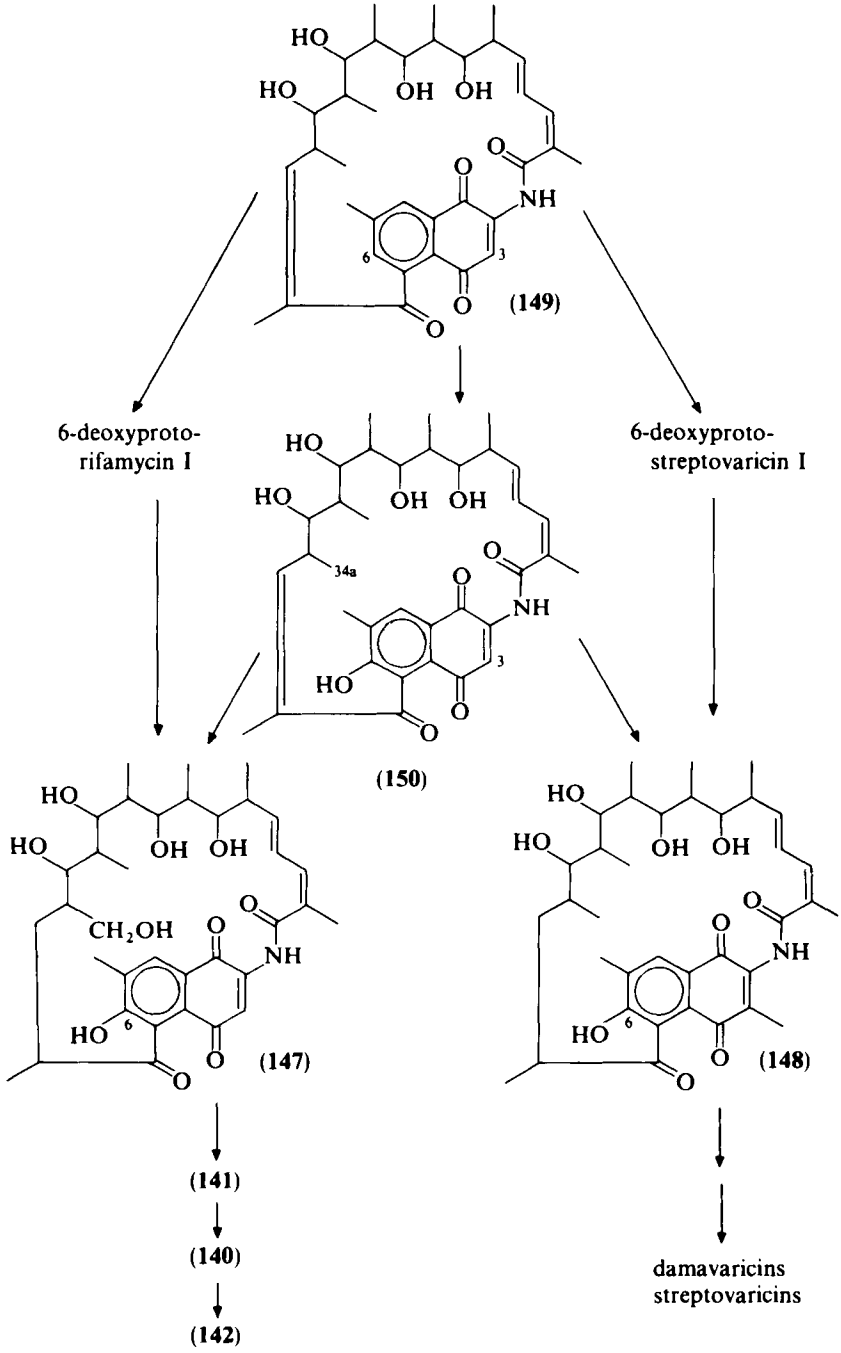
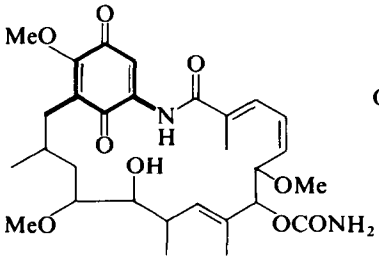

HO
HO
OH
OH
O
NH
6
3
O
O
(149)
6-deoxyproto-
rifamycin I
6-deoxyproto-
streptovaricin I
34a
HO
(150)
CH2OH
(147)
(148)
(141)
(140)
(142)
damavaricins
streptovaricins

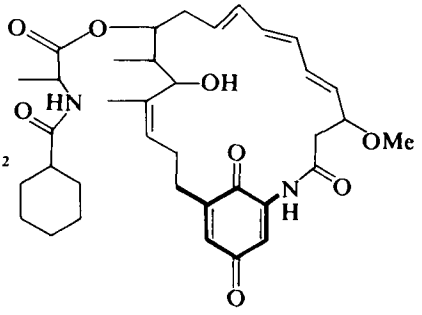
FIGURE 26

(**148**) would be formed by two different steps. At present, it is not known which of these hypothetical proansamycins is more likely to be the common precursor for the above ansamycins. **147** gives rifamycin S (**140**) via rifamycin W (**141**), while **148** is converted to streptovaricins and damavaricins. Rifamycin S (**140**) is, on the other hand, the key intermediate for several other rifamycins (A, B, C, D, E and some others)[145].

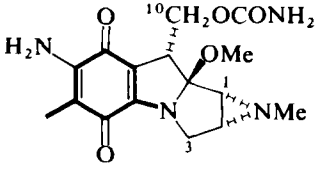
The ansa chain in benzoquinone-type ansamycins such as geldanamycin (**151**)[146-148] and mycotrienin I (**152**)[149] also proved to be formed from acetate (or glycerate/glycolate in geldanamycin) and propionate units. The incorporation pattern of [^{13}C]glucose in the benzoquinone portion of geldanamycin (**151**) was in accordance with the presumed precursorship of AHBA (**144**)[150]. AHBA is also shown to be involved in the biosynthesis of profiromycin (**153**), a mitomycin antibiotic[151]. Regarding the biosynthesis of mitomycin, it was found that the chain of six carbons from C(3) to C(10) and the attached aziridine nitrogen are derived from D-glucosamine[152-155] and the carbamate function from L-citrulline[154,155].



(**151**)



(**152**)



(**153**)

FIGURE 27

5. *Others*

a. Streptonigrin This quinone is a very potent anticancer antibiotic produced by *Streptomyces flocculus*. The 4-phenylpicolinate portion proved to be derived from tryptophan (**154**)[156]. NMR spectra of streptonigrin (**155**) which was isolated after feeding synthetic [2-^{13}C, ^{15}Nb]tryptophan (**154**) to *S. flocculus* showed a coupling of ^{13}C–^{15}N, suggesting that an unprecedented cleavage occurred in the hetero ring of tryptophan[157]. The tryptophan-derived portion underwent hydroxylation and methylation during the biosynthetic process. In spite of various feeding experiments, the origin of the quinoline quinone portion remained at first unknown. However, NMR studies of [U-$^{13}C_6$]-D-glucose (**156**)-enriched streptonigrin (**155**) revealed that D-glucose was incorporated into

the quinone by the mode shown in Figure 28. This fact strongly suggests that the intermediate would be 4-aminoanthranilic acid (**157**) derived from shikimic acid[158]. Glucose was also incorporated into the phenylpicolinic acid portion. It was used as the internal standard in the NMR analysis because the biosynthetic pathway of tryptophan and its mode of incorporation into streptonigrin (**155**) were already known.

4-Aminoanthranilic acid (**157**) also seems to play an intermediary role in the biosynthesis of some antibiotics such as nybomycin (**158**)[159] and lavendamycin (**159**)[160]. The structure of the latter compound is particularly suggestive of the biosynthesis of streptonigrin (**155**). Streptonigrin would be biosynthesized by cleavage of the hetero ring of an intermediate which has a β-carboline structure like **159**.

b. Bis-indolylbenzoquinones Cochlidinol (**160**)[161], isocochlidinol (**161**) and neocochlidinol (**162**)[162] produced by *Chaetomium* spp., asterriquinone (**163**)[163], produced by *Aspergillus terreus*, and hinuliquinone (**164**)[164, 165], elaborated by *Nodulisporium hinuleum*, are bis-indolyl-2,5-dihydroxybenzoquinones prenylated at different positions (Figure 29). The biogenesis of these compounds is explained by the self-condensation of two indolylpyruvic acid (**165**) molecules which are formed by transamination of tryptophan in the same way as in the formation of bis-phenyl-benzoquinones from two phenylpyruvic acid molecules and subsequent prenylation. This interpretation was supported by feeding tryptophan and mevalonic acid to some fungi[161, 163–166].

c. Naphthyridinomycin Naphthyridinomycin (**166**) is an antibiotic which is a metabolite of *Streptomyces lusitanus*. Feeding experiments of labelled precursors demonstrated that its carbon skeleton is derived from the three amino acids tyrosine (**167**), serine (**168**) and ornithine (**169**)[167–169] (Figure 29). Three methyl groups were shown to be derived from methionine and the nitrogen atom from the amino acids mentioned above. However, the origin of C(9) and C(9′) is still unknown.

C. Pure Isoprenoid Quinones

In addition to the quinones described in the preceding section, there are many other quinones with complete isoprenoid carbon skeleton, particularly among the diterpenoids. However, there have been virtually no administration experiments on these quinones in the last decade. The natural products chemistry of this type of quinones has been treated by Eugster[170]. Hibiscoquinone A (**170**) is given in Figure 30 as an example of this type of quinone. The structural relationship between **170** and a related diterpenoid phenol, viz. gossypol (**171**), is obvious. Feeding experiments carried out on roots of *Gossypium herbaceum* showed that mevalonic acid is incorporated into gossypol (**171**) with a folding mechanism as shown in Figure 30[171] and as is known from sesquiterpenes of the cadalane type. The cation of the ten-membered ring system undergoes a 1,3-hydride shift. It is safe to assume that hibiscoquinone A (**170**) is derived in a very similar way.

III. METABOLISM OF QUINONES

A. Naphthoquinones

Today it is very well accepted that natural products are no metabolic end products but subject to a turnover[172]. This turnover is also experienced in lipids[173] of chloroplasts including lipoquinones[174]. A photoautotrophic cell culture of *Morinda lucida* has been described recently in which the degradation of lipoquinones can be induced when the cell

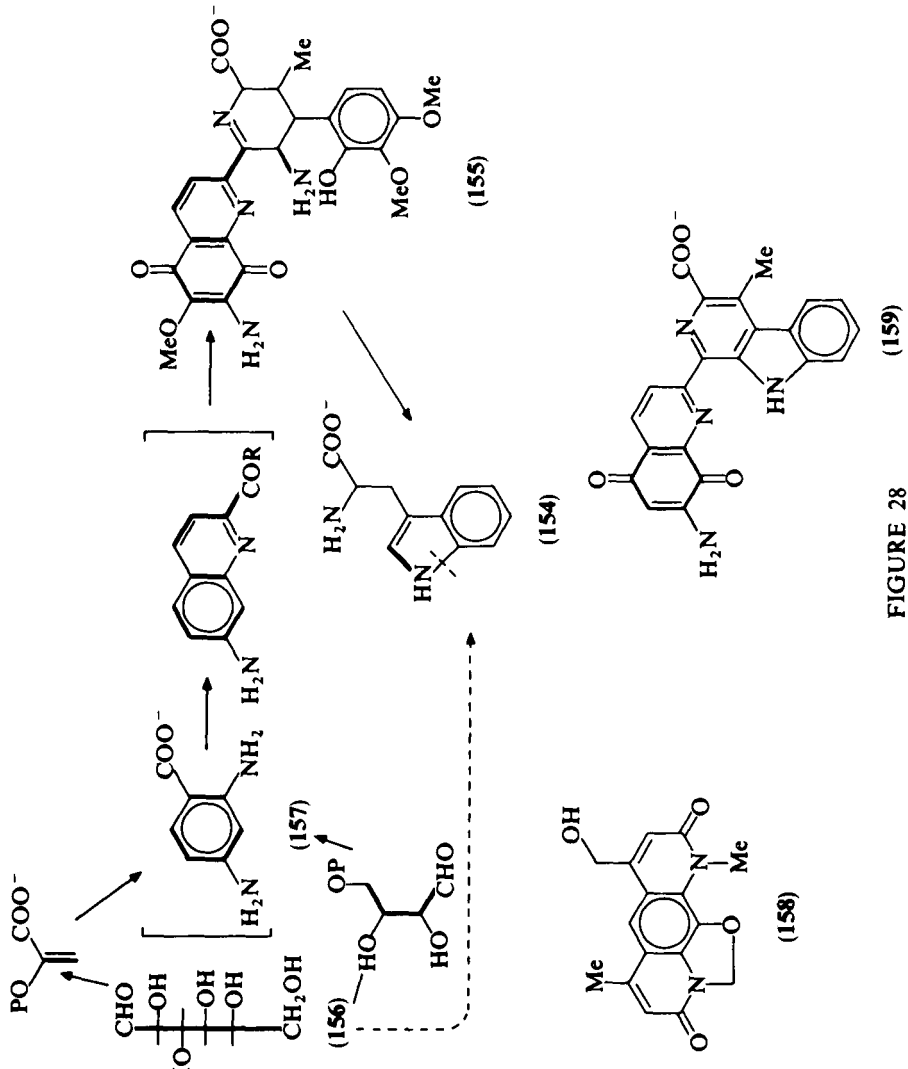


FIGURE 28

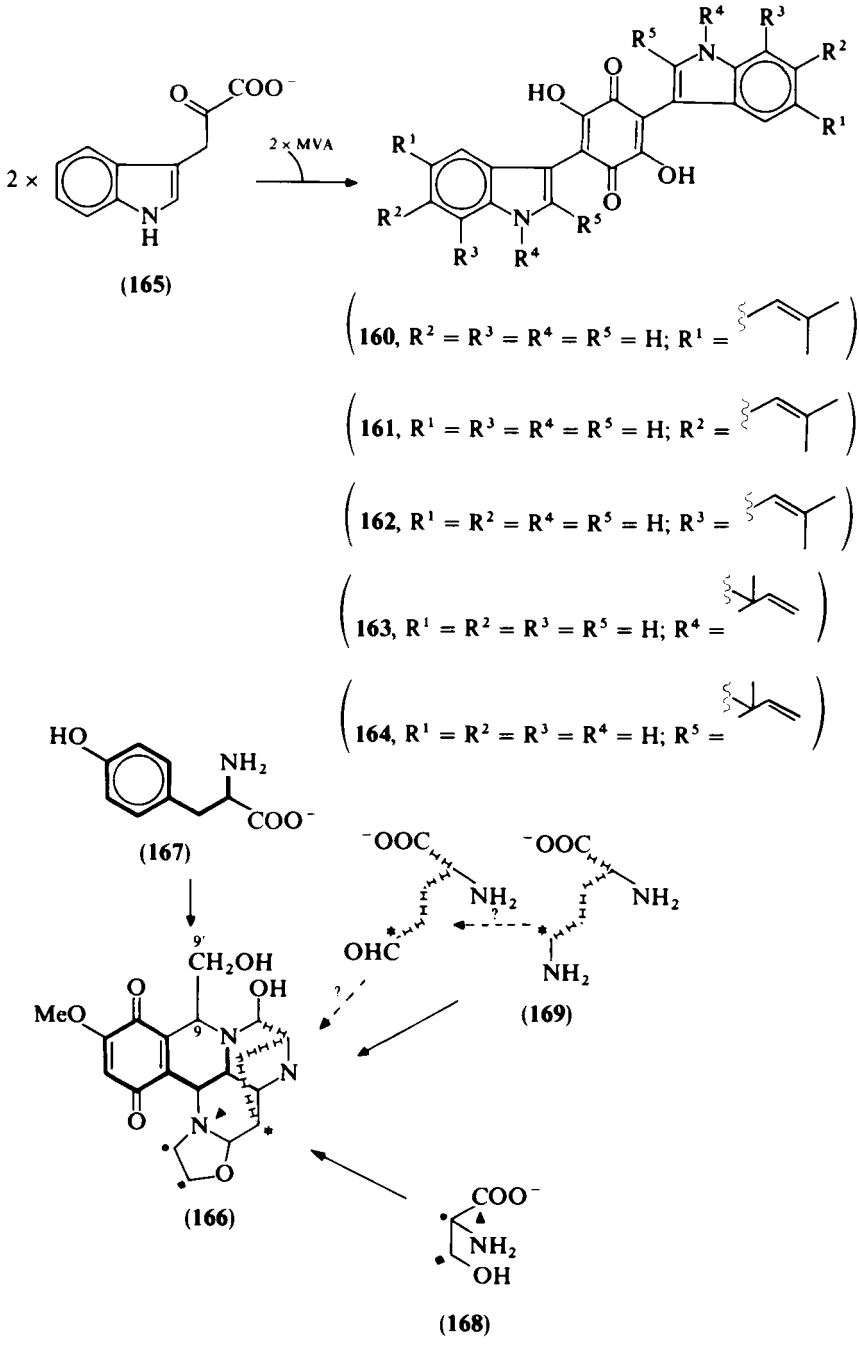

2 ×
2 × MVA
(165)
(160, R² = R³ = R⁴ = R⁵ = H; R¹ =
(161, R¹ = R³ = R⁴ = R⁵ = H; R² =
(162, R¹ = R² = R⁴ = R⁵ = H; R³ =
(163, R¹ = R² = R³ = R⁵ = H; R⁴ =
(164, R¹ = R² = R³ = R⁴ = H; R⁵ =
(167)
(169)
(166)
(168)

FIGURE 29

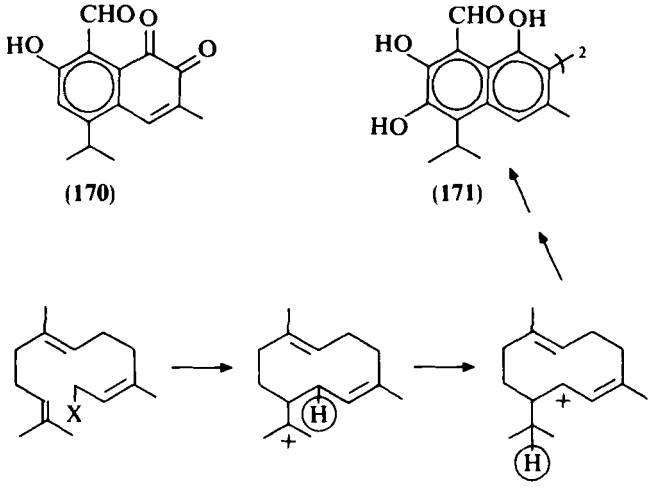
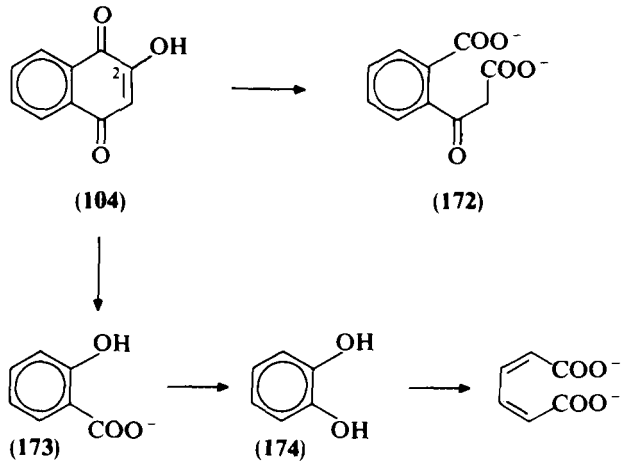


FIGURE 30

culture is transferred to heterotrophic culture conditions[175]. Addition to the photoautotrophic culture of sucrose and cultivation in darkness results in concomitant degradation of chlorophyll and lipoquinones.

A typical secondary plant product, viz. lawsone (**104**), seems to be degraded in *Impatiens balsamina* to 3-(2'-carboxyphenyl)-3-oxopropionate (**172**) by ring fission of the 1,2-bond in the hydroxylated quinone[176].

Degradation of **104** was also observed in a bacterial culture isolated from soil[177]. The bacterium which was identified as a *Pseudomonas putida* strain grows on **104** as the only carbon and energy source. It is unknown whether this bacterium utilizes the same ring fission assumed to occur in *Impatiens balsamina*[176] because only late metabolites in the degradation pathway such as salicylate (**173**) and catechol (**174**) were detectable. This *Pseudomonas* strain is also capable of degrading other naphthoquinones including juglone (**105**). Another *Pseudomonas putida* strain was isolated from garden soil[178]. It grows slowly



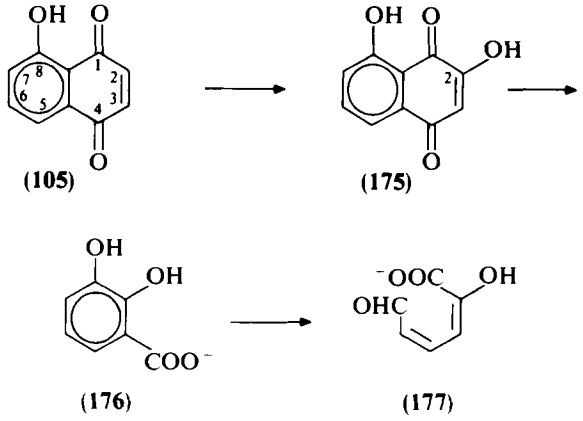


FIGURE 31

in the presence of **105** alone but growth is rapid in the presence of **105** and glucose. Degradation of juglone (**105**) in this strain proceeds via 2-hydroxyjuglone (**175**), 2,3-dihydroxybenzoate (**176**) and 2-hydroxymuconate semialdehyde (**177**) as depicted in Figure 31. It is unclear whether ring fission occurs between C atoms 1 and 2 or 2 and 3. The former mechanism would correspond to the assumed degradation of lawsone (**104**) in *Impatiens balsamina*[176] whereas the latter would correspond to what is known from degradation of lapachol (**178**) and dichloroallyllawsone by *Penicillium notatum* and other microorganisms, where the intermediacy of an epoxide (**179**) and ring fission between C atoms 2 and 3 in a monooxygenase reaction was postulated[179].

This epoxide (**179**) is assumed to be converted to the ketol **180** shown in Figure 32. Metabolism of lapachol (**178**) has also been observed in *Beauveria sulfurescens* and *Streptomyces albus*[180].

These organisms oxidize the prenyl side chain of lapachol (**178**) with excellent yield, a reaction which is not readily achieved chemically. The metabolites isolated are lomatiol (**181**), lomatate (**182**) and the acetate (**183**) of lomatiol. The side chain in these metabolites exhibits *E*-stereochemistry.

B. Anthraquinones

Anthraquinones may be stable in certain biological systems such as *Morinda citrifolia*[181] or *Galium mollugo*[182] cell cultures where they are deposited in the vacuole. In other biological systems, such as plants[183] or microorganisms (*vide infra*), however, they may be degraded.

1. Secoanthraquinones

Fungal metabolites, such as tajixanthone (**184**), ravenelin (**185**), secalonic acids, sulochrin (**186**) and geodin (**187**) belong to secoanthraquinones which are formed by oxidative cleavage of octaketide anthraquinones or anthrones. They are divided into two groups according to the site of cleavage of the central ring. One group is represented by tajixanthone (**184**), ravenelin (**185**), secalonic acids, etc., and the other group by sulochrin (**186**), geodin (**187**), etc. The ring fission is supposed to proceed by a Baeyer–Villiger-type oxidation of an anthraquinone[184] or by cleavage of a hydroperoxide derived from an anthrone or anthranol[185, 186].

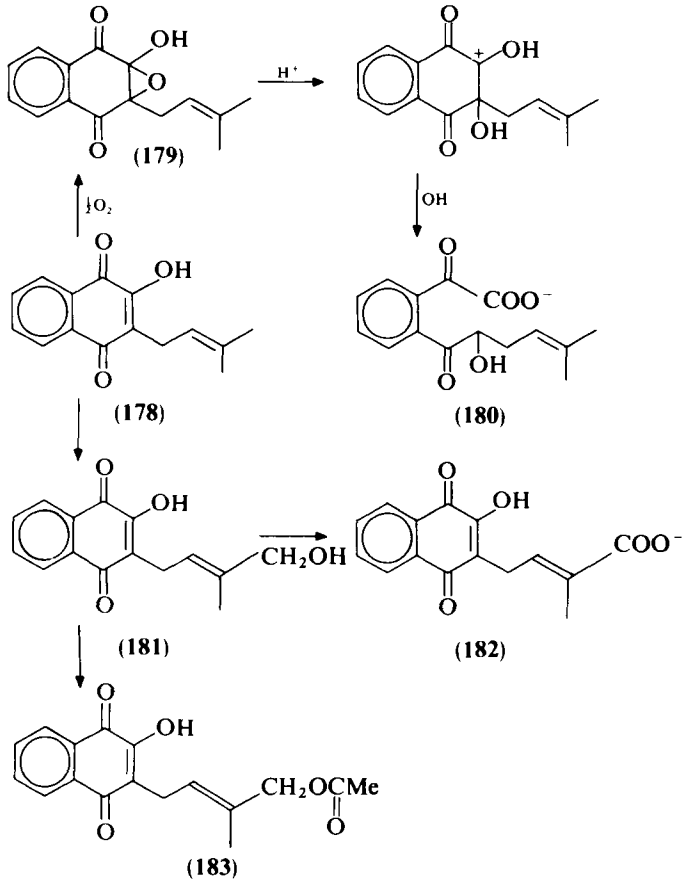


FIGURE 32

The former mechanism seems to be involved in the ring fission of questin (**188**), an anthraquinone that is derived from emodin (**35**) by methylation[187]. The benzophenone sulochrin (**186**) formed in turn from questin (**188**) undergoes methylation and chlorination to give dihydrogeodin (**189**) (Figure 33). The latter compound is subject to an intramolecular phenol coupling reaction yielding (+)-geodin (**187**)[188]. The phenol oxidase (dihydrogeodin oxidase) involved in this reaction was purified to homogeneity. It is a blue copper protein with a molecular weight of 153 000 consisting of two subunits. Phenol coupling reactions have been postulated many times but this work[188] represents the first example in which an enzyme catalysing a phenol oxidative coupling in natural product biosynthesis has been purified and characterized.

It has been reported that secalonic acid D (**190**) (Figure 34) incorporates anthrone at a rate 4.5 times higher than anthraquinone in *Penicillium oxalicum*[189]. However, there is other evidence suggesting that anthraquinone might be a precursor of tajixanthone (**184**) (*vide infra*). The mechanism of ring cleavage is still open for discussion.

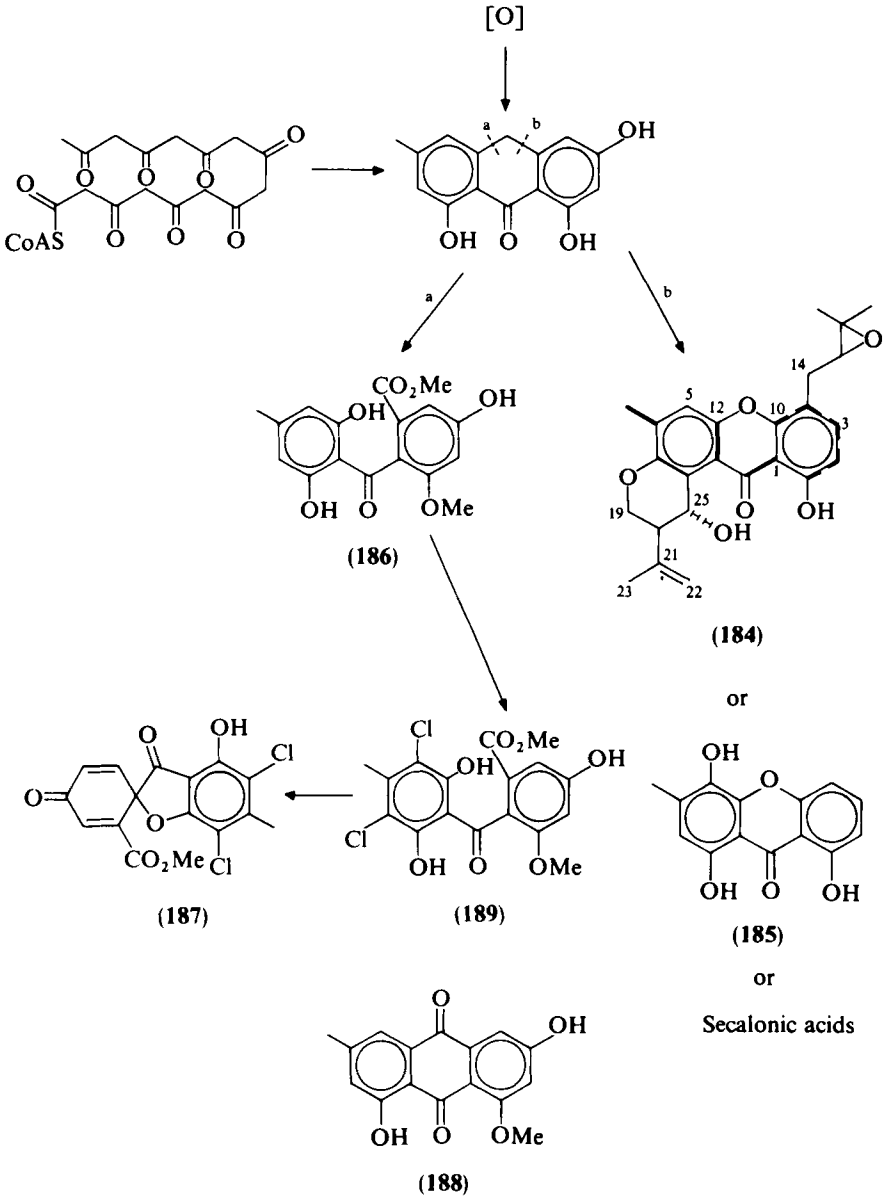


FIGURE 33

Tajixanthone (**184**) is a prenylated xanthone produced by *Aspergillus variecolor* as are shamixanthone (**191**) (Figure 35) and many other structurally related minor metabolites[190-192]. The following information on the biosynthetic processes was obtained by feeding experiments in which [^{13}C]acetates and [$^{2}H_3$]acetate[193, 194] were employed. The

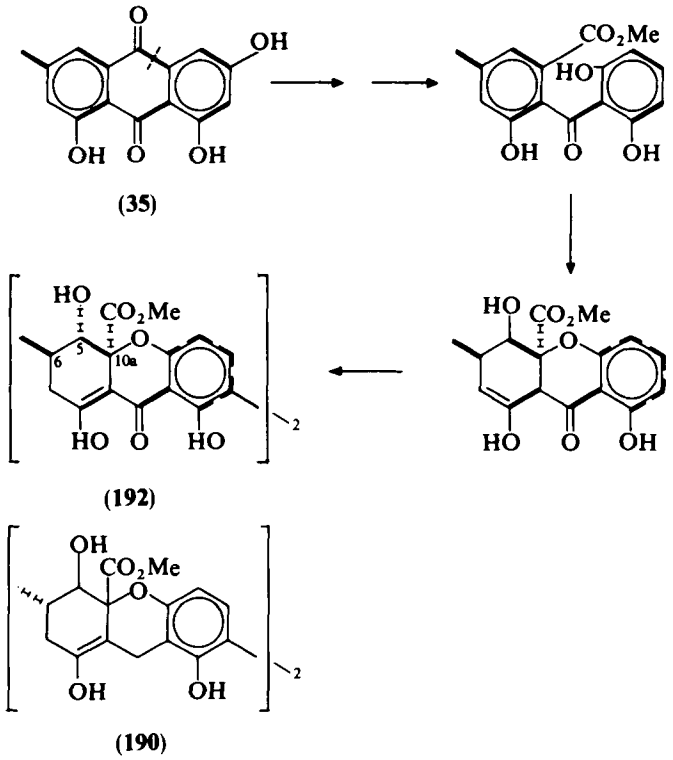


FIGURE 34

acetate assembly pattern was consistent with that of islandicin (**36**) and other similar compounds, but scrambling of ^{13}C–^{13}C coupling was observed in the C ring. This means that cycloaddition occurred prior to C-prenylation at two *ortho* positions of the symmetrical C ring of benzophenone which resulted from cleavage of the central ring. On the other hand, the sterospecificity of the dihydropyran ring indicates that this ring was formed by a concerted ene reaction at the *o*-prenylaldehyde portion, i.e. dihydropyran formation preceded cyclodehydration to the xanthone ring. If xanthone formation preceded, this reaction should be hindered by highly unfavourable interaction between the xanthone carbonyl and aldehyde groups. As mentioned before, the absence of the acetate-derived ^{2}H on the 25-position suggests that the ring was split at the stage of the anthraquinone, rather than an anthrone. Finally, non-retention of ^{2}H on C(5) suggests that decarboxylation occurred after cyclization and aromatization of the octaketide chain.

The acetate assembly pattern of ravenelin (**185**), elaborated by *Helminthosporium ravenelii* was consistent with that of tajixanthone (**184**). The central ring of islandicin (**36**), chrysophanol (**43**) or the corresponding anthrones is cleaved, followed by randomization in the C ring, and then cycloaddition[195, 196]. In **185** enriched by [1-^{13}C, $^{18}O_2$]acetate an ^{18}O-isotope shift was observed at C(1), C(8), C(9) and C(10a), but not at C(4a). This means that the ring-closure occurred by the nucleophilic attack of the hydroxy group of ring C on the *ortho* position of the ring A[197]. The substituent of the ring A, which should be eliminated, need not be hydroxyl. However, the benzophenone shown in Figure 35 is also a

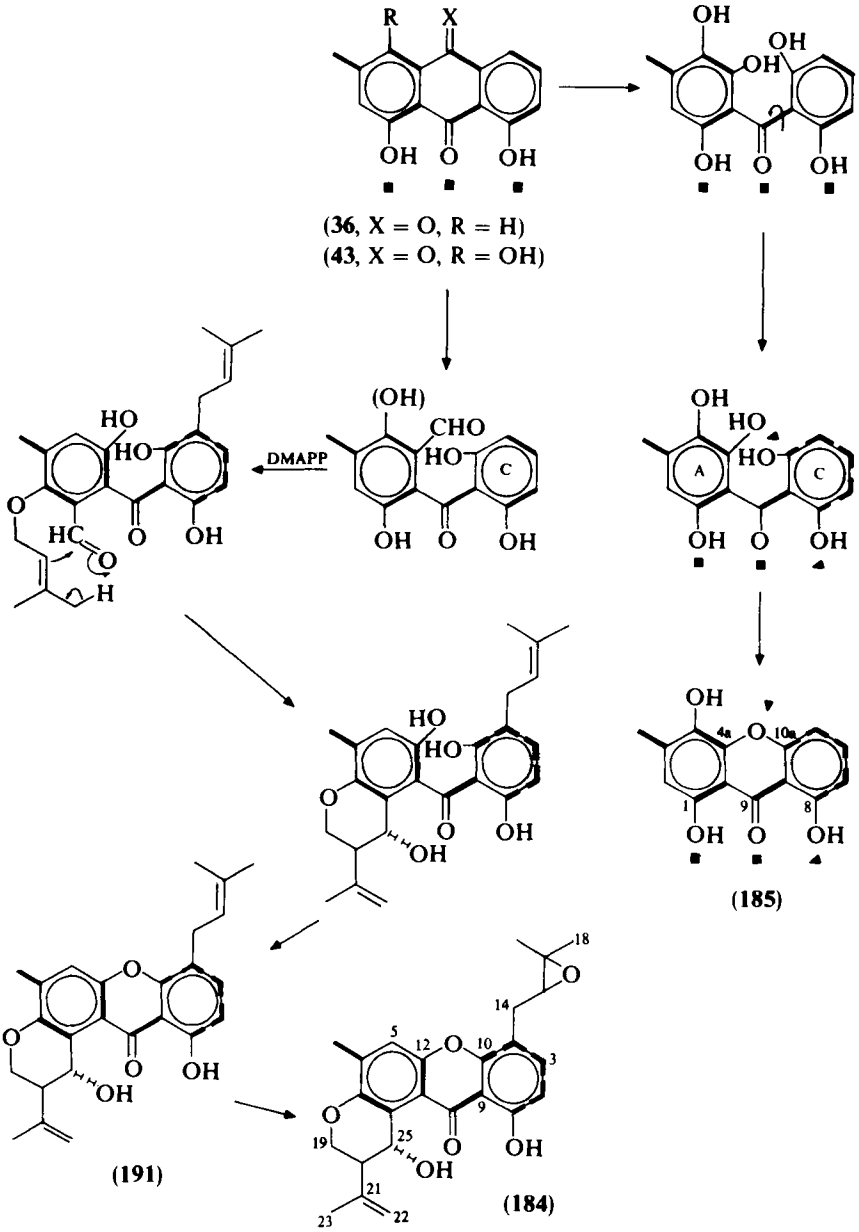


FIGURE 35

chemically reasonable hypothetical intermediate. There is still no direct evidence that islandicin (**36**) or chrysophanol (**43**) is the genuine precursor of ravenelin (**185**), but trace amounts of both substances are contained in *H. ravenelii*.

Besides the above-mentioned experiments on secalonic acid D (**190**)[189], the biosynthesis of other secalonic acids was studied by feeding [$^{13}C_2$]acetate to *Pyrenochaeta terrestris*. Secalonic acid A (**192**) (Figure 34) is shown to be biosynthesized through cycloaddition of benzophenone, the ring cleavage product of emodin (**35**) or emodinanthrone (**50**), to tetrahydroxanthone under randomization of ^{13}C–^{13}C coupling in the ring and the subsequent dimerization of the resulting tetrahydroxanthone[198]. Monomeric tetrahydroxanthone has stereoisomers due to the configuration at positions 5, 6 and 10a. The dimerization of these stereoisomers in various combinations results in formation of various secalonic acids[199].

2. *Aflatoxins and congeners*

Aflatoxins represented by aflatoxin B_1 (**193**) are carcinogenic mycotoxins produced by some species of *Aspergillus* such as *A. flavus* and *A. parasiticus*. They themselves are not quinones, but coumarin derivatives, which are biosynthesized from a polyketide chain via various intermediates including several anthraquinones. These intermediates and their congeners are also produced by *A. versicolor* and other *Aspergillus* species. This group of substances has been one of the targets for very intensive studies during the last decade.

Studies on the biosynthesis of metabolites in the aflatoxin series began with feeding labelled acetates. Incorporation into the whole carbon skeleton of aflatoxin and an intermediate, sterigmatocystin (**194**) was demonstrated[200–202]. These studies were followed by feeding norsolorinic acid (**195**)[203], averufin (**196**)[204], versiconal acetate (**197**)[205], versicolorin A (**198**)[206] and sterigmatocystin (**194**)[207] to *A. parasiticus* and its mutants. Recently averantin (**199**) feeding was also carried out[208]. The observed significant incorporation of the fed susbstances into aflatoxin B_1 (**193**) suggested their likely precursorship.

For the construction of the carbon skeleton of these molecules two modes (a) and (b) of the acetate folding pattern were conceivable. All the demonstrated labelling pattern of averufin (**196**)[209–211], versiconal acetate (**197**)[212–214], versicolorin A (**198**)[215], sterigmatocystin (**194**)[216] and aflaxtoxin B_1 (**193**)[217] enriched by [^{13}C]acetates were consistent with mode (a) (Figure 36).

Very recently the side chain of these compounds proved to be formed from a starter hexanoate (**200**)[218, 219], i.e. when [1-^{13}C]hexanoate (**200**) was fed to an averufin (**196**)-accumulating mutant of *A. parasiticus*, the spectrum of isolated averufin (**196**) showed only the resonance of C(1′) to be strongly enhanced. Although the secondary incorporation of [1-^{13}C]acetate, which resulted from degradation of the original hexanoate, was also observed, resonances other than that of C(1′) were much weaker. Comparative studies using [1-^{13}C]butyrate, [1-^{13}C]-5-oxohexanoate, and [1-^{13}C]-3-oxooctanoate also showed only secondary incorporation.

The pivotal precursor in the biosynthesis of aflatoxins is averufin (**196**) which is formed from norsolorinic acid (**195**) via averantin (**199**). The biosynthetic relationship of averufin (**196**) and some subsequent intermediates were suggested by experiments using two mutants of *A. parasiticus*, deficient in aflatoxin production[220]. One accumulated averufin and the other versicolorin A (**198**). The averufin-accumulating mutant converted ^{14}C-labelled versiconal acetate (**197**), versicolorin A (**198**) and sterigmatocystin (**194**) to aflatoxin B_1 (**193**). In the presence of dichlorovos (dimethyl-2,2-dichlorovinyl phosphate), an inhibitor of aflatoxin biosynthesis, versicolorin A (**198**) and sterigmatocystin (**194**) were converted into aflatoxin by this mutant unaffectedly, but the conversion of versiconal acetate (**197**) into versicolorin A (**198**) was noticeably impeded. In contrast, the versicolorin A-accumulating mutant converted ^{14}C-labelled acetate, averufin (**196**) and versiconal acetate (**197**) up to versicolorin A (**198**) but in the presence of dichlorovos the conversion was impaired at the step of versiconal acetate. The intermediacy of averufin in

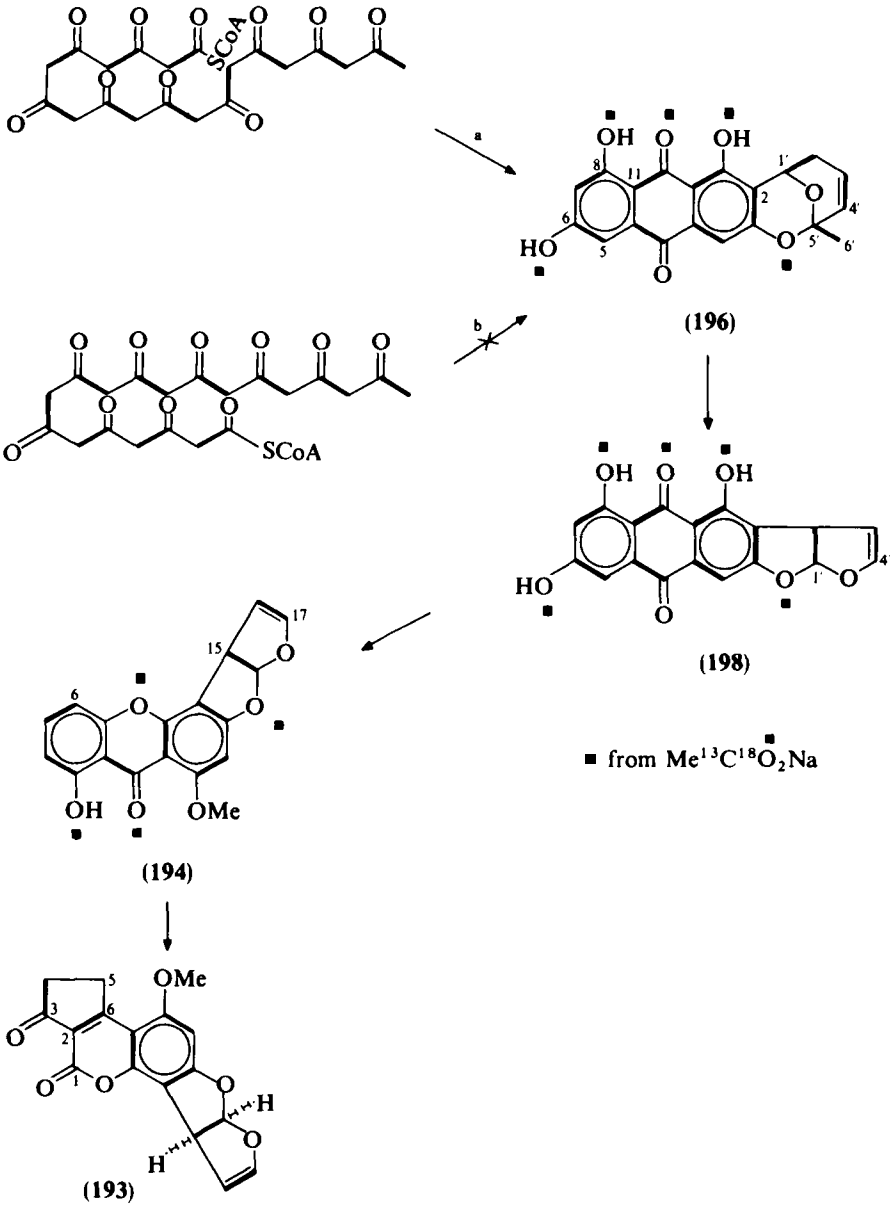


FIGURE 36

aflatoxin biosynthesis was finally unambiguously demonstrated by regiospecific incorporation of specifically labelled **196** into aflatoxin as follows. Feeding of [4'-^{2}H]averufin to *A. flavus* and of [4'-^{13}C]- and [1-^{13}C, 1'-^{2}H]averufin to *A. parasiticus* (ATCC 15517)

indicated that 4-^{2}H and 4-^{13}C were incorporated into the 16-position of aflatoxin B_1 (**193**), while label from 1'-^{13}C and 1'-^{2}H were retained in the 13-position[221, 222]. Feeding of [5, 6-^{13}C]- and [8, 11-^{13}C]averufin to the same mutant of *A. parasiticus* further showed that C(8)–C(11) of averufin was intactly incorporated into C(2)–C(3) of **193**, whereas only C(6) of averufin was introduced into C(5) of **193** with loss of C(5) of averufin in the process, which is also in accordance with the assumed acetate assembly of **193**[223].

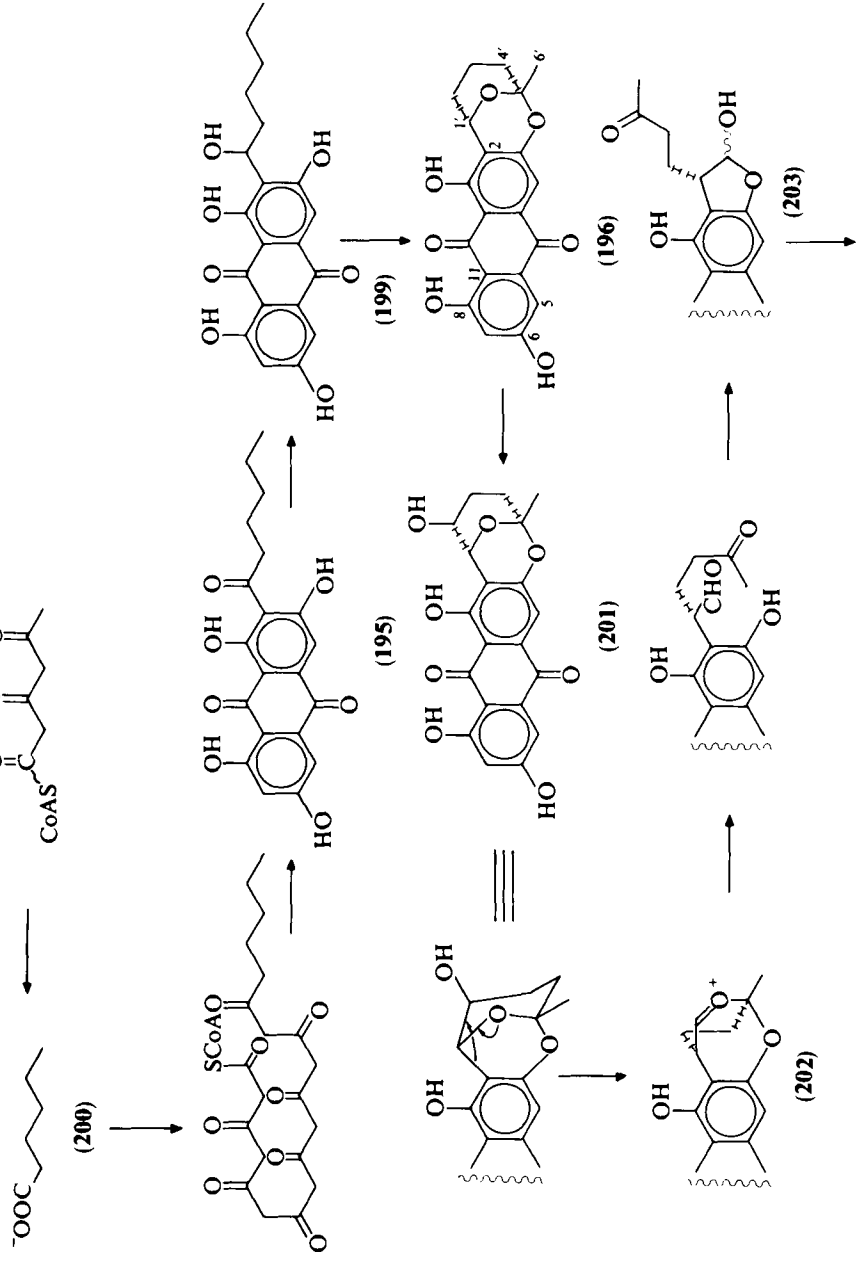
Averufin (**196**) was also shown to be regiospecifically incorporated into versicolorin A (**198**) and versiconal acetate (**197**). When [1'-^{13}C, 4'-$^{2}H_2$, 6'-$^{2}H_3$]averufin was fed to the dichlorovos-inhibited cultures of *A. parasiticus*, the labels were incorporated into the 1',4',6'-position of **197** without significant loss[224]. The retention of ^{2}H at the 6'-position indicates that **197** is formed by a Baeyer–Villiger-type oxidation. When the above-mentioned [4'-^{13}C]- and [1'-^{13}C, 1'-^{2}H]averufin was fed to a mutant (ATCC 36537) of *A. parasiticus*, 4'-^{13}C of averufin was incorporated into C(4') of versicolorin A (**198**), whereas 1'-^{13}C of averufin was retained together with the bearing ^{2}H in the 1'-position of **198**[218]. The retention of the ^{2}H label at C(1') of averufin throughout the process via **197**, **198** to aflatoxin excludes a Favorskii type reaction in the rearrangement of the side chain.

The above results clarified the pathway from averufin (**196**) to versicolorin A (**198**), which further leads to aflatoxin B_1 (**193**). For the explanation of the course of rearrangement in the side chain, nidurufin (**201**) (a known metabolite of *A. nidulans*) was proposed as an intermediate. The process was assumed to involve the rearrangement of **201** to an oxonium species (**202**) which would be converted to versiconal acetate (**197**) through hydrolysis followed by cyclization to a hemiacetal (**203**) and Baeyer–Villiger-type oxidation[218].

Application to *Aspergillus* species of acetates labelled with stable isotopes gave important suggestions on the process subsequent to versicolorin A (**198**). An example is the feeding of [^{13}C] acetate to a mutant (NRRL 5219) of *A. versicolor*[225]. The labelling pattern in the ring A of sterigmatocystin (**194**) enriched by [$^{13}C_2$] acetate in this way indicated that no randomization of ^{13}C–^{13}C coupling occurred, differing from what was seen in tajixanthone (**184**), ravenelin (**185**), etc. Therefore, a symmetrical structure would appear to be unlikely for the ring A of the intermediate which undergoes ring-closure to a xanthone structure. Sterigmatocystin (**194**) obtained after feeding [1-^{13}C, $^{2}H_3$] acetate to the same mutant incorporated ^{2}H only in positions 6, 15 and 17. The retention of ^{2}H at C(6) rules out any mechanism which proceeds through hydroxylation at this position in the course from versicolorin A (**198**) to sterigmatocystin (**194**). Feeding of [1-^{13}C, 1-$^{18}O_2$] acetate to mutants of *A. parasiticus* further indicated the distribution of the acetate-derived oxygen atoms in **196**, **198** and **194** as shown in Figure 36[226–229]. Coupled with the loss of the hydroxy group at C(6) of **198** in the process leading to **194**, the observed transformation of the hydroxy group at C(1) of **198** to the oxygen atom of the xanthone ring of **194** was also very suggestive of the process. All these findings appear most likely to be accounted for by assuming a process which involves the intramolecular oxidative coupling of benzophenone (**204**) to spirodienone (**205**) followed by reduction to spirodienol (**206**) and dienol–benzene rearrangement[229].

Finally, regarding the process from sterigmatocystin (**194**) to aflatoxin B_1 (**193**) an important suggestion came up by the finding that [$^{2}H_3$] acetate enriched aflatoxin B_1 (**193**) retained ^{2}H also at C(5)[230]. The presence of ^{2}H at C(5) which is originally derived from a carboxyl carbon indicates the migration of the ^{2}H label from the adjacent carbon in the biosynthetic process. Assuming 6-hydroxysterigmatocystin as an intermediate, it can be interpreted as the result of an NIH shift.

The complete pathway from the polyketide chain to aflatoxin B_1 (**193**) is shown in Figure 37. Aflatoxin B_1 is, on the other hand, a precursor of most other aflatoxins (B_2, **207**; B_2a, G, G_2 (**208**), G_2a)[231]. In addition to the above-mentioned products, many other biogenetically related metabolites are also isolated from *Dothistroma pini*[232], *Aspergillus*


(200)
(195)
(199)
(201)
(196)
(203)
(202)

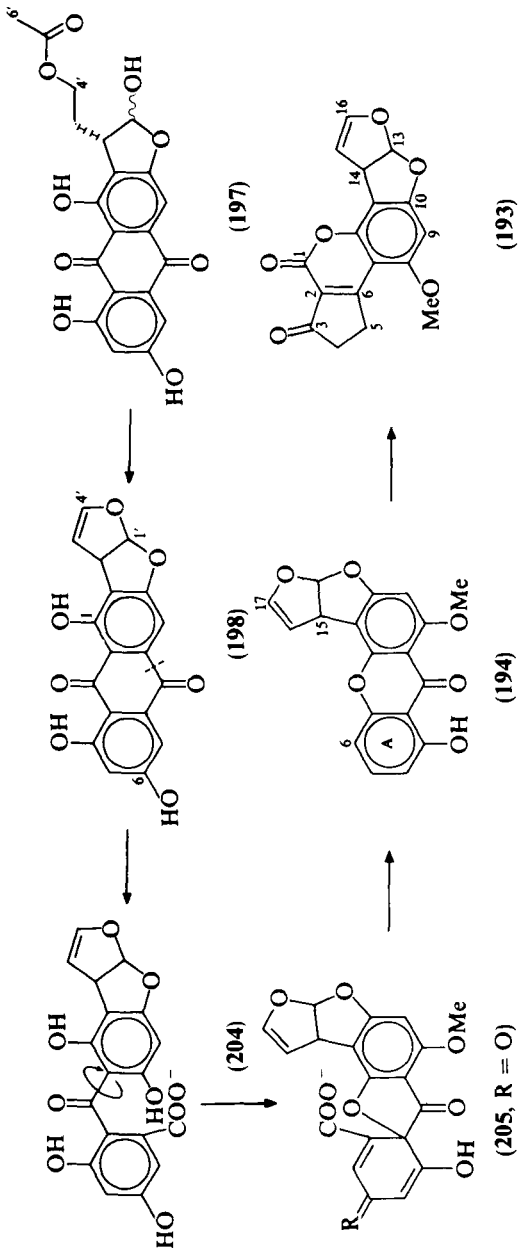
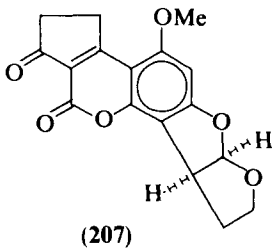
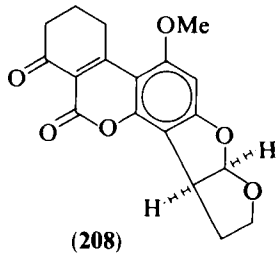


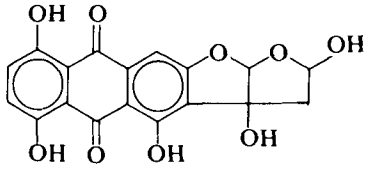
FIGURE 37



(207)



(208)



(209)

FIGURE 38

utsus[233], *Bipoloris sorokiniana*[234], etc. They include xanthones with linear fusion of the xanthone and bisdifuran portions such as dothiostromin (**209**)[232] (Figure 38).

IV. THE ROLE OF VITAMIN K IN BLOOD COAGULATION

Vitamin K_1 (i.e. phylloquinone, **103**) is a chloroplast-associated lipoquinone. Its possible role in photosynthesis is under discussion[174]. In contrast, a body of information has accumulated in the past ten years on the role of vitamin K in the blood coagulation process[235]. The vitamin K required in blood coagulation stems from two sources, viz. intestinal bacteria and green plants ingested with food. An important internal level of vitamin K_2 (**108**) is maintained by anaerobic intestinal bacteria like *Bacteroides fragilis*[236]. Vitamin K exhibits its function in the liver, where it is involved in the post-translational conversion of glutamyl residues (**210**) in precursor proteins to γ-carboxyglutamyl residues (**211**) in blood clotting factors (e.g. prothrombin) and other proteins. Mature carboxylated proteins are involved in the regulation of the activity of thrombin, a key event in the coagulation process[237]. The carboxylation leading to prothrombin takes place at the *N*-terminal region where approximately 10 glutamyl residues are carboxylated in the presence of a microsomal vitamin K-dependent carboxylase. The *in vitro* reaction requires CO_2, O_2, vitamin K hydroquinone (**212**) and a protein (e.g. 'preprothrombin') or a peptide, for example Phe-Leu-Glu-Glu-Val which is homologous to residues 5–9 of the bovine prothrombin precursor.

If the reaction is carried out in the absence of CO_2 the enzyme specifically exchanges the 4-pro S hydrogen of the glutamyl residue[238]. During this exchange a glutamyl carbanion is possibly formed which attacks CO_2. During the carboxylation vitamin K is converted to vitamin K epoxide (**213**) (Figure 39). The exact reaction mechanism for epoxide (**213**) formation and carboxylation is unknown but it has been observed that the reaction is inhibited in the presence of peroxidase. This and additional results[239] led to the

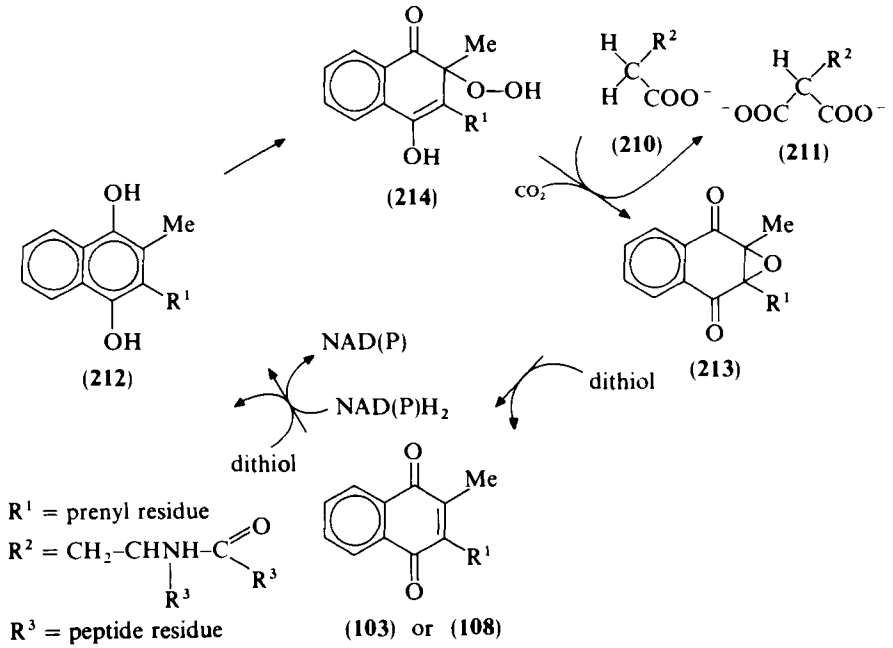


FIGURE 39

assumption that vitamin K hydroperoxide (**214**) (rather than vitamin K) is the true cofactor in the carboxylase reaction. Alternate reaction mechanisms have been discussed[235].

A prerequisite for the functioning of the carboxylation process is that the vitamin K hydroquinone (**212**) is regenerated from vitamin K epoxide (**213**)[240] (Figure 39). This reduction ensures that sufficient intracellular concentrations of vitamin K hydroquinone (**212**) are maintained to support normal rates of γ-carboxyglutamyl formation. The reduction is catalysed by microsomal fractions of the liver. The reduction is inhibited by anticoagulants like warfarin[240] resulting in a low vitamin K hydroquinone (**212**) level. This in turn leads to diminished carboxylation reactions and an impaired blood clotting process.

V. EPILOGUE

Quinones are very closely related to phenols which may easily be oxidized to give quinones provided an *ortho* or *para* diphenol grouping is present. Similarly, reduction of a quinone will easily give a phenol. Thus the quinonoid keto functions are rather artificial critera to classify the type of natural products treated in this review.

It follows that quinones are as heterogeneous as phenols when investigated under the aspects of structure, chemistry, biogenesis, physiology, chemosystematics or genetics.

It is the intent of this epilogue to call attention to this heterogeneity and to supply references for further readings. Where possible attention was drawn in this review to investigation on the genetics of quinone production; such data, however, are rare.

Physiological work on quinones such as localization of biosynthetic processes within chloroplasts or the participation of vitamin K in the blood clotting process has also been presented in this review. In this context attention should also be given to the preceding article in this series compiled by Campbell and Bentley[1].

Little information is available on the metabolism of quinones which to the authors' knowledge has been reviewed in this article for the first time. A relatively large body of information, however, is available on the biosynthesis of quinones. From the present and previous reviews it is evident that many different pathways lead to quinones[241-245]. Hence it is potentially dangerous to use quinones as chemotaxonomic markers because quinones of different biogenetic origin are taxonomically non-equivalent. The relation between distribution of quinones and biosynthesis has been outlined[242, 245]. Occurrence of a quinone within a certain plant family and the structure of a quinone are usually sufficient to propose a reasonable hypothesis as to the origin of a quinone from primary precursors.

Thus acetate-derived quinones have a very characteristic substitution pattern. Enzyme systems, catalysing the synthesis of polyketides *in vitro*, however, have been detected in very few cases only[246]. Therefore NMR studies[247] mentioned in this review turned out to be particularly useful because they provided insight into reaction mechanisms involved in polyketide biosynthesis.

Among quinones enzymological work on plastoquinone, tocopherols (*vide supra*), ubiquinones[248] and vitamin K (see Ref. 249 and references therein) is most advanced.

Part of the work mentioned in this review deals with toxins[241] and antibiotics[250]. Quinones, however, may also exhibit other physiological properties. It is well known that they may be used as laxatives. Some are allergenes and others exhibit cytotoxic, mutagenic or even neurotoxic properties (see Ref. 241 and references therein).

A review on quinones would be incomplete if Thomson's work in this field was not mentioned[251].

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CHAPTER 23

Quinones as oxidants and dehydrogenating agents*

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I. INTRODUCTION

When the Chapter on 'Quinones as oxidants and dehydrogenating agents' was written for the first volume of *The Chemistry of the Quinonoid Compounds* which appeared in 1974, two decades of fascinating and fruitful exploratory research, originating with the investigations by Braude, Linstead, and their coworkers, were reviewed and evaluated[1]. A stepwise mechanism of dehydrogenation by quinones involving initial transfer of a hydride ion had been proposed, quinones were being applied as convenient oxidants in various branches of organic chemistry, and numerous types of compounds were found to be oxidizable by quinones. As a result, typical applications of quinones, such as in the aromatization of hydroaromatic compounds, benzylic oxidations, or the selective oxidation of allylic alcohols have become textbook examples in organic chemistry. When the present chapter was being written in the beginning of 1986, quinone dehydrogenation as a laboratory procedure had become so commonplace as to make selective rather then exhaustive coverage of the literature of the past 12 years mandatory.

Out of the large number of known quinones, the high potential quinones, namely, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), tetrachloro-1,4-benzoquinone (*p*-chloranil), and tetrachloro-1,2-benzoquinone (*o*-chloranil) are most frequently applied as oxidants in synthetic organic chemistry. They have become 'reagents for organic synthesis', and examples of their application are found in every volume of the series of books by Fieser and Fieser[2]. For mechanism studies, however, numerous other quinones are also investigated, and less common quinones may find very specific applications. For example, 2,5-dibromo-6-isopropyl-3-methyl-1,4-benzoquinone is commercially available because of its use as an inhibitor of electron transfer in the photosynthesis system of chloroplasts[3]. On the other hand, anthraquinone and its derivatives are rarely used as dehydrogenating agents in synthetic organic chemistry, though they continue to be oxidants of outstanding industrial importance[4].

The examples of quinone oxidations discussed below were selected from the literature so as to supplement the chapter on 'Quinones as oxidants and dehydrogenating agents' published in 1974[1]. In particular, novel results and reactions, such as the oxidation of various silyl derivatives (cf. Sections II, III.B and VI.B), or the oxidative removal of the 4-methoxybenzyl group as a deprotection procedure (Section IV.D), have been considered. As for a comprehensive review of virtually all aspects of dehydrogenation of polycyclic hydroaromatic compounds, however, the reader is referred to an authoritative article published in 1978[5]. Also, DDQ and its applications as oxidant in organic chemistry, first comprehensively reviewed in 1967[6], were discussed in 1977[7], and in 1983[8].

By and large, the disposition of topics reviewed below is similar to that of the corresponding contribution to the first volume of *The Chemistry of the Quinonoid Compounds*[1]. Thus, the role of quinones in biological oxidations has been considered to be beyond the scope of the present review, though some recent results pertinent to the mechanism of quinone dehydrogenation are included in Section II.

The terms 'dehydrogenation' and 'oxidation' will be used indiscriminately throughout this chapter.

II. MECHANISM STUDIES

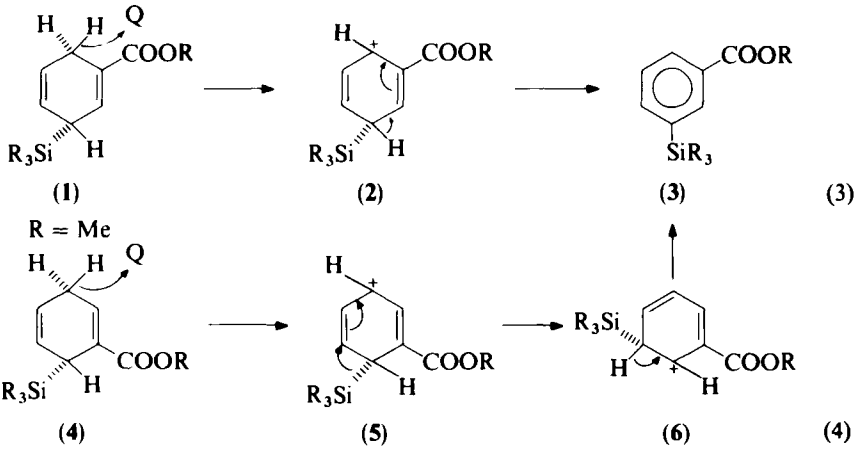
The seemingly simple two-step mechanism of quinone dehydrogenation of compounds AH_2, involving rate-determining hydride ion transfer to the quinone followed by fast loss

of proton from AH^+ according to reactions 1 and 2 (cf. Ref. 1, p. 340), is a subject of recurring investigations[9-16]. However, neither the hydrogen group transfer by a concerted mechanism[10,11], nor the stepwise ene-mechanism involving the formation of an intermediate[12], postulated in recent years, has been substantiated in subsequent investigations[13-16]. The results of a recent kinetic study dealing with the aromatization of numerous 1,4-dihydroarenes by DDQ convincingly support the stepwise ionic mechanism[14]. Likewise, in the dehydrogenation of 1,2-dihydronaphthalene by *o*-chloranil and *o*-bromanil, regioselective hydride ion transfer from the 2-position to the carbonyl oxygen was found to be the rate-determining step[15]. The reaction proceeds *cis*-stereoselectively, as is in agreement with the involvement of tight ion pair. The regioselectivity of dehydrogenation by DDQ is such as to be explicable by hydride ion transfer from the 1-position of 1,2-dihydronaphthalene, suggestive of a transition state geometry of parallel donor–acceptor arrangement.*

$$AH_2 + Q \rightarrow AH^+ + QH^- \quad (1)$$

$$AH^+ + QH^- \rightarrow A + QH_2 \quad (2)$$

Important experimental results of mechanistic significance which provide evidence against a concerted hydrogen transfer in quinone dehydrogenation were obtained in a study dealing with the aromatization of trimethylsilyl derivatives of isomeric methoxycarbonyl-substituted cyclohexa-1,4-dienes[16]. Dehydrogenation of cyclohexadiene **1** with DDQ in benzene at room temperature was found to proceed smoothly to give the *m*-trimethylsilyl derivative of methyl benzoate (**3**) in 89% yield. Unexpectedly, the *meta*-substituted compound **3** also was obtained (94% yield) by DDQ oxidation of the vicinal-substituted cyclohexa-1,4-diene **4**. As depicted in reactions 3 and 4, this latter result is explicable by a stepwise ionic mechanism in which the trimethylsilyl group in the intermediate cationic species **5** undergoes 1,2 migration.



The formation of the rearranged product **3** from **4** is remarkable and mechanistically significant because the route of 'normal' dehydrogenation to give the *ortho*-trimethylsilyl methyl benzoate is available. In the dehydrogenation with palladium, which does not

* Added in proof: Recent results on the *cis*-selective hydrogen transfer from deuterium labelled 1,4-dihydroaromatic substrates are in agreement with the two-step mechanism: M. Brock, H. Hintze and A. Heesing, *Chem. Ber.*, **119**, 3727 (1986).

proceed according to reactions 1 and 2, cyclohexadiene **4** is indeed aromatized without concomitant rearrangement[17].

The syn-stereoselectivity of the dehydrogenations by DDQ of cyclohexa-1,4-dienes as outlined above is supported by the results of the DDQ oxidation of *cis*- and *trans*-3,6-dideuterio-cyclohexa-1,4-dienes. Also, the observed enchanced rate of aromatization by DDQ of *cis*-9,10-diisopropyl-9,10-dihydroanthracene, relative to that of the *trans* isomer, in refluxing benzene is explicable in terms of *syn*-stereoselectivity[18].

In the ionic mechanism of quinone dehydrogenations discussed above, the hydride ion is transferred to the carbonyl oxygen of the acceptor to give the hydroquinone anion. By contrast, dehydrogenation of hydroaromatic systems by concerted transfer of two hydrogens should proceed either by 1,4 addition to the enone system of the quinone (from 1,4-dihydroaromatic compounds), or by 1,2 addition (from 1,2-dihydroaromatic compounds) to the carbon–carbon double bond of the quinone. In both cases, the hydroquinone will be formed by subsequent tautomerization. Most recently, the kinetics and the isotope effects of the dehydrogenation of tetralin by DDQ, thymoquinone and anthraquinone were interpreted in these terms[19].

Oxidations by anthraquinone in alkaline solution are of considerable current interest in conjunction with recent progress in wood pulping [20,21]. Several mechanisms involving either the formation of addition products and/or electron transfer reactions from anthrahydroquinone anion have been advanced and may be operative. For the reduction of anthraquinone by hydroxide ion in aprotic media, experimental evidence has been obtained for a one-electron mechanism which involves nucleophilic addition of hydroxide to the carbonyl double bond[22].

The oxidation of coenzyme NADH or its model compounds by quinones continues to be of mechanistic interest within the general context of electron transfer phenomena[23–26]. Unequivocal evidence for one-electron transfer from *N*-methylacridan to 2,3-dicyanobenzoquinone was obtained by spin-trapping technique[27]. For the oxidation of 1-benzyl-1,4-dihydropyridine by a series of quinones of different redox potentials, the rate constants were found to span over a range of 11 orders of magnitude, so as to suggest a fleeting transition from one-electron transfer to hydride ion transfer mechanism, depending on the nature of the substrate and that of the quinone[28]. However, for numerous other model compounds and NADH itself, the kinetics of the oxidation by various *o*- and *p*-quinones were found to be in agreement with the hydride ion transfer mechanism[25].

In strongly acidic media, quinones undergo protonation (cf. Ref. 1, p. 413), and may then oxidize aromatic compounds by way of one-electron transfer. For example, 9,10-diphenylanthracene (DPA) upon oxidation with DDQ or *p*-chloranil in methylene chloride containing trifluoroacetic acid gives the DPA radical cation according to reactions 5 and 6[29]

$$DPA + Q + H^+ \rightarrow DPA^+ + QH^\cdot \quad (5)$$

$$DPA + QH^\cdot + H^+ \rightarrow DPA^{+\cdot} + QH_2 \quad (6)$$

$$2\,DPA + Q + 2H^+ \rightarrow 2\,DPA^{+\cdot} + QH_2 \quad (7)$$

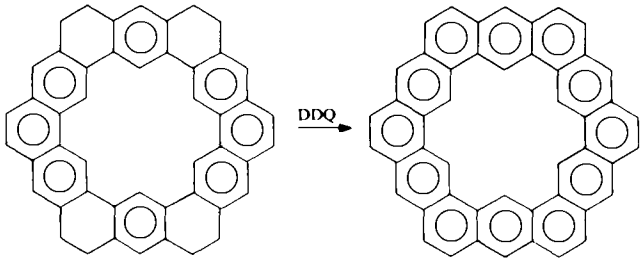
The intermediate semiquinone radical is not detectable by spectroscopic means, and the kinetics of the overall reaction (7) indicate that QH in acidic media is more rapidly reduced than the quinone Q. (For a recent comparison of redox potentials of various quinonoid compounds as established by cyclic voltammetry, see Ref. 30).

III. DEHYDROGENATION OF HYDROAROMATIC COMPOUNDS

The dehydrogenation of hydroaromatic compounds was reviewed comprehensively in 1978[5]. Consequently, the discussion in this section will be limited to novel examples of quinone dehydrogenation.

A. Aromatization of Polycyclic Hydrocarbons

A survey of the literature readily reveals that high-potential quinones frequently are the reagents of choice for the aromatization of hydroaromatic compounds. Thus, in the synthesis of kekulene (**8**)[31], the final step involving dehydrogenation of its octahydro-derivative **7** was accomplished in 80% yield by oxidation with DDQ in 1,2,4-trichlorobenzene (reaction 8). The solvent used in this reaction was 'freshly purified by two distillations', and the dehydrogenation was carried out by keeping the reaction mixture at 100°C for three days under nitrogen.

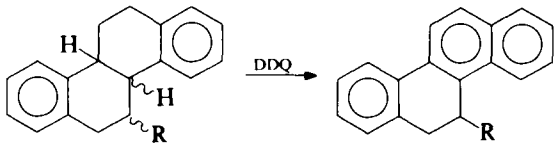


(8)

(7) (8)

More typical examples of dehydrogenation, generally by DDQ in benzene solution, include the aromatization of 1,4-dihydrophenanthrenes[32], various hydroanthracenes[33], photodimers of tetrahydronaphthacene[34], numerous hydropyrenes[35-37], 4,5-dihydro-1,12-methylenebenz[a]anthracene[38], 3,4-dihydrobenzo[g]chrysene[39], and various hydrobenzofluoranthenes[40].

Oxidation of hexahydrochrysene (**9**; R=H) with DDQ yields chrysene. However, with 5-alkylhexahydrochrysenes (**9**; R=Me or Et) the quinone oxidation surprisingly stops at the stage of dihydrochrysene **10** (reaction 9), although complete aromatization of **9** can be accomplished with palladium-charcoal[41].

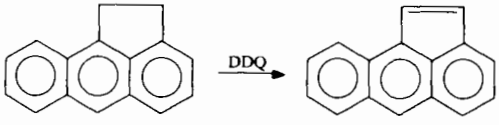


(9)

(9) (10)

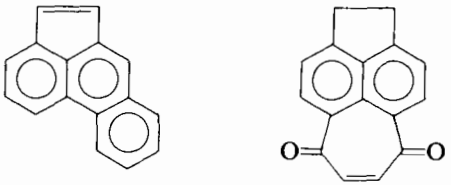
Both aceanthrylene (**12**)[42,43] and acephenanthrylene (**13**)[44] have been prepared recently from hydroaromatic precursors by dehydrogenation with DDQ (cf. reaction 10). The formation of acenaphthylene from acenaphthene by quinone dehydrogenation also proceeds smoothly (cf. Ref. 1, p. 365), but attempted dehydrogenation of the cycloheptenedione annelated acenaphthene **14** by DDQ failed[45] (cf. also Section VI.A).

Bridged bicyclic hydrocarbons such as 9,10-dihydro-9,10-ethenoanthracene have been prepared by dehydrogenation of hydroaromatic precursors, but the yields can be quite low[46]. Moderate yields (30%) were obtained in the synthesis of chiral triptycenes with an anthracene chromophore when the dehydrogenations were carried out in boiling benzene for prolonged periods of time[47]. It is not obvious why these dehydrogenations should require both elevated temperature and long reaction times. Similar aromatizations were accomplished with structurally related 'dihydrotriptycenes' under mild conditions in higher yields. For example, the formation of the novel triptycene **16** by DDQ oxidation of



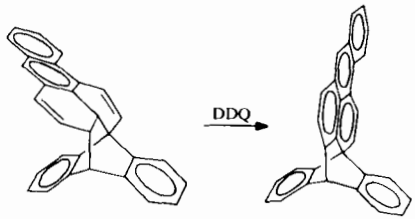
(11) (12)

(10)



(13) (14)

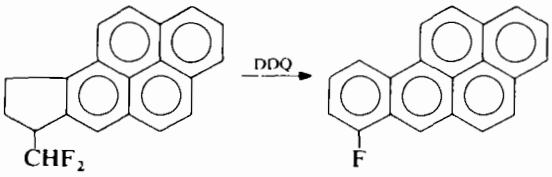
15 for 1 h proceeded at room temperature in dichloromethane (reaction 11)[48]. (Under rather drastic conditions, i.e. in benzene solution at 240°C in a sealed tube, the hydrocarbon **16** can be obtained in 70% yield directly from 1,2-di(9-anthryl)ethane by oxidation with two molar equivalents of DDQ[49].) Dehydrogenations of tetrahydro or hexahydro derivatives of **16** indeed were found to require longer reaction times and elevated temperature than those of 1,2-dihydroaromatic systems[49].



(11)

(15) (16)

An unexpected aromatization involving oxidative ring expansion was encountered in the dehydrogenation by DDQ of the difluoromethyl-substituted polycyclic hydrocarbon **17**[50]. Reaction 12 proceeds in 60% yield in refluxing benzene, but the mechanism of this intriguing transformation remains to be elucidated.

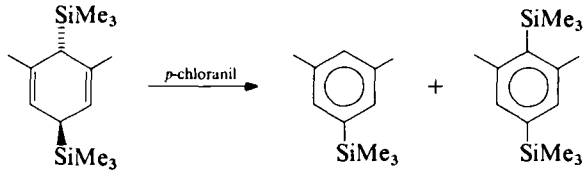


(12)

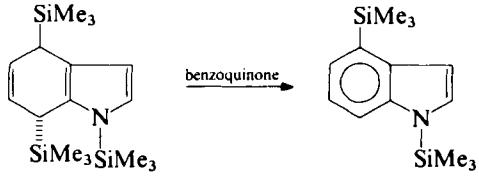
(17) (18)

B. Dehydrogenation of Silyl-substituted Hydroaromatic Compounds

Bis-trimethylsilyl-substituted hydroaromatic compounds react with *p*-quinones predominantly by intermolecular transfer of one silyl group to give mono-silyl substituted aromatic hydrocarbons. Thus, oxidation of the *trans*-substituted 1,4-cyclohexadiene derivative **19** with chloranil in refluxing toluene gives mainly the mono-trimethylsilyl-substituted *m*-xylene **20** (80%), but only 10% of the bis-trimethylsilyl derivative **21**[51]. The oxidation of the 4,7-dihydroindole derivative **22** with *p*-benzoquinone under nitrogen at 0°C in methylene chloride affords 1,4-bis(trimethylsilyl)indole **23**[52]. The stereochemistry of compounds **19** and **22** has not been established, but the dehydrosilylations as shown in reactions 13 and 14 are in agreement with the *syn*-selectivity of quinone dehydrogenation discussed in Section II for trimethylsilyl-substituted 1,4-cyclohexadienes[16]. The dehydrosilylation of bis-trimethylsilyl acenaphthene by DDQ or chloranil to give the mono-silyl-substituted acenaphthylene[53] also is indicative of a *syn*-selective reaction. The observed regioselectivity of reaction 14 has been attributed to steric factors which, most likely, also govern the course of reaction 13. Although the fate of the silyl moiety in dehydrosilylations has not been investigated in the reactions presented above, the first step probably involves hydride ion transfer to the quinone. The subsequent step will be the transfer of the trimethylsilyl group to the hydroquinone mono-anion (cf. the analogous transfer of trimethylstannyl groups to *p*-benzoquinone, in Ref. 1, p. 403).



(19) (20; 80%) (21; 10%) (13)

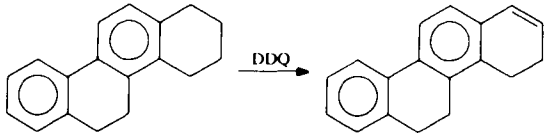


(22) (23) (14)

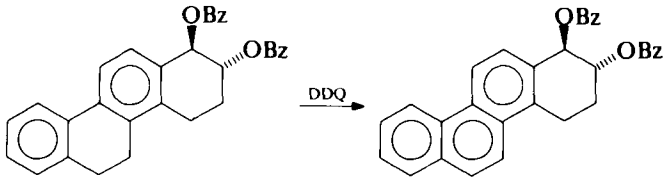
C. Selective Dehydrogenation of Polycyclic Hydroaromatic Compounds

The application of quinones for the selective dehydrogenation, rather than straightforward aromatization, of hydroaromatic compounds has become of increasing importance in recent years. In connection with studies on carcinogenic metabolites of polyarenes, which are mainly dihydrodiols and diol epoxides, the selective dehydrogenation of various diol derivatives of hydroaromatic compounds frequently is part of synthetic schemes[54-59]. In general, dehydrogenations are accomplished with DDQ or *o*-chloranil. For example, in the chrysene series the hexahydrochrysene **24** undergoes rapid selective dehydrogenation with one molar equivalent of DDQ in refluxing benzene to give mainly the tetrahydrochrysene **25** (reaction 15)[54]. The observed regioselectivity of the oxidation correlates with the delocalization energies of the various possible benzylic carbocations, as calculated by

perturbational MO methods[5, 54], unless the course of the oxidation is affected by steric factors. For example, oxidation of the dibenzoate **26** with two molar equivalents of DDQ in refluxing dioxane for three days gives the tetrahydrochrysene **27** in 91% yield (reaction 16)[54]. Differences in the rate of dehydrogenation of hydroaromatic diol esters are observed, but they are not easily rationalized. In certain instances, quinone dehydrogenation of hydroaromatic esters or carbinols has been found to lead to aromatized products by way of elimination reactions[56, 60].



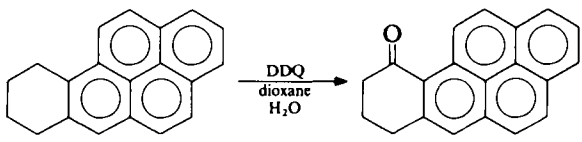
(24) (25) (15)



(26) (27) (16)

D. Functionalization of Hydroaromatic Compounds

The reaction of DDQ with hydroaromatic compounds in the presence of water in either chloroform or dioxane results in benzylic oxidation to give ketones in fair to good yields (reaction 17)[61]. The formation of ketone **29** is explicable by the hydride ion transfer mechanism in which the carbocation formed from hydrocarbon **28** is trapped by water. The resulting benzylic alcohol then undergoes further oxidation. If there is more than one benzylic position, the functionalization takes place preferentially at the site for which the calculation of delocalization energies suggests the cationic intermediate to be the most stable. Side reactions competing with the functionalization may be the straightforward dehydrogenation of the hydroaromatic compound, or elimination of water from the intermediate benzylic carbinol. The choice of solvent appears to be of critical importance, most likely because charge-transfer complex formation between the substrate and the quinone is essential for the benzylic oxidation (cf. also Ref. 1, page 392.). Consequently, the functionalization is preferably carried out in solvents like chloroform or dioxane where donor:acceptor complex formation appears to be favored. Nevertheless, the yields of ketones greatly depend on the solvent. In the case of reaction 17, the yield of ketone **29** is 40% in chloroform, but 75% in dioxane.



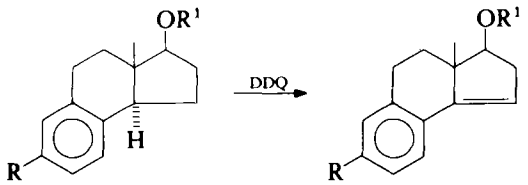
(28) (29) (17)

IV. BENZYLIC AND ALLYLIC OXIDATIONS

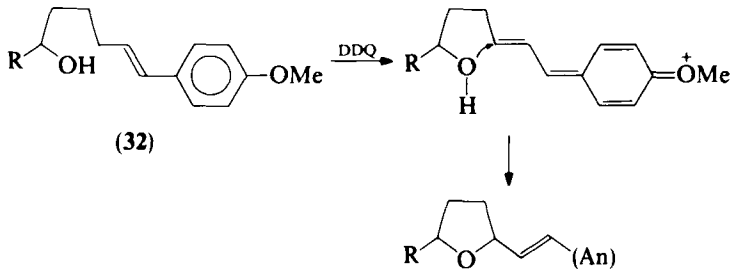
A. Benzylic and Allylic Dehydrogenations

The effect of aryl substitution on the dehydrogenation by quinones has been discussed in detail in Ref. 1. Mechanistic features of benzylic and allylic dehydrogenations closely parallel those outlined for the dehydrogenation of hydroaromatic compounds in Section III. Therefore, the following discussion can be limited to selected novel examples of benzylic and allylic oxidations.

DDQ oxidation of the des-A-steroids **30** to the styrenes **31** (reaction 18) proceeds rapidly in dioxane at room temperature[62]. Interestingly, the rate of dehydrogenation is sensitive to changes in the substituent at the 17-position. Similar rate ratios for alcohol/acetate pairs are found for both free phenols and their methyl ethers (R = OH and OMe, respectively), suggesting direct attack by DDQ at the tertiary benzylic C–H bond. In aromatic steroids, seemingly subtle and remote structural changes may drastically affect the rate and course of benzylic dehydrogenation by high-potential quinones[63–65]. Differences in molecular geometry indeed affect the reactivity of benzylic or allylic carbon–hydrogen bonds, not only because attack by the hydride ion acceptor may be impaired for steric reasons (which may explain why only one of the stereoisomeric photodimers of 6,6-dimethyl-2,3-benzo-2,4-cycloheptadienone undergoes dehydrogenation by *o*-chloranil[66]), but also because the sterochemistry of conjugated systems has electronic consequences. For example, the *trans*-isomeric *p*-methoxystyrene derivatives **32** upon oxidation with DDQ give tetrahydrofurans **33** (reaction 19), but the *cis*-isomeric compounds are stable towards DDQ[67]. Obviously, only in the *trans* isomer **32** is the molecular geometry such as to permit coplanar arrangement of the carbon–carbon double bond with the aromatic π system. Reaction 19 also has been extended to the synthesis of tetrahydropyrans[67].



(30) (31) (18)



(32) (19)

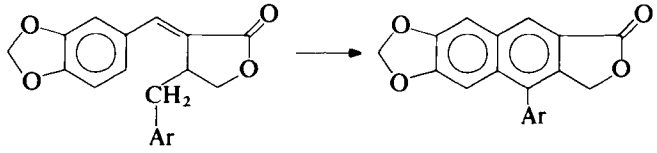
An = 4-methoxyphenyl (33)

As for the formation of cyclic conjugated olefins, quinone dehydrogenation has been applied to the synthesis of azulenes (cf. Ref 1, p. 366), but the yields can vary greatly. For example, oxidation of 4,5-dihydro-4-phenylazulene with chloranil in boiling xylene gives 4-phenylazulene in only 11% yield[68], while azulene-5-carboxylic acid (**35**) was obtained in 65% yield from its hexahydro precursor **34** by DDQ oxidation in boiling benzene (reaction 20)[69].

(20)

(**34**) (**35**)

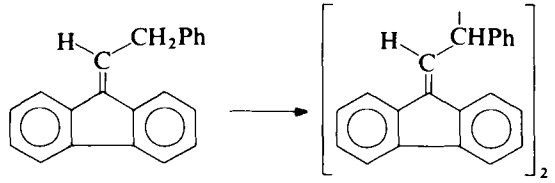
The dehydrogenation of aryl-substituted compounds for which double bond formation is structurally impossible may give rise to products whose formation is explicable by either ionic or radical intermediates. The oxidation of lignan **36** with two molar equivalents of DDQ in boiling benzene affords the naphthalide **37** (reaction 21), most likely by way of an electrophilic substitution following hydride ion abstraction from the benzylic position[70]. By contrast, benzylic oxidation of the fluorenylidene derivative **38** with *o*-chloranil in benzene (four weeks at room temperature) was found to give 1,4-di(fluorenylidene)-2,3-diphenylbutane (**39**), conceivably by radical dimerization (reaction 22)[71].



(21)

(**36**) (**37**)

Ar = 3,4-dimethoxyphenyl



(22)

(**38**) (**39**)

Even if straightforward dehydrogenation is formally possible, quinone oxidation may result in the formation of thermodynamically more stable products by way of ionic fragmentation. In the recently reported DDQ oxidation of a *t*-butoxy-substituted methanoannulene in refluxing benzene, the cationic intermediate formed by hydride ion abstraction from a benzylic position apparently gives the final product by elimination of *t*-butyl cation[72].

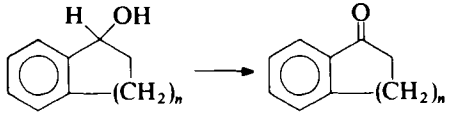
B. Oxidation of Aryl Carbinols and Related Alcohols

The results of a kinetic study of the oxidation of benzylic alcohols by DDQ and *p*-chloranil are in agreement with the two-step ionic mechanism in which the transfer of a hydride ion from the benzylic C–H bond is rate determining[73]. The yields of

propiophenone by oxidation of phenylpropanol with *p*-chloranil were found to be highest in solvents like chloroform and methylene chloride which favor the formation of an alcohol: quinone charge-transfer complex.

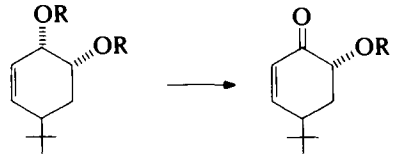
The experimental details of the oxidation of numerous primary and secondary benzylic alcohols with DDQ in dioxane, to give the corresponding carbonyl compounds (cf. Ref. 1, pp. 379–382), have now been published in full[74]. Significantly, the nature of the products obtained in the DDQ oxidation of phenolic benzyl alcohols is dependent on the solvent. The formation of oxidatively coupled products obtained in methanol solution is indicative of hydrogen transfer from the phenolic hydroxyl group to the quinone[74].

A stereoelectronic effect is apparent in the oxidation of benzocycloalkenols **40** by DDQ in refluxing benzene which gives the corresponding ketones **41** (reaction 23)[75]. The observed order of reactivity, i.e. α-tetralol > indan-1-ol ≫ 2,3-benzocyclohepten-1-ol parallels the decrease in the dihedral angle (82, 72, and 48 degrees) between the benzylic C–H bond and the plane of the benzene ring. Steric hindrance probably also accounts for the fact that the benzylic alcohol moiety in an azaphenanthrene alkaloid resisted oxidation by DDQ (and other oxidants as well)[76].



(40) (41) (23)

As for the oxidation of allylic alcohols, the usefulness of DDQ is apparent from a recent investigation dealing with the selective oxidation of cyclohexene-3,4-diols[77]. Thus, oxidation of the *cis*-enediol **42** with 2.7 molar equivalents of DDQ in benzene at 60° C for 12 hours afforded ketol **43** in quantitative yield. Likewise, oxidation of shikimic acid with three molar equivalents of DDQ in THF at 65°C gave dehydroshikimic acid (60% yield). DDQ is superior to other oxidants such as manganese dioxide which lead to the corresponding catechols. Interestingly the selective oxidation by DDQ also was found to be applicable to the bis (*t*-butyldimethylsilyl) ether **44** which gave the ketol derivative **45** (reaction 24)[77].



(24)

(**42**; R = H) (**43**; R = H)
(**44**; R = TBDMS) (**45**; R = TBDMS = *t*-BuMe$_2$Si)

An apparent economical improvement for the oxidation of allylic alcohols involves catalytic amounts of DDQ in a two-phase system consisting of benzene, aqueous hydrochloric acid (0.1 normal), and periodic acid[78]. The yields of propenones **47** obtained in this fashion from propenols **46** range between 80 and 90% (reaction 25), and steroidal allylic alcohols can be oxidized selectively in the same manner. The role of the periodic acid in these reactions is that of an oxidant for $DDQH_2$ to regenerate DDQ. However, the mechanism of the catalytic oxidation is not readily understood: high-yield conversions are brought about with 10 mol% of DDQ in conjunction with a molar ratio of DDQ:periodic

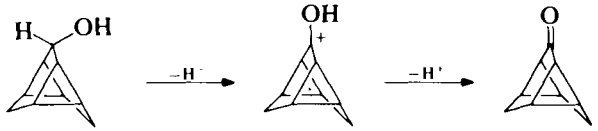
acid of 1:3. Consequently, also oxidation states of iodine lower than + 7 must be involved in the oxidation.

$$RCH = CHCHOHR' \rightarrow RCH = CHCOR' \qquad (25)$$

e.g. R = phenyl, R' = H

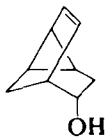
(46) **(47)**

Analogous to benzylic and allylic alcohols, cyclopropyl carbinols undergo oxidation by DDQ according to the hydride ion transfer mechanism. Oxidation of dicyclopropylmethanol with two molar equivalents of DDQ in anhydrous benzene gives dicyclopropyl ketone[79]. Likewise, DDQ oxidation of triasteranol **48** affords the triasteranone **50** via the intermediate triasteryl cation **49** (reaction 26). By contrast, carbinol **51**, in which hydride ion abstraction no longer gives rise to a cyclopropyl conjugated ionic intermediate, was found to be stable towards DDQ[79].



(26)

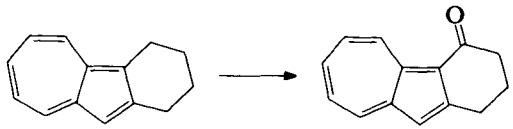
(48) **(49)** **(50)**



(51)

C. Functionalization of Benzylic and Allylic Positions*

Analogous to the functionalization of hydroaromatic compounds described in Section III. D, benzylic or allylic positions will be functionalized by oxidation with quinones, if the cationic intermediate formed by hydride ion abstraction can be trapped by nucleophiles such as water, alcohols, or acids (cf. Ref. 1, pp. 372–378). Thus, oxidation of methyl- and ethyl-substituted polycyclic aromatic hydrocarbons with DDQ in chloroform in the presence of water gives the corresponding carbonyl derivatives[61]. By and large, the yields of aldehydes or ketones decrease with decreasing number of aromatic rings. The oxidation of 1-methylpyrene and 9-methylphenanthrene gave the corresponding aldehydes in 33% and 20% yield, respectively, but 1-naphthaldehyde could not be obtained by oxidation of 1-methylnaphthalene[61]. Alkyl-substituted azulenes undergo regioselective oxidation by DDQ in aqueous acetone or dioxane to give acyl-substituted azulenes in good yields, as exemplified by the conversion of **52** into **53** (reaction 27)[80, 81].

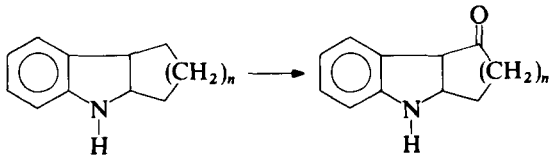


(27)

(52) **(53)**

* Added in proof: Since the completion of the manuscript, the asymmetric functionalization by DDQ of the benzylic position has been reported. The asymmetric control of the oxidative acetoxylation is attributed to stereoselective donor:acceptor interaction between the substrate and DDQ: M. Lemaire, A. Guy, D. Imbert and J.-P. Guetté, *J. Chem. Soc., Chem. Commun.*, 741 (1986).

Selective oxidation of the side chain of indoles can be achieved by using DDQ in aqueous tetrahydrofuran[82]. Thus, tetrahydrocarbazole (**54**; $n = 2$) upon treatment with two molar equivalents of DDQ at 0°C gives tetrahydrocabazol-4-one (**55**; n = 2) in 83% yield (reaction 28). Analogous selective oxidations were accomplished with various cycloalkan-[b] indoles **54**, and their *N*-substituted derivatives[82]. However, 2,3,5-trimethylindole is oxidized less selectively giving the 3-formyl and 2-formyl derivatives in 30% and 8% yield, respectively[82].

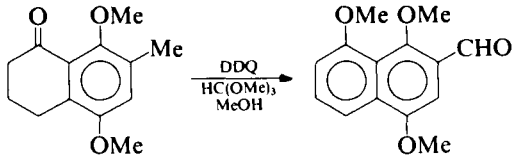


(28)

(**54**) (**55**)

The functionalization of indol derivatives has been extended to the synthesis of 3- and 4-acylindoles from 1,2,3,4-tetrahydro-β-carbolines by DDQ oxidation in aqueous THF[83]. The regioselectivity of the oxidation increases by lowering the reaction temperature.

DDQ has been shown to oxidize *p*-methyl groups of *o*-substituted aromatic amines[84]. For example, mesidine in dioxane is converted into 4-amino-3,5-dimethylbenzaldehyde in 49% yield. Likewise, *o*-chloro- and *o*-bromo-toluidines are oxidized to give the corresponding aldehydes in 46% and 64% yield, respectively. Steric hindrance of the amino group is a prerequisite for aldehyde formation, as *p*-toluidine gave no aldehyde at all, and 2,4-dimethylaniline gave only a 10% yield of aldehyde. (*N*-Acetyl derivatives are unreactive.) Obviously, the oxidation of *p*-methyl-substituted anilines resembles the benzylic oxidation of *p*-methyl-substituted phenols (Ref. 1, p. 392). Similar selective benzylic oxidations by DDQ in refluxing benzene to give aldehydes have been reported for 4-methoxytoluene and similarly substituted 1,2-dihydronaphthalenes and chromenes[85], and methyl-substituted tetralins[86]. More remarkable, however, is the one-pot conversion of the substituted tetralone **56** to the trimethoxy-substituted naphthaldehyde **57** (reaction 29)[87]. Three equivalents of DDQ are required, and the reaction is run for 24 hours in refluxing methanol in the presence of trimethyl orthoformate for *in situ* methylation of the intermediate enol.

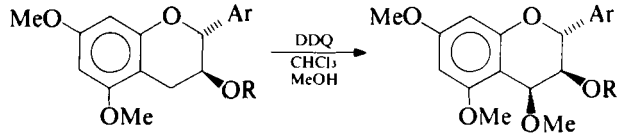


(29)

(**56**) (**57**)

Benzylic oxidation with DDQ in the presence of methanol under anhydrous conditions leads to benzyl methyl ethers or dimethyl ketals of arylcarbonyl compounds[88]. The oxidation of tetramethoxy-substituted flavan-3-ol derivatives **58** by DDQ in chloroform containing methanol has been found to result in stereospecific methoxylation of the benzylic position to give compounds **59** (reaction 30)[89]. A double molar excess of DDQ was employed in order to achieve short reaction times so as to avoid side reactions.

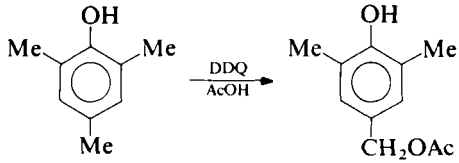
Examples of intramolecular benzyl ether formation by way of quinone oxidation have previously been encountered in the dehydrogenation of phenolic arylalkanes (cf. Ref. 1, pp. 386–387).



(58) (59) (30)

R = H or Ac
Ar = 3,4-dimethoxyphenyl

The reaction of DDQ in anhydrous acetic acid at room temperature with electron-rich arylalkanes gives benzyl acetates in high yields. Thus, mesitol (**60**) is smoothly converted into 3,5-dimethyl-4-hydroxybenzyl acetate (**61**; reaction 31)[90]. Likewise, 4-methoxydiphenylmethane upon oxidation with DDQ in acetic acid gives the acetate of 4-methoxydiphenyl carbinol. Both 4-hydroxy- and 4-methoxy-substituted ethylbenzenes undergo benzylic acetoxylation in the same fashion[90].



(60) (61) (31)

Toluene in refluxing acetic acid was found to be stable towards oxidation with DDQ, but a variety of other methyl-substituted benzenes reacted under the same conditions to give mono-acetoxylated products in drastically varying yields (see Table 1)[91]. The observed effect of substituents on the rate of reaction was found to be such as to support the hydride ion transfer mechanism. The absence of nuclear acetoxylation products precludes the involvement of radical ion intermediates in the oxidation.

$$ArMe \xrightarrow[AcOH]{DDQ} ArCH_2OAc \qquad (32)$$

TABLE 1. Acetoxylation of methyl-substituted aromatic compounds by DDQ in acetic acid (reaction 32)

Compound	Yield (%) of benzyl acetate
Hexamethylbenzene	80
P-Xylene	44
m-Xylene	10
Toluene	0

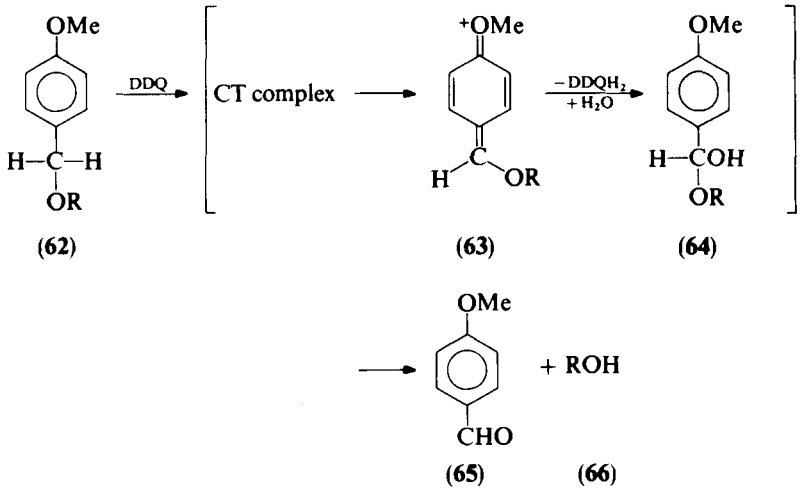
D. Oxidative Conversions of 4-Methoxybenzyl Derivatives by DDQ

1. O-Methoxybenzyl deprotection

The functionalization of benzylic positions is greatly facilitated by electron-donating substituents such as hydroxy or methoxy groups in the *p*-position, and the oxidative cleavage of 4-hydroxy and 4-methoxybenzyl ethers by DDQ in the presence of water has

been discussed previously (Ref. 1, p. 392). However, the synthetic potential of this cleavage reaction has only recently been recognized, and its usefulness as a deprotection method has been demonstrated in the synthesis of numerous natural products[92]. The significance of the methoxybenzyl ether deprotection lies in the remarkable selectivity of the DDQ oxidation, as other common hydroxyl protecting groups, such as benzyl, methoxymethyl, *t*-butyl-dimethylsilyl, or acetyl, virtually remain unchanged. Moreover, the reaction is carried out in neutral solution, so that acid- or base-sensitive groups are left intact.

The principle of deprotection by oxidative cleavage of *p*-methoxybenzyl ethers **62** rests on the electron acceptor property of DDQ to form charge-transfer complexes with electron-rich aromatic compounds. Hydride ion transfer to the quinone from the benzylic position by way of heterolytic dissociation of the CT complex gives the semiquinone anion and a cationic species **63** which undergoes nucleophilic attack by water. The final products of the reaction, i.e. *p*-methoxybenzaldehyde (**65**) and the deprotected alcohol **66**, are obtained in high yields from the intermediate hemiacetal (reaction 33)[92, 93].



(33)

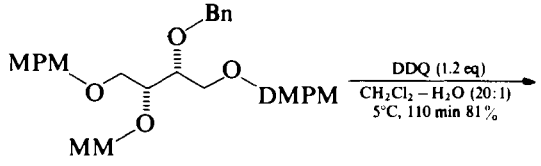
e.g. R = phenethyl

The stability of the charge-transfer complex and, consequently, the rate of oxidation is greatly affected by solvent polarity (cf. Table 2). In 18:1 methylene chloride/water mixtures, the oxidative deprotection of *p*-methoxybenzyl ethers proceeds rapidly at room temperature.

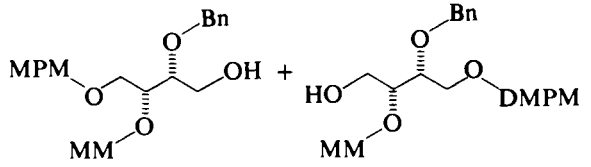
TABLE 2. Effect of solvent composition on the oxidative cleavage of *p*-methoxybenzyl ether **62** at room temperature

Solvent	**62**: DDQ	Reaction time (h)	Yield of alcohol **66** (%)
MeOH	1:1	24	86
THF/H_2O (10:1)	1:1	24	85
CH_2Cl_2/MeOH (4:1)	1:1	6	87
CH_2Cl_2/H_2O (18:1)	1:1	0.6	89
CH_2Cl_2/H_2O (18:1)	1:1.1	0.2	84

The oxidative 3,4-dimethoxybenzyl ether cleavage also has been used for the deprotection of hydroxyl groups[94]. Because of their lower oxidation potential, 3,4-dimethoxybenzyl ethers undergo DDQ oxidation even more rapidly than *p*-methoxybenzyl ethers. The selectivity of the deprotection reaction is apparent from the DDQ oxidation of the protected tetraol **67** which gives deprotected alcohols **68** and **69** in a ratio 92:8 (reaction 34)[94].



(67)



(92:8)

(68) (69) (34)

Bn: benzyl; MM: methoxymethyl; MPM: 4-methoxybenzyl; DMPM: 3,4-dimethoxybenzyl

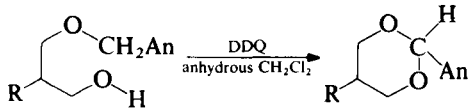
Both *p*-methoxybenzyl ether and 3,4-dimethoxybenzyl ether deprotection are finding extensive use in the synthesis of natural products[95–97].*

(The oxidation of 2,6-dimethoxybenzyl esters by DDQ also has been described as a deprotection method[98]. However, the formulae shown in Ref. 98 actually show 2,4-dimethoxybenzyl esters of carboxylic acids to undergo oxidative deprotection.)

2. *Oxidative acetalization of 1,2- and 1,3-diols*

In agreement with the ionic mechanism for the DDQ oxidation of methoxy-substituted benzyl ethers (cf. reaction 33), intramolecular nucleophilic attack by hydroxyl groups results in the formation of *p*-methoxybenzal acetals **71** (reaction 35)[99]. The DDQ oxidation of ethers **70** proceeds smoothly in anhydrous methylene chloride, and the reaction has also been extended to 3,4-dimethoxybenzyl ethers[99].

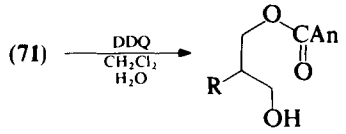
The absence of water is of critical importance for the formation of acetals **71** in high yields, as they may undergo further benzylic oxidation by DDQ to give 'deprotected' hydroxy-substituted esters **72** (reaction 36)[99].



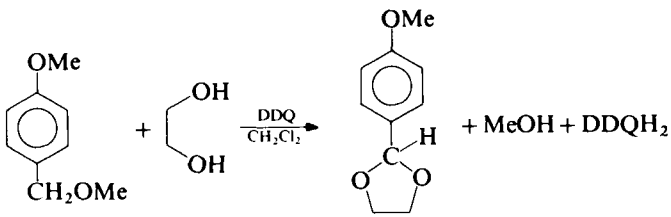
(70) (71) (35)

* Added in proof: Several interesting examples of selective deprotection by DDQ oxidation in the synthesis of macrolides have been reported since the completion of this manuscript: Y. Oikawa, T. Tanaka and O. Yonemitsu, *Tetrahedron Lett.*, **27**, 3647 (1986); T. Tanaka, Y. Oikawa, T. Hamada and O. Yonemitsu, *Tetrahedron Lett.*, **27**, 3651 (1986); N. Nakajima, T. Hamada, T. Tanaka, Y. Oikawa and O. Yonemitsu, *J. Am. Chem. Soc.*, **108**, 4645 (1986).

Interestingly, the protection of 1,2- and 1,3-diols by *p*-methoxybenzal acetalization can be accomplished by DDQ oxidation of *p*-methoxybenzyl methyl ether (**73**) in the presence of an appropriate 1,2- or 1,3-diol which reacts as a nucleophile (reaction 37)[100].



(72) (36)



(73) (74) (75) (37)

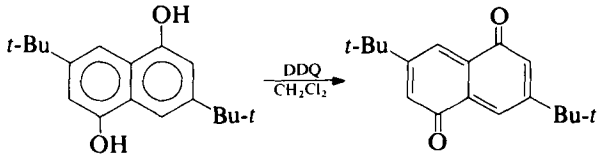
As the reaction does not require acid catalysis, the resulting acetals **75** do not undergo the stereochemical equilibration by which thermodynamically controlled mixtures of isomers are formed. This 'kinetic acetalization' of 1,2- and 1,3-diols by DDQ oxidation of *p*-methoxybenzyl methyl ether (**73**) is of considerable interest for the synthesis of chiral compounds[101] and may even be applied in those cases where conventional acid-catalyzed acetalization fails.

V. DEHYDROGENATION OF AROMATIC HYDROXY AND AMINO COMPOUNDS

A. Oxidation of Monohydric and Dihydric Phenols

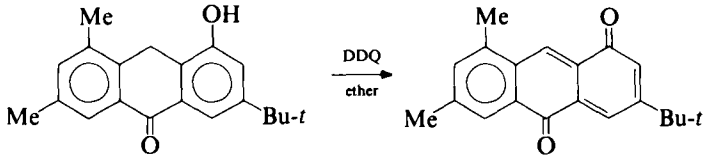
High-potential quinones continue to find application as convenient oxidants for catechols and hydroquinones. A recent detailed study of the kinetics of oxidation of triazoliothiohydroquinones by 1,4-benzoquinones reveals deuterium isotope effects of ca. 3–6, and the results are in agreement with an apparent hydride transfer mechanism[102]. It is conceivable that the overall two-electron oxidation consists of two sequential one-electron transfers from the hydroquinone to the quinone. However, as the first step would lead to two semiquinones of drastically different redox potentials, the second step is expected to be so fast as to preclude kinetic detection of one-electron transfer products.

For preparative oxidations of catechols, hydroquinones, or related aromatic dihydroxy compounds, both DDQ and *o*-chloranil are the reagents of choice. Thus, DDQ in methylene chloride at 20°C has been used in the synthesis of benzoquinone-bridged porphyrins from the corresponding hydroquinones[103]. Likewise, oxidation of the di-*t*-butyl-substituted 1,5-dihydroxynaphthalene **76** with DDQ in methylene chloride under nitrogen gives the 1,5-naphthoquinone **77** in excellent yield (reaction 38)[104].



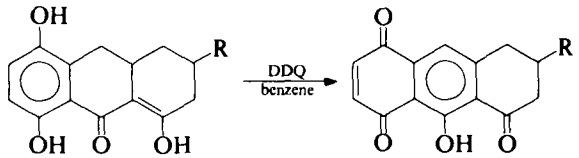
(76) (77) (38)

As for the oxidation of 1,10-dihydroxy-substituted anthracenes (or their keto forms), appropriate substitution by alkyl groups is a prerequisite for the stability of the 1,10-anthraquinone system with respect to reaction with water and subsequent dehydrogenation, which ultimately leads to hydroxy-substituted 9,10-anthraquinones. Thus, 3-*t*-butyl-5,8-dimethyl-1,10-anthraquinone (**79**) was obtained by oxidation of the hydroxyanthrone **78** with DDQ in dry ether at $-5°C$ (reaction 39)[105]. The course of the dehydrogenation of 1,4,9,10-tetrahydroxy-substituted anthracenes can be governed by the choice of the quinone. For example, DDQ oxidation may give rise to the 9,10-anthraquinone, while oxidation by *o*-chloranil can lead to the 1,4-anthraquinone[106]. *o*-Chloranil also is used for the oxidation of catechols to give the corresponding *o*-quinones (cf. Ref. 1, p. 384) in remarkably high yields[107].



(78) (79) (39)

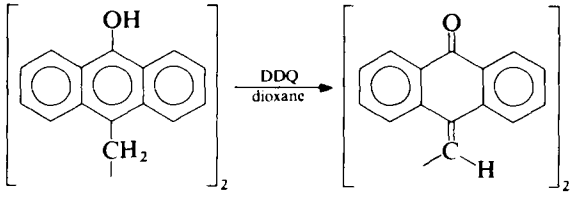
The selective oxidation of the hydroquinone system in compound **80**, and concomitant partial aromatization to give the naphthoquinone derivative **81** was accomplished by oxidation with two molar equivalents of DDQ in benzene at room temperature (reaction 40)[108].



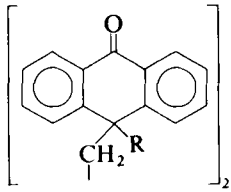
(80) (81) (40)

R = CH=CHCH$_3$

The course of the oxidation of hydroxy-substituted anthracenes can be governed by the nature of the solvent which affects the position of the keto–enol equilibrium. Thus, DDQ oxidation of the dihydroxy-substituted dianthrylethane **82** in refluxing dioxane gives the stilbenequinone **83** (reaction 41), but the reaction of the keto-tautomer **84** with DDQ in refluxing chloroform containing ethanol affords the diethoxy derivative **85**[109]. The formation of **85** is indicative of a carbocationic intermediate which has been trapped by ethanol.



(82) (83) (41)

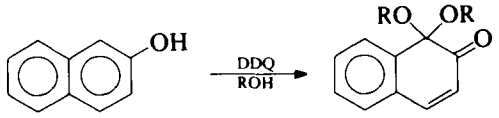


(41)

(**84**; R = H)
(**85**; R = ethoxy)

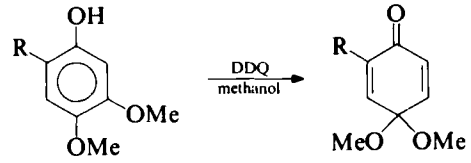
The reaction of 2-naphthol (**86**) with DDQ in solvents such as methanol, ethylene glycol, and 2,2-dimethylpropane-1,3-diol results in the formation of *o*-quinone ketals **87** by way of oxidative nucleophilic substitution (reaction 42)[110,111]. *p*-Quinone ketals **89** are formed in similar fashion by DDQ oxidation of hydroquinone monoalkyl ethers **88** in methanol solution containing catalytic amounts of *p*-nitrophenol (reaction 43)[112]. (The reaction is of synthetic interest insofar as it complements other means of oxidative ketalization, such as the oxidation of phenols with thallium(III) nitrate.) Analogous *p*-naphthoquinone dimethyl ketals have been obtained by DDQ oxidation in methanol in the absence of *p*-nitrophenol[113]. Presumably, DDQ itself may act as a catalyst by virtue of its Lewis acid properties.

The reaction of substituted 1- and 2-naphthols with either DDQ or *o*-chloranil gives rise to a variety of coupling products whose formation may be rationalized by one-electron transfer processes. Thus, oxidation of *o*-methyl-substituted naphthols leads to spiro-compounds via intermediate *o*-quinone methides[114,115]. The straightforward dehydrogenation by DDQ of bis(2-hydroxy-1-naphthyl)methanes results in the formation of spiro-quinol ethers by carbon–oxygen coupling[116,117]. In a recent detailed study, the oxidation of dinaphthol methane **90** was found to give *cis*- and *trans*-isomeric spiro-quinol ethers whose formation has been rationalized by the involvement of the 2,3-dichloro-5,6-dicyanohydroquinone ether **91** (reaction 44)[117].



(42)

(**86**) (**87**)



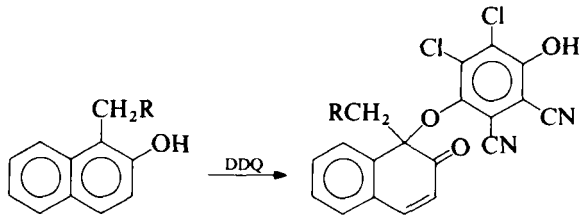
e.g. R = allyl

(43)

(**88**) (**89**)

The oxidation of 2-hydroxystilbenes with DDQ may lead to either benzofuran structures by way of intramolecular coupling, or to benzopyrans derived from intermolecular carbon–oxygen coupling to give flavones[119].* DDQ oxidation of prenylated hydroxy-substituted isoflavones results in the formation of cyclodehydrogenation pro-

* Added in proof: 2'-Hydroxychalcones upon dehydrogenation with DDQ in dioxane have recently been reported to undergo cyclization to flavanones, flavones and aurones: K. Imafuku, M. Honda and J. F. W. McOmie, *Synthesis*, 199 (1987).



(44)

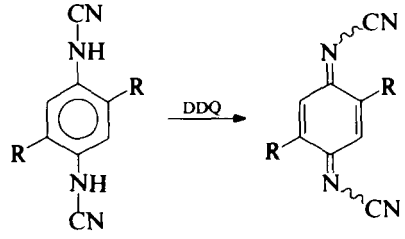
(90) (91)

R = 2-hydroxynaphthyl

molecular carbon–oxygen coupling to give flavones[119]. DDQ oxidation of prenylated hydroxy-substituted isoflavones results in the formation cyclodehydrogenation products[120]. Oxidation of 4-hydroxy-3-methoxyphenylpropan-2-one by DDQ in dioxane gives mainly a polymer linked through the benzylic position[88]. In the case of 2-cinnamyl-4,5-methylenedioxyphenol, DDQ oxidation in acetone or ether solution was found to give a crystalline *o*-quinone methide[121].

B. Dehydrogenation of Aromatic Amino Compounds

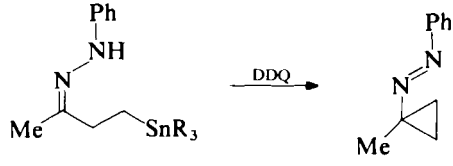
The oxidation of sterically hindered *p*-methyl-substituted anilines resulting in benzylic oxidation has been discussed in Section IV. C. Two novel quinone oxidations of aromatic amino compounds were reported recently. The oxidation of dicyano-substituted *p*-phenylenediamines **92** by DDQ in refluxing benzene gives *N,N'*-dicyanoquinonediimines **93** (reaction 45)[122]. DDQ oxidation failed in the case of the dichloro derivative (**92**, R = Cl) whose oxidation potential exceeds that of DDQ.



(45)

(92) (93)

An interesting oxidation by DDQ involving hydrogen abstraction from the nitrogen of stannyl-substituted hydrazone **94** was found to give azocyclopropane **95** in 88% yield (reaction 46). The reaction proceeds rapidly at −20°C in methylene chloride, and is suggested to occur by a radical mechanism[123].



(46)

(94) (95)

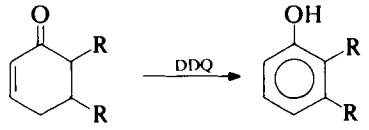
R = *n*-butyl

VI. OXIDATION OF CYCLIC KETONES, ENOLS AND SILYL ENOL ETHERS

A. Dehydrogenation of Cyclic Ketones and Their Silyl Enol Ethers

Saturated cyclic ketones are difficult to dehydrogenate with quinones under normal conditions, but the reaction can be catalyzed by acids which enhance formation of the corresponding enols (cf. Ref. 1, pp. 352, 354). Certain derivatives of cyclohexanone have recently been found to give the corresponding cyclohexenones by oxidation with DDQ in dry HCl-saturated dioxane, though chloro-enones also are formed in substantial yields[124]. More conveniently, the dehydrogenation of cyclic ketones can be carried out with DDQ in benzene solution in the presence of a catalytic amount of *p*-toluenesulfonic acid[125].

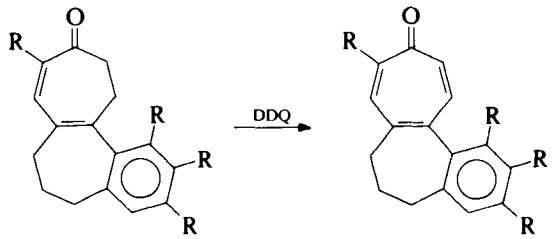
Cyclohexenone **96** upon treatment with DDQ smoothly aromatizes in refluxing dioxane to give phenol **97** in 80% yield (reaction 47)[126]. Conceivably, the dehydrogenation of **96** is facilitated by naphthyl substitution. Attempts to convert 4-acetyl-4-methylcyclohexenone into the corresponding 2,5-cyclohexadienone by dehydrogenation with DDQ in refluxing benzene were unsuccessful. Instead, the reaction afforded (after 11 days!) a modest yield of 4-methylphenyl acetate[127]. Acyl migration was also observed in the DDQ oxidation of a bicyclic enone (Wieland–Miescher ketone)[127].



(96) (97) (47)

R = 1-naphthyl

The reaction of DDQ with the tricyclic compound **98** in refluxing benzene is interesting because formation of the tropolone system **99** (reaction 48) is favored over the structurally possible benzylic dehydrogenation[128].



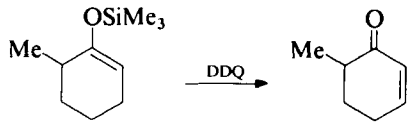
(98) (99) (48)

R = methoxy

If cyclic ketones are first converted into their enol acetates, dehydrogenation by high-potential quinones will then lead to the formation of the acetate of the corresponding linearly conjugated dienol. Numerous acetates of hydroxy-substituted aromatic hydrocarbons have been prepared in that fashion by oxidation with either *o*-chloranil or DDQ[129–131].

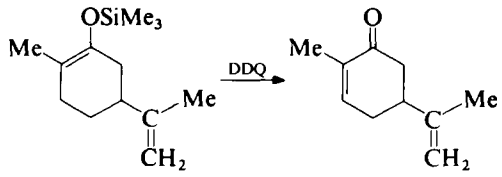
A significant improvement of the dehydrogenative conversion of cyclic ketones into the corresponding cyclic enones consists in the two-electron oxidation of silyl enol

ethers[132,133]. These oxidations with molar equivalents of DDQ generally proceed smoothly in benzene at room temperature. In some cases, oxidations are carried out with small excess of DDQ in the presence of 2,4,6-collidine, which may suppress hydrolysis of the silyl enol ether. Cyclohexenone has been prepared in 60% yield from 1-trimethylsiloxycyclohexene by oxidation with DDQ (but not with chloranil)[133]. DDQ oxidation of 1-methoxycyclohexene, by contrast, gives anisole. The DDQ oxidation of silyl enol ethers has been utilized in key steps (reactions 49 and 50) of the synthesis of carvone (**103**)[134] and for the synthesis of heterocyclic enones[135,136]. As the rate of dehydrosilylation exceeds that of straightforward dehydrogenation, the oxidation of silyl enol ether moieties with high-potential quinones proceeds selectively[137]. The mechanism of dehydrosilylation has not been studied in detail, but the reaction most likely proceeds stepwise[132,133] and parallels the dehydrosilylation of hydroaromatic compounds discussed in Section III. B.



(49)

(**100**) (**101**)

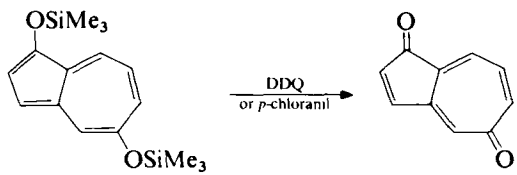


(50)

(**102**) (**103**)

Trimethylsilyl enol ethers also may be dehydrosilylated to give enones by oxidation with Pd(II) acetate in acetonitrile in the presence of *p*-benzoquinone[138–140]. As these oxidations proceed smoothly in the absence of *p*-benzoquinone if equimolar amounts of Pd(II) acetate are used, *p*-benzoquinone obviously only serves to oxidize reduced Pd(II) acetate (cf. also Section VIII).

Interestingly, bis(trimethylsilyl) ethers of hydroquinones also undergo oxidative desilylation by high-potential quinones. This reaction has been applied in the synthesis of various quinones of azulenes, as exemplified by the conversion of silyl derivative **104** into azuloquinone **105** (reaction 51)[141,142].



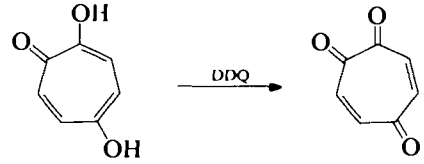
(51)

(**104**) (**105**)

B. Oxidation of Stable Enols and Enolized 1,3-Dicarbonyl Compounds

Enols and dienediols can be oxidized by quinones in a fashion which, in principle, is analogous to the oxidation of phenols and catechols or hydroquinones (cf. Ref. 1, p. 357).

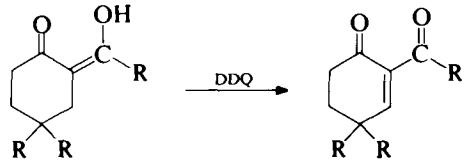
For example, the dihydroxy tropolone **106** upon oxidation with DDQ in methanol at room temperature is converted into tropoquinone **107** (reaction 52)[143,144].



(52)

(106) **(107)**

The dehydrogenation of numerous enolized 2-acyl-substituted cyclohexanones by DDQ has recently been investigated[145]. Oxidation of enolized acylcyclohexanones **108** with one molar equivalent of DDQ in dioxane at room temperature was found to proceed rapidly and gave acyl ketones **109** in generally good yields (reaction 53). DDQ oxidation of enolized 2-acetyl-4,4-dimethylcyclohexanone (**108**, R = Me) does give the 2-acetylcyclohexenone **109** (R = Me) in 67% yield, but the reaction is very much slower than in the case of the formyl derivatives, and requires the presence of a catalytic amount of acetic acid[145].

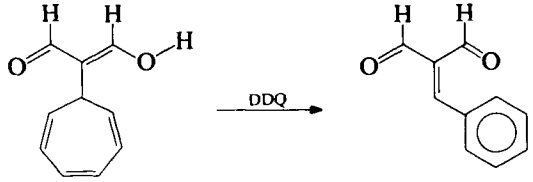


(53)

(108) **(109)**

e.g. R = H
R = Me

Quite recently, the enol of (cycloheptatrienyl)malonaldehyde (**110**) was found to undergo a remarkable skeletal rearrangement upon oxidation with DDQ (and also with silver oxide). Rather than giving (cycloheptatrienylidene)malonaldehyde, the reaction of DDQ with **110** in methylene chloride at −10°C afforded benzylidenemalonaldehyde (**111**) in 94% yield (reaction 54)[146]. (The mechanism of the oxidative ring contraction has not been investigated.)



(54)

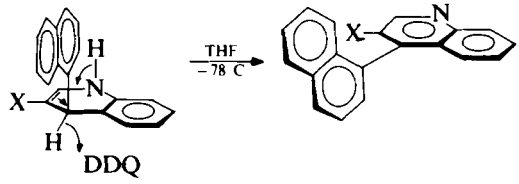
(110) **(111)**

VII. DEHYDROGENATION OF HETEROCYCLIC COMPOUNDS

A. Nitrogen Heterocycles

The DDQ oxidation of enantiomerically pure naphthyl-substituted 1,4-dihydroquinoline derivatives described recently[147] represents a significant example of quinone dehydrogenation insofar as it has provided unequivocal experimental evidence for the

intramolecular transfer of a central chiral element to an axial chiral element. Dehydrogenation of the *R*-enantiomer **112** with DDQ in THF at −78°C results in the formation of the *R*-enantiomeric naphthylquinoline **113** (reaction 55). The correspondingly substituted *S*-enantiomer was obtained by DDQ oxidation in THF at −78°C of the *S*-enantiomeric dihydroquinoline[147].

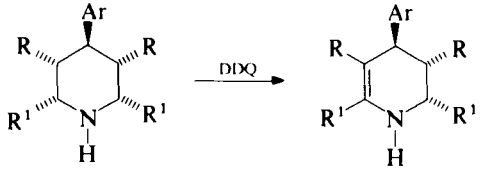


(55)

(112) **(113)**

e.g. X = CHO

Less stringent temperature control is usually required in straightforward dehydrogenations of various nitrogen heterocycles. For example, the oxidation of the piperidine derivative **114** with DDQ in refluxing benzene proceeds selectively and gives the 1,2,3,4-tetrahydropyridine **115** (reaction 56)[148]. Similarly, phthalazines and quinazolines are obtained from their dihydro precursors by oxidation with DDQ in refluxing dioxane[149] and pyrrolines are converted into pyrroles by DDQ oxidation in benzene at 70°C[150].



(56)

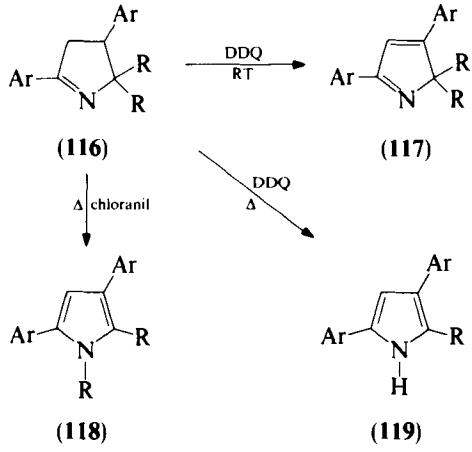
(114) **(115)**

Ar = *o*-tolyl
R = methoxycarbonyl
R^1 = Me

However, proper choice of the reaction temperature was recently found to be of critical importance in the quinone dehydrogenation of 3,4-dihydro-2*H*-pyrroles **116**[151]. Oxidation with DDQ in benzene at room temperature gives the expected 2*H*-pyrrole **117**, whereas oxidation in boiling benzene results in the loss of one carboethoxy group and the formation of the 1*H*-pyrrole **119**. Oxidation of **116** with chloranil in boiling xylene, by contrast, gives the 1*H*-pyrrole **118** whose formation involves a thermally induced acyl migration from carbon to nitrogen (cf. Scheme I; reactions 57–59)[151].

Quinone dehydrogenation of heterocyclic compounds containing more than one hetero atom usually proceeds in straightforward fashion.* 4-Aryl- and 4-phenacyl-substituted 3,4-dihydropyrimidinones are readily converted to the fully conjugated pyrimidinones by DDQ in benzene at room temperature[152,153]. The dehydrogenation of 4,5-dihydropyridazines with DDQ in boiling anhydrous benzene in the absence of oxygen affords pyrazines[154]. Δ^2-Isoxazolines are converted into isoxazoles by dehydrogenation with excess DDQ in refluxing benzene in excellent yield[155], but dehydrogenation of oxazolines under similar conditions appears to be more difficult[76].

* Added in proof: In a recent report on the synthesis of a heteroaromatic 14π system, both *p*-chloranil and DDQ have been used as dehydrogenation agents, but only the application of DDQ was found to lead to the aromatic ring system: R. Neidlein and L. Tadesse, *Chem. Ber.*, **119**, 3862 (1986).

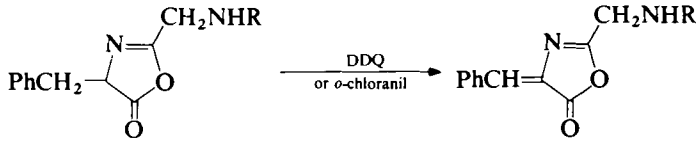


(57–59)

Ar = phenyl; R = ethoxycarbonyl

SCHEME 1

During recent years, high-potential quinones such as *o*-chloranil and DDQ have found useful synthetic application in the dehydrogenation of dipeptide azlactones **120**[156]. These oxidations usually proceed at room temperature in dioxane or 1,2-dimethoxyethane in the presence of a base such as pyridine, imidazole, or collidine, but yields of dehydropeptides **121** are only close to 50% (reaction 60) (cf. also Ref. 136, dealing with the formation of dehydrolactones by way of dehydrosilylation as discussed in Section VI. A).



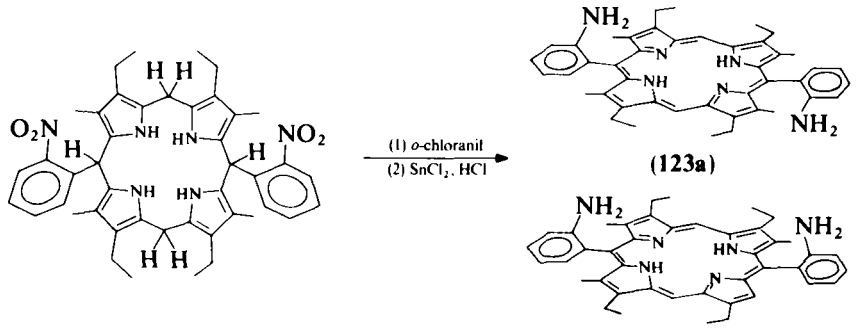
(60)

(120) (121)

For the conversion of porphyrinogens into porphyrins (cf. Ref. 1, p. 408), high-potential quinones are most convenient oxidizing agents. For example, the dehydrogenation of the *o*-nitrophenyl-substituted compound **122** by *o*-chloranil in THF proceeds at room temperature, and subsequent reduction of the nitro group affords atropisomeric *meso*-diphenylporphyrins **123a** and **123b** (reaction 61)[157]. Similarly, the dehydrogenation of porphyrinogens has been carried out with DDQ at room temperature in degassed acetonitrile/ether[158].

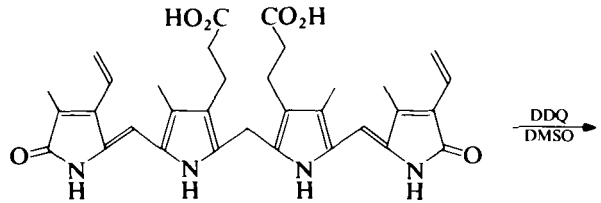
The formation of biliverdin (**125**) by quinone dehydrogenation of bilirubin (**124**) has been studied in detail, and DDQ in DMSO at room temperature was found to be the reagent of choice (reaction 62)[159]. Low concentration of bilirubin and excess of DDQ are necessary in order to avoid concomitant formation of biliverdin isomers. (The order of mixing of the reagents is also of importance.) It has been suggested that the oxidation of bilirubin by DDQ proceeds by one-electron transfer steps involving resonance-stabilized tetrapyrrole radicals[159, 160].

In the dehydrogenation of nitrogen heterocycles by DDQ, the formation of colored charge-transfer complexes is frequently noticeable and, for that reason, DDQ may be used

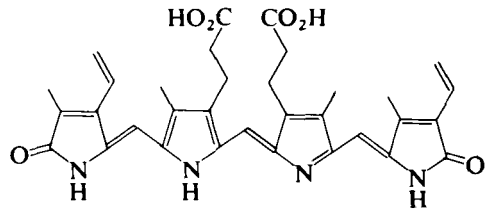


(122) (123a) (123b)

(61)



(124)

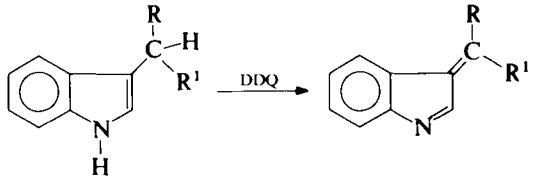


(125) (62)

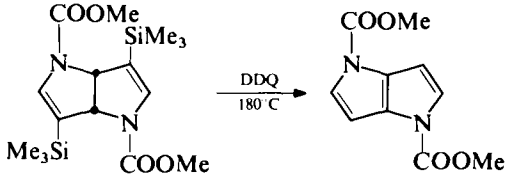
as a spray reagent for chromatographic detection[161]. The stability of these colored complexes depends largely on the nature of the solvent. For example, indole and DDQ form a crystalline charge-transfer complex which is stable in methylene chloride. In methanol or dioxane, by contrast, indole reacts with DDQ to give a substitution product whose formation can be rationalized by nucleophilic attack on the quinone[162]. Upon heating, the substitution product eliminates HCN and gives an indoloquinone. Similar substitution–elimination reactions have previously been noted in the reaction of *p*-chloranil with quinindine derivatives (cf. Ref. 1, pp. 408–409).

As for 3-alkyl-substituted indoles **126**, their reaction with DDQ results in straightforward dehydrogenation and gives 3-alkylidene-3*H*-indoles **127** (reaction 63)[162]. The oxidation of an *N*-acetyl-dihydropyridylindole with DDQ in ethyl acetate was found to result in an acyl group transfer[162].

Finally, the reaction of DDQ with the bis-trimethylsilyl-substituted nitrogen heterocycle **128** in dichlorobenzene at 180°C deserves mention because the product **129** seemingly is not formed by dehydrogenation but by twofold oxidative desilylation (reaction 64)[163].



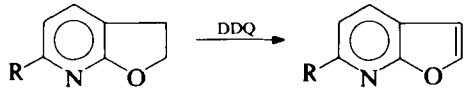
(126) (127) (63)



(128) (129) (64)

B. Oxygen and Sulfur Heterocycles

In most examples of oxygen heterocycles undergoing dehydrogenation by high-potential quinones, substrate activation is provided by the presence of aromatic substituents. However, reaction times may vary greatly, and yields of dehydrogenation products frequently are modest (cf. Ref. 1, p. 409). Oxidation of dihydrobenzofurans with DDQ in refluxing dioxane gives benzofurans in yields of 46–70%[164, 165]. Remarkably, in the case of dihydrofuropyridines **130**, their oxidation with two molar equivalents of DDQ in refluxing dioxane affords furopyridines **131** only when the pyridine ring is substituted (reaction 65)[166].



(130) (131) (65)

As for six-membered oxygen heterocycles, DDQ in benzene has been used for the dehydrogenation of chroman moieties in alkaloids[167]; (cf. also Ref. 168). However, attempted dehydrogenation of a 4-chlorochroman with DDQ in benzene at room temperature was found to result instead in dehydrochlorination[169].

The dehydrogenation of heterocyclic ketones by quinones generally proceeds smoothly. For example, the conversion of flavanones into flavones by DDQ oxidation in refluxing dioxane proceeds in high yields in far shorter reaction times than in refluxing benzene[170]. Oxidation by DDQ in benzene was found to be the method of choice for the dehydrogenation of benzothienoannelated dihydrocoumarins (dihydrothiacoumestans)[171]. In methanol solution, however, the reaction of high-potential quinones with 3,4-dihydrocoumarins results mainly in the formation of ring-opened products by way of lactone solvolysis[172].

The oxidation of the tetrakis(t-butylthio)-substituted thiophene derivative **132** with chloranil in refluxing acetonitrile was recently reported to give the cyclic trithioanhydride **133** in 92% yield (reaction 66)[173].

(132) (133) (66)

An interesting formation of the thiadiazole system **135** (90% yield) involves the oxidative cyclization of a semithiacarbazone **134** by DDQ in refluxing dioxane (reaction 67)[174].

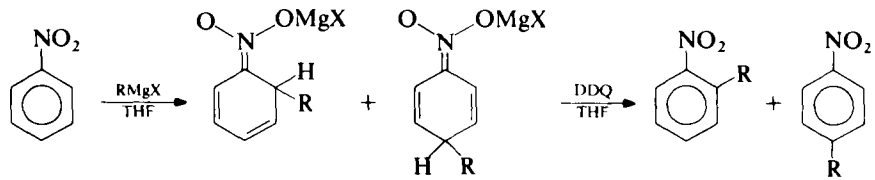
(134) (135) (67)

VIII. OXIDATIONS INVOLVING ORGANOMETALLIC COMPOUNDS

The oxidation of various organometallic compounds by quinones has been discussed in Ref. 1, p. 411. The reaction of ferrocene with DDQ was then described to give rise to ferrocenium cation radical and the hydroquinone anion radical. In a subsequent study, the crystalline 1:1 charge-transfer complex between DDQ and decamethylferrocene has been investigated by X-ray diffraction, and was found to consist of the expected ferrocenium cation radical and the hydroquinone anion (rather than the anion radical)[175]. In the oxidation of nickel(0) complexes by certain *p*-quinones, hydroquinone anion radical formation has been established by ESR spectroscopy[176, 177].

The role of *p*-benzoquinone in the oxidative formation of enones from silyl enol ethers in the presence of palladium(II) chloride has been mentioned in Section VI. *p*-Benzoquinone is also used frequently as oxidant in synthetically interesting palladium-catalyzed reactions of olefins, such as the rearrangement of 1-vinyl-1-cyclobutanols[178], or the Wacker-type oxidative conversion of terminal olefins into methyl ketones[179] (cf. also Ref. 1, p. 345). Likewise, *p*-benzoquinone functions as oxidant in the conversion of cyclohexene into 2-cyclohexenyl acetate which is catalyzed by palladium(II) chloride in acetic acid[180]. Similarly, *p*-benzoquinone is used in the palladium(II) chloride-catalyzed 1,4-diacetoxylation of 1,3-dienes[181–183]. In these and related palladium(II)-catalyzed reactions, benzoquinone acts both as electron acceptor and as ligand for the metal complex.

The oxidation of arylmagnesium halides with quinones gives rise to diaryl compounds (cf. Ref. 1, p. 411). In a novel reaction of considerable synthetic potential, organomagnesium compounds like **136** and **137**, formed by conjugate addition of alkyl-



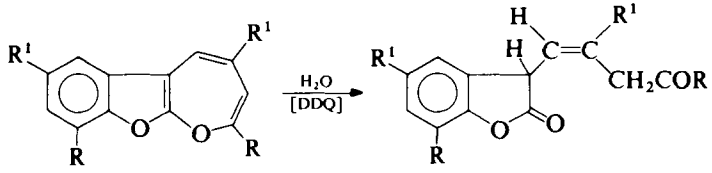
R = methyl; ethyl (136) (137) (138) (139)

(68)

Grignard reagents to nitroarenes, are smoothly oxidized by DDQ in THF at 0°C to give the corresponding alkyl-substituted nitroarenes **138** and **139** in quantitative yields (reaction 68)[184, 185].

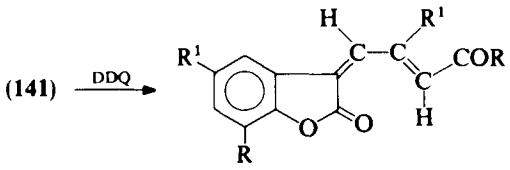
IX. MISCELLANEOUS OXIDATIONS BY DDQ

Among the few quinones commonly used as oxidants and dehydrogenating agents in synthetic organic chemistry, DDQ is unique because of its high oxidation potential and its versatile reactivity. Being an exceptionally strong electron acceptor, DDQ has been found to induce and bring about some remarkable reactions. For example, oxepinobenzofurans **140** are valence isomers of 2,2'-diphenoquinones (previously believed to have a spiroquinol ether structure; cf. Ref. 1, p. 390) which in the presence of water are oxidized by DDQ to give benzofuranylidene derivatives such as **142**[186]. It has been suggested that DDQ catalyzes the addition of water to compound **140** (reaction 69) so as to give the intermediate **141** which is then dehydrogenated (reaction 70).



(69)

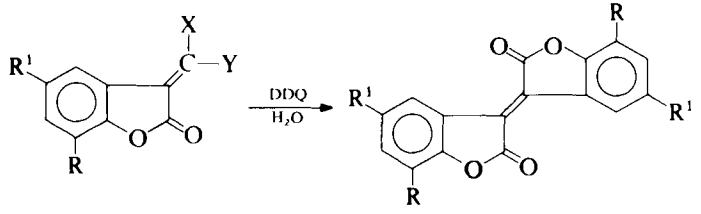
(140) **(141)**



(70)

(142)

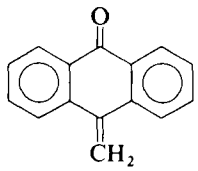
Upon oxidation with two molar equivalents of DDQ in the presence of water, benzofuranylidene derivatives **143** are converted into isoxindigos **144** in high yield[186]. The mechanism of this remarkable reaction is also believed to involve an initial benzylic oxidation of an intermediate which is formed by DDQ-catalyzed addition of water to the exocyclic carbon–carbon double bond of compound **143**[186].



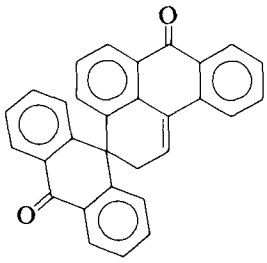
(71)

(143) **(144)**

Methyleneanthrone (**145**) was found to react with DDQ in refluxing dioxane to give a tetramer whose formation conceivably involves the oxidative dimerization of the intermediate dimer **146**[187].



(145)



(146)

Diazomethane reacts with DDQ by elimination of nitrogen and addition of methylene to the cyano-substituted carbon–carbon double bond to give a bicycloheptene derivative[188]. The reaction of DDQ with diphenyldiazomethane (**147**) in the presence of alcohols results in the reduction of DDQ and gives acetals **148** in excellent yields (reaction 72)[188–190]. Macrocyclic acetals have been prepared by this method from α, ω-diols[191]. It has been suggested that acetals **148** are formed via an intermediate DDQ:diazonium betaine.

(147) (148) (72)

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CHAPTER **24**

Azulene quinones

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I. INTRODUCTION

From the earliest days of organic chemistry, quinones have figured prominently in the chemistry of aromatic compounds[1]. Most quinones can be viewed as derivatives of benzene, naphthalene, or some higher benzenoid aromatic hydrocarbon, and collectively these constitute the class of benzenoid quinones. The family of aromatic hydrocarbons, however, is no longer confined solely to benzenoid molecules; the last three decades have witnessed an almost explosive growth in the field of non-benzenoid aromatics, i.e. compounds that display aromatic character despite the absence of benzene rings[2-5]. Quinones of these hydrocarbons constitute the class of non-benzenoid quinones. This volume on *The Chemistry of the Quinonoid Compounds* and its predecessor[6] both contain chapters devoted to non-benzenoid quinones. The present chapter focuses on an important subset of this family, the azulene quinones. In keeping with the traditional naming of benzoquinones and naphthoquinones, the quinones of azulene have sometimes been referred to as azuloquinones.

Foremost among the non-benzenoid aromatic hydrocarbons, azulene has attracted considerable attention for many years[7,8]. Numerous pathways to azulenes have been reported since the first synthesis of the parent hydrocarbon in 1937 by Plattner and Pfau[9]; however, work on the corresponding quinones did not begin for almost 40 years. As of 1974, when the first volume of this book was published, no quinones of azulene had yet been reported.

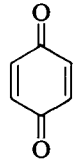
Figure 1 shows the numbering system for azulene and the eleven possible azulene quinones that can be constructed with two carbonyl groups and four double bonds (Kekulé quinones). Azulene quinones related to *meta*-benzoquinone (non-Kekulé quinones) are discussed briefly in Section V. For ease of reference, abbreviated names rather than arbitrary numbers will be used for the azulene quinones throughout this chapter. Thus, for example, 1,2-azuloquinone will be referred to simply as 1,2-AQ (see Figure 1).

In the present context, azulene quinones are defined as the fully unsaturated derivatives of the various isomeric bicyclo[5.3.0]decadiones. Benzenoid quinones bearing an aromatic azulene nucleus, either fused to one side or attached as a pendant group, fall outside the scope of this chapter. Polycyclic molecules with an embedded azuloquinone and quinomethides have also been excluded.

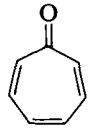
II. THEORY

It has long been recognized that the special effects of cyclic conjugation normally associated with a ring of p orbitals are virtually absent in quinones such as *para*-benzoquinone (**1**) as a result of the cross-conjugating interruptions introduced by two carbonyl groups in the cycle[1,10]. Odd-membered ring annulenones with only a single carbonyl group, such as tropone (**2**) and cyclopentadienone (**3**), on the other hand, retain a measure of aromatic or antiaromatic character that depends on the number of π electrons in the olefinic bonds[11]. The presence of these two annulenones in many of the azulene quinones provides a basis for preliminary predictions about the properties of these novel compounds.

Tropone (**2**) is a stable, planar molecule that exhibits little tendency to dimerize, polymerize, or decompose under ordinary laboratory conditions[12,13]. By contrast, **3** is



(1)



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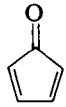
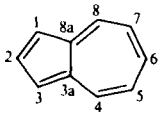
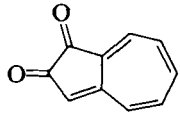


(3)

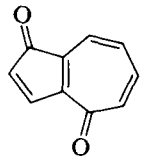
exceedingly unstable and dimerizes rapidly even at very low temperatures[14,15]. Accordingly, one might expect those azulene quinones that contain a tropone but no cyclopentadienone (1,5-AQ and 1,7-AQ) to be more stable than those that contain a cyclopentadienone but no tropone (2,4-AQ and 2,6-AQ) and those that contain both subunits (1,4-AQ, 1,6-AQ and 1,8-AQ) to be intermediate in stability. The term 'stability',



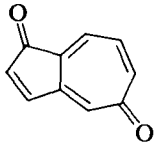
Azulene



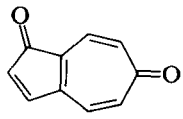
1,2-AQ



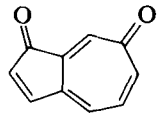
1,4-AQ



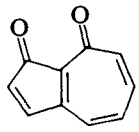
1,5-AQ



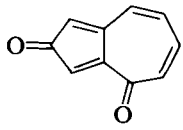
1,6-AQ



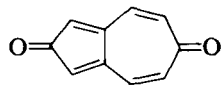
1,7-AQ



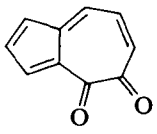
1,8-AQ



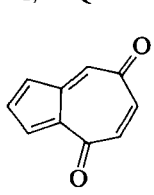
2,4-AQ



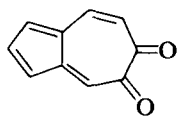
2,6-AQ



4,5-AQ



4,7-AQ



5,6-AQ

FIGURE 1. Azulene and the eleven possible Kekulé quinones thereof

as used here, refers to kinetic stability toward bimolecular destruction, i.e. isolability, which may or may not correlate with thermodynamic stability or heats of formation.

This rudimentary analysis suggests which azulene quinones might be better than others as targets for synthesis (1,5-AQ and 1,7-AQ), but it leaves many questions unanswered. The relative ordering of quinones *within* each set above, e.g. 1,4-AQ vs. 1,6-AQ vs. 1,8-AQ, cannot be predicted easily 'by inspection', nor can this treatment handle the isomers in which both carbonyl groups reside in the same ring (1,2-AQ, 4,5-AQ, 4,7-AQ and 5,6-AQ).

Unsatisfied with such a crude and incomplete theoretical prognosis, the author of this chapter persuaded chemists from several other laboratories in the late 1970s to carry out detailed molecular orbital calculations on the azulene quinones in a systematic manner. The resulting international collaborative effort produced comprehensive sets of data from both Hückel and MINDO/3 calculations[16], selected portions of which are collected in Table 1. In several instances, predictions based on the Hückel and semi-empirical MINDO/3 results were reinforced by single point *ab initio* STO-3G calculations on the MINDO/3-optimized geometries of representative compounds. PPP π-electron calculations of electronic transitions were employed for predictions on the UV–VIS spectra and colors of the azulene quinones. Calibration of the various theoretical methods was achieved by extending them to include calculations on the isomeric naphthoquinones for which experimental data could be obtained from the literature.

TABLE 1. Selected calculated energies of azulene quinones[16]

	ΔH_f	π-DE	E-LUMO	
Compound	MINDO/3 kcal mol^{-1}	MINDO/3 kcal mol^{-1}	MINDO/3 eV	Hückel β
1,2-AQ	−0.4	+12.7	−0.70	−0.24
1,4-AQ	−0.8	+9.1	−1.03	−0.11
1,5-AQ	−6.4	+14.7	−0.63	−0.24
1,6-AQ	−0.6	+8.9	−1.17	−0.11
1,7-AQ	−5.3	+13.6	−0.66	−0.23
1,8-AQ	−0.6	+8.9	−0.94	−0.11
2,4-AQ	+4.7	+3.6	−1.16	−0.05
2,6-AQ	+4.7	+3.6	−1.28	−0.05
4,5-AQ	+7.0	+5.3	−0.95	−0.03
4,7-AQ	+7.2	+1.1	−1.16	−0.04
5,6-AQ	+9.5	+2.8	−0.96	−0.04

When these calculations and predictions were first published in 1980[16], very little experimental work on the azulene quinones had been reported. Since that time, however, certain indices of reactivity have emerged as more reliable than others[17]. The following discussion covers only those aspects of the theoretical treatment that have withstood preliminary testing and still appear valid.

First it should be noted that the reactions most common in quinone chemistry, e.g. Michael additions, Diels–Alder cycloadditions, charge-transfer complex formation, reduction, etc., all involve the interaction of external electrons with the lowest unoccupied molecular orbital (LUMO) of the quinone. As a general rule, the lower the energy of the LUMO (E-LUMO), the greater the susceptibility of the quinone to all of these reactions[18,19]. Thus, the E-LUMO should represent a fairly universal index of reactivity for quinones[20].

Within the family of azulene quinones, the order of chemical stability (isolability) of the various isomers can be expected to follow the E-LUMOs, those with the lowest-lying

LUMOs being the most easily destroyed by bimolecular processes and, therefore, the most difficult to isolate. Those isomers with high-lying LUMOs, on the other hand, ought to enjoy somewhat greater kinetic stability. In accord with this theoretical viewpoint, the three azulene quinones with relatively high E-LUMOs (1,2-AQ, 1,5-AQ and 1,7-AQ) have now all been synthesized and isolated in crystalline form (*vida infra*). By contrast, all attempts to prepare isomers with lower E-LUMOs or derivatives thereof under ordinary laboratory conditions have failed to yield monomeric quinones, although their existence as fleeting intermediates has been established in several cases. The E-LUMO, therefore, does indeed seem to provide a good index for isolability, at least among the azulene quinones. It was gratifying that the calculations affirmed the qualitative theoretical predictions, which took into account only the presence or absence of certain annulenone subunits.

The first three isomers to be isolated (1,2-AQ, 1,5-AQ and 1,7-AQ) not only have the highest E-LUMOs, they also have the largest π-delocalization energies. The π-DEs listed in Table 1 were obtained simply by taking the difference between the MINDO/3 calculated heats of formation (ΔH_f) and the ΔH_f^{ref} values obtained from the additivity scheme of Dewar and coworkers[21,22], as extended by Gleicher and coworkers[10], and correcting for ring strain[16]. The calculated heats of formation clearly reveal the thermodynamic stabilizing effect of a tropone moiety (cf. 1,4-AQ vs. 2,4-AQ: $\Delta\Delta H_f = 5.5$ kcal mol^{-1}) and the destabilizing effect of a cyclopentadienone moiety (cf. 1,4-AQ vs 1,5-AQ: $\Delta\Delta H_f = 5.6$ kcal mol^{-1}).

Electronic $\pi\pi^*$ transition energies for some of the azulene quinones were calculated by the PPP π-electron method (see Table 2)[16]. MINDO/3 geometries served as initial input, and a π-bond order/length criterion was used to reoptimize geometries. Confidence in the results derives from the reasonable agreement observed between the experimental absorption spectra of 1,2- and 1,4-naphthoquinone and those calculated by this method. Although these calculations do not include the long-wavelength $n\pi^*$ transitions, it was predicted[16] that the colors of the azulene quinones should range from yellow (1,5-AQ and 1,7-AQ) to purple (e.g., 4,7-AQ) to blue-green (e.g., 2,6-AQ). As discussed in Section IV.B, these predictions have proven surprisingly accurate.

TABLE 2. Calculated electronic absorption spectra (PPP)[16]

Compound	$\lambda_{max}(f)$
1,2-AQ	527 (0.04), 397 (0.40), 309 (0.13)
1,5-AQ	371 (0.38), 347 (0.00), 341 (0.14)
1,6-AQ	549 (0.05), 332 (0.07), 321 (0.23)
1,7-AQ	394 (0.31), 349 (0.19), 314 (0.03)
2,4-AQ	596 (0.07), 367 (0.22), 316 (0.08)
2,6-AQ	597 (0.02), 350 (0.60), 304 (0.03)
4,7-AQ	529 (0.05), 344 (0.13), 304 (0.62)

In the chemical reactions of any single azulene quinone, competing pathways involving attack at different sites must be considered. These will be important, for example, in all Michael additions and cycloaddition reactions. Houk and coworkers have shown[23] that LUMO coefficients can be used as reliable indicators for the site of nucleophilic attack (Michael addition) on quinones, and electron-rich cycloaddends will also attack a quinone where the LUMO coefficients are large. Table 3 gives the calculated LUMO coefficients for all atoms in all eleven of the Kekulé azulene quinones[16].

Incorporation of donor substituents on an electron-deficient azulene quinone framework should raise the LUMO energy, with the greatest effect resulting from substitution on the position with the largest π-LUMO coefficient[19]. Since those same positions are

TABLE 3. Calculated LUMO coefficients of azulene quinones (MINDO/3)[16]

Compound	C(1)	C(2)	C(3)	C(3a)	C(4)	C(5)	C(6)	C(7)	C(8)	C(8a)	O(1)	O(2)
1,2-AQ	0.28	0.22	0.15	−0.25	−0.38	0.33	0.34	−0.36	−0.22	0.33	−0.27	−0.21
1,4-AQ	0.29	0.29	−0.28	−0.48	−0.12	−0.25	−0.02	−0.36	0.17	0.44	−0.28	−0.11
1,5-AQ	0.33	0.25	−0.33	−0.23	0.08	0.28	0.34	−0.35	−0.28	0.36	−0.29	−0.24
1,6-AQ	−0.29	−0.31	0.28	0.47	0.13	−0.34	−0.01	0.32	−0.11	−0.44	0.29	0.01
1,7-AQ	0.25	0.37	−0.34	−0.41	0.34	0.34	−0.37	−0.22	0.03	0.12	−0.22	0.19
1,8-AQ	0.28	0.31	−0.25	−0.45	−0.19	0.37	0.38	−0.23	0.08	0.46	−0.28	−0.08
2,4-AQ	0.37	0.30	0.37	−0.27	−0.23	−0.24	0.24	0.28	−0.26	−0.32	−0.30	−0.24
2,6-AQ	0.38	0.30	0.38	−0.31	−0.23	0.25	0.23	0.25	−0.23	−0.31	−0.30	−0.23
4,5-AQ	−0.33	0.27	0.39	−0.27	−0.16	0.12	−0.33	0.24	0.43	−0.33	0.11	0.05
4,7-AQ	0.33	−0.25	−0.42	0.25	0.22	0.23	−0.20	−0.29	−0.38	0.32	−0.22	−0.28
5,6-AQ	−0.42	−0.28	0.34	0.31	−0.43	−0.19	−0.12	−0.24	0.21	0.31	0.13	0.05

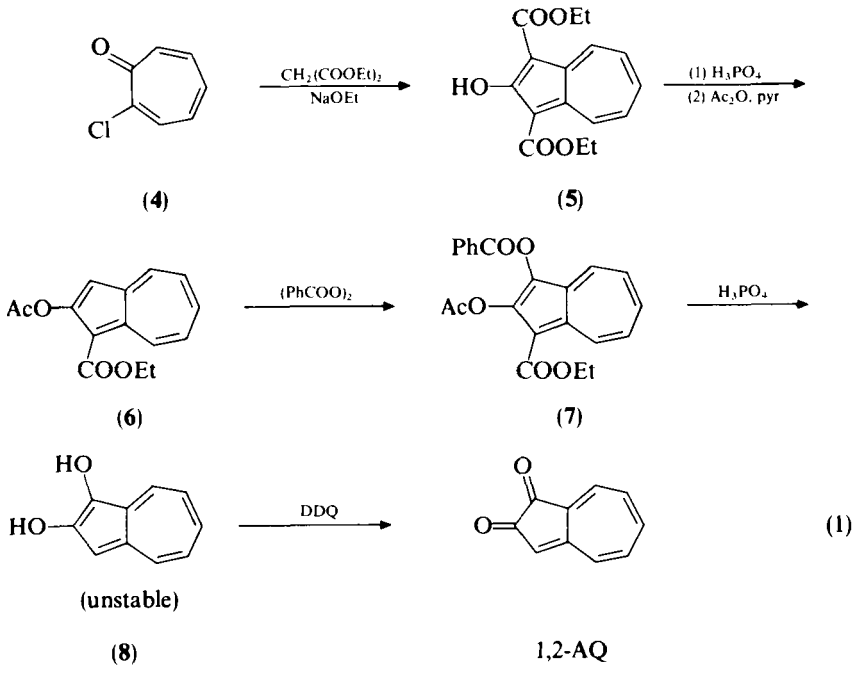
predicted to be the most likely sites for nucleophilic attack, a judicious placement of alkyl groups could impede Michael additions to the quinones not only by raising the LUMO energy but also by simple steric hindrance. The positions at which alkyl substitution should have the most 'stabilizing' effect can be read directly from Table 3. On 2,4-AQ and 2,6-AQ, for example, bulky alkyl groups at the 1- and 3-positions should have the most stabilizing effect.

Throughout the foregoing theoretical treatment, the dominance of the LUMO has been apparent. Other molecular orbitals will also contribute to the overall reactivity of azulene quinones; however, it is not unreasonable to expect the effects of the LUMO to prevail in most circumstances[18,19].

III. SYNTHESIS

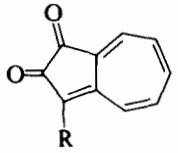
A. 1,2-Azulene Quinone

Morita, Karasawa and Takase reported the first unsubstituted quinone of azulene, the parent 1,2-AQ, in 1980[24]. Their synthesis (equation 1) begins with the preparation of diethyl 2-hydroxyazulene-1,3-dicarboxylate (**5**) from 2-chlorotropone (**4**) according to a procedure developed much earlier under the direction of Professor Nozoe in the same laboratories at Tohoku University. Partial deethoxycarbonylation of **5** and acetylation gives the disubstituted azulene **6**, which, on direct oxygenation with benzoyl peroxide, yields the hydroquinone derivative **7**. Hydrolysis and deethoxycarbonylation then gives the very unstable 1,2-dihydroxyazulene (**8**), which can be oxidized with DDQ to the green



(1)

1,2-quinone. Variations on this synthetic scheme have provided also the 3-ethoxycarbonyl and the 3-cyano derivatives (**9**)[24].

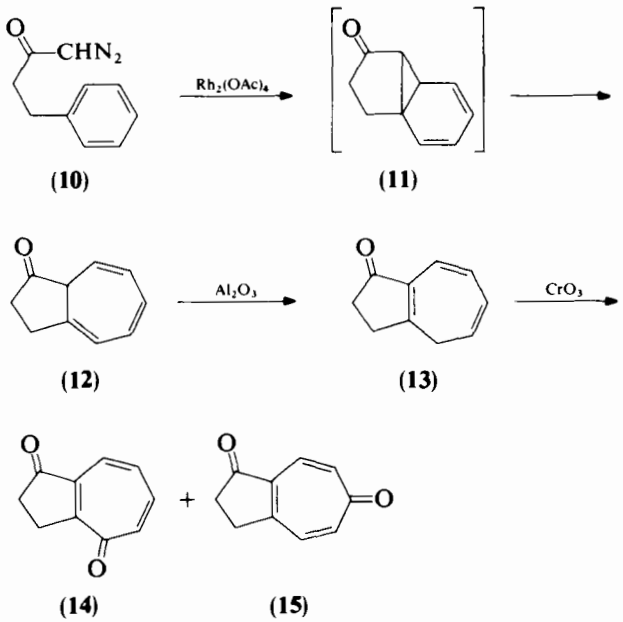


(9, R = COOEt, CN)

B. 1,4-Azulene Quinone

In Reno, a general approach to the synthesis of 1,*n*-AQs has been developed[25,26]. The first step involves intramolecular addition to a benzene ring by the carbene derived from diazoketone **10** (equation 2)[27]. Rhodium acetate is superior to the copper salts formerly used to catalyze the loss of nitrogen in this reaction[28]. Norcaradiene (**11**), the initial product of this cyclization reaction, opens spontaneously to the acid-sensitive bicyclic trienone **12**, which isomerizes to the more stable trienone **13** on exposure to basic alumina. The readily available **13** serves as a common precursor to several of the azulene quinones (*vida infra*).

For the synthesis of 1,4-AQ, **13** was oxidized with chromium trioxide pyridine[25]. This reaction gives the two isomeric tropones **14** and **15** in roughly equal amounts. It should be

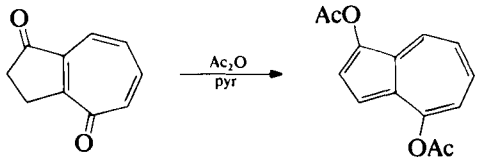


(**10**) (**11**) (**12**) (**13**) (**14**) (**15**) (2)

noted that neither of these tropones exhibits any tendency to tautomerize to the corresponding dihydroxyazulene. Apparently, the aromaticity of azulene does not suffice to overcome the strength of two carbonyl π bonds and any special thermodynamic stability associated with the tropone ring. Such behavior contrasts with that of 1,2-dihydroxyazulene (**8**)[24], which would gain no tropone moiety on tautomerization to a diketone.

Unlike compound **8**, neither **14** nor **15** could be oxidized to the corresponding azulene quinone with DDQ[28]. Conventional methods for introducing a double bond directly into

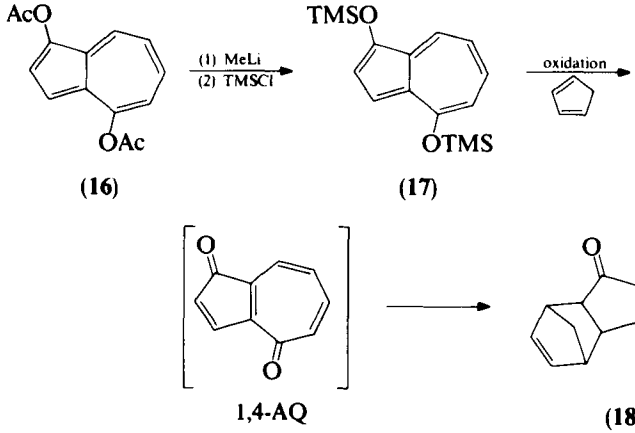
the five-membered ring of these 2,3-dihydroquinones also proved unsatisfactory[25]. Fortunately, the beautiful blue azulene diacetate **16**, a hydroquinone derivative of **14**, could be obtained simply by stirring the tropone with acetic anhydride and pyridine in hot ethyl acetate (equation 3).



(3)

(14) **(16)**

On treatment with an excess of methyllithium in tetrahydrofuran, 1,4-diacetoxyazulene (**16**) yields a blue-green solution of the azulene-1,4-hydroquinone dianion by nucleophilic cleavage of the ester groups. Quenching the reaction mixture with chlorotrimethylsilane then gives the labile bis-trimethylsilyl ether **17**. Subsequent oxidation of **17** in the presence of cyclopentadiene produces 1,4-AQ, which is immediately trapped in a Diels–Alder reaction (equation 4). An *endo* stereochemistry best accounts for the observed coupling

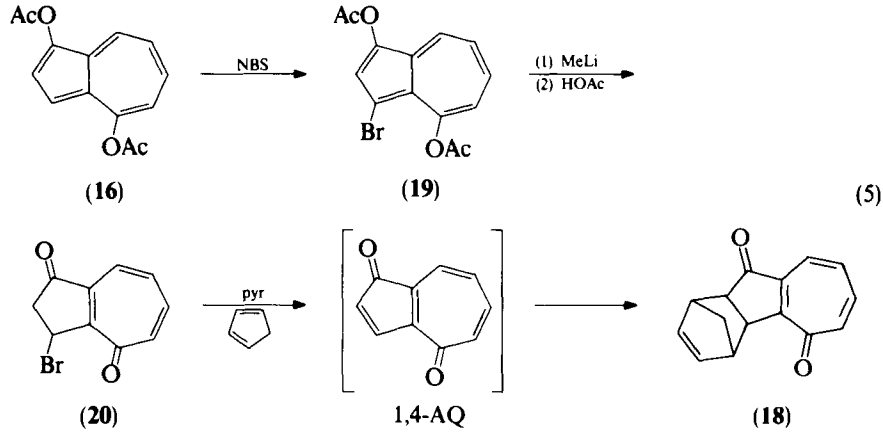


(4)

(16) **(17)** 1,4-AQ **(18)**

constants in the ^{1}H-NMR spectrum of **18**. Omission of the cyclopentadiene from this reaction has not yet permitted isolation of the monomeric quinone; under the conditions explored to date, only higher molecular weight materials are obtained. Useful oxidizing agents for the reaction in equation 4 include pyridinium chlorochromate (PCC) and tetrachloro-*p*-benzoquinone (*p*-chloranil)[25].

An alternative route to 1,4-AQ[25] takes advantage of the well-known susceptibility of azulenes to electrophilic substitution at the α-postition in the smaller ring. Thus, bromination of 1,4-diacetoxyazulene (**16**) with *N*-bromosuccinimide yields the 3-bromo derivative **19**. Cleavage of the ester groups at this stage followed by protonation with acetic acid gives back the tropone ring system, substituted now with a good leaving group β to the carbonyl in the five-membered ring (**20**). Addition of **20** to a solution of pyridine and cyclopentadiene smoothly generates 1,4-AQ, which once again is trapped to produce the Diels–Alder adduct **18** (equation 5).

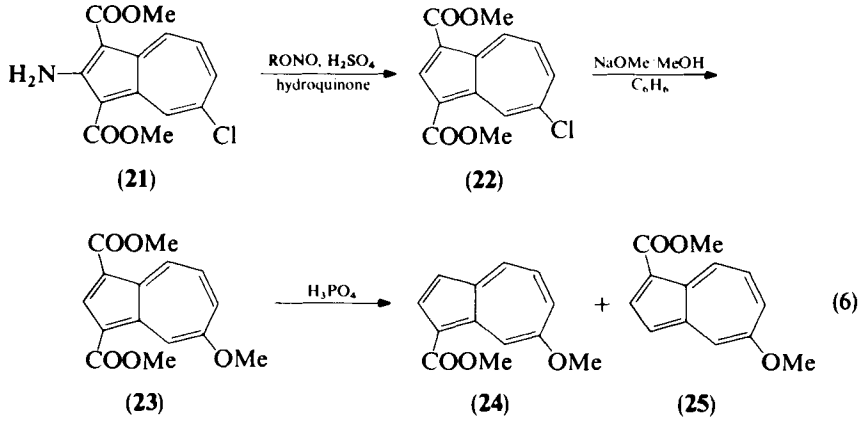


As anticipated from the theoretical considerations presented above, this quinone is too reactive under ordinary laboratory conditions to be isolated.

C. 1,5-Azulene Quinone

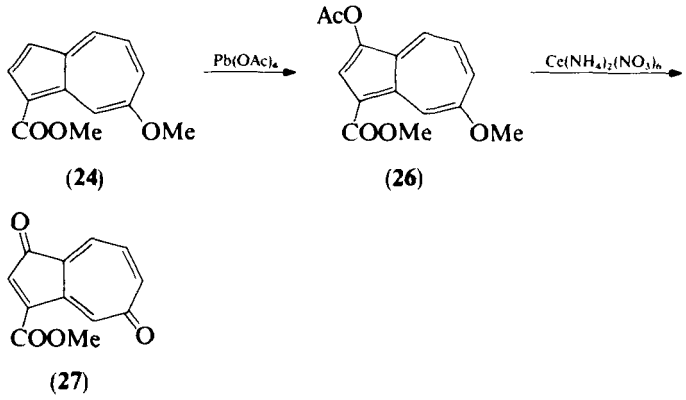
In sharp contrast to the 1,4-quinone of azulene, the 1,5-quinone is quite stable, just as predicted.

The first example of a 1,5-AQ to be prepared was the 3-methoxycarbonyl derivative reported by Morita and coworkers in 1982[29]. Using again the Nozoe method for constructing substituted azulenes from tropolone derivatives, they began by preparing the 5-chloroazulene **21**. Deamination of **21** to **22** occurs smoothly on diazotization with isopentyl nitrite and sulfuric acid in the presence of hydroquinone (equation 6). Heating of **22** with NaOMe–MeOH in anhydrous benzene gives the 5-methoxyazulene **23**. Partial demethoxycarbonylation of diester **23** then gives a mixture (1 : 1) of the monoesters **24** and **25**, which can be separated by column chromatography.



Direct oxygenation of **24** is effected with 3 equivalents of lead tetraacetate in benzene–pyridine–DMSO (equation 7). Subsequent oxidation of the resulting hydro-

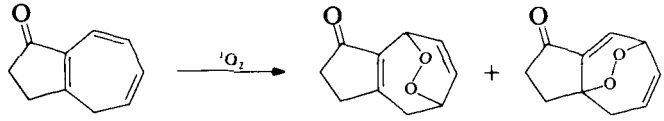
quinone derivative (**26**) with ceric ammonium nitrate gives the corresponding yellow 1,5-quinone **27**.



(24) (26) (27) (7)

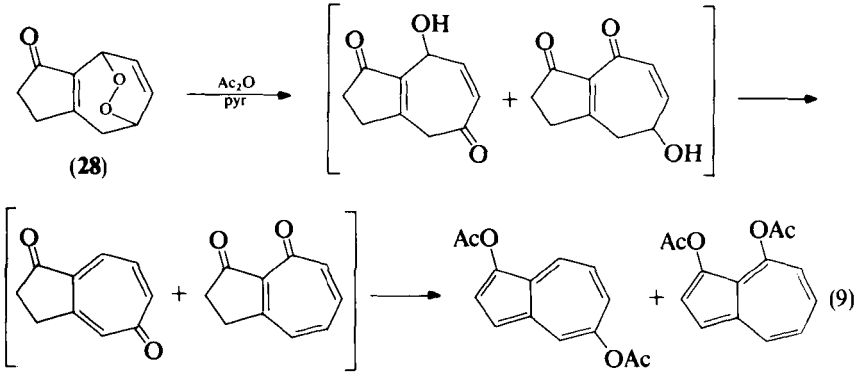
Attempts to extend this route to a synthesis of the parent 1,5-AQ have been thwarted by oxidative coupling at the (no longer blocked) 3-position of the azulene hydroquinone derivatives[30].

The first synthesis of unsubstituted 1,5-AQ was published by Scott and Adams in 1984[26]. They began with the versatile bicyclic trienone **13**, prepared as in equation 2. Photooxygenation of **13** gives the two endoperoxides **28** and **29** in high overall yield, with the former predominating (equation 8). Separation of **28** from **29** can be achieved by



(13) (28) (29) (8)

chromatography, and each endoperoxide can be carried on to a single azulene quinone (**28** to 1,5-AQ; **29** to 1,7-AQ); however, it is far more efficient to carry both isomers through

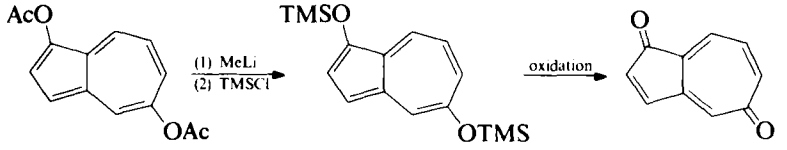


(28) (30) (31) (9)

together and separate the two quinones at the end. For clarity, only the synthesis of 1,5-AQ will be described in this section.

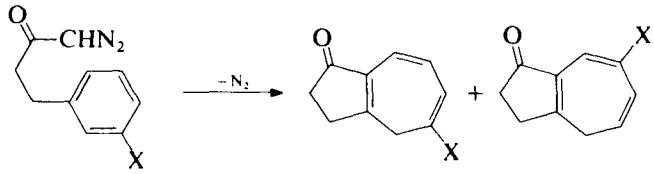
Treatment of endoperoxide **28** with pyridine and acetic anhydride triggers a marvelous cascade of events which continues all the way to the new azulene diacetates **30** and **31**, presumably via the pathway depicted in equation 9. The base-catalyzed isomerization of such singlet oxygen adducts to γ-hydroxy enones has ample precedent[31], and the final conversion of tropone intermediates to diacetoxyazulenes parallels the reaction in equation 3. The 1,8-isomer (**31**) is easily removed by chromatography and has been examined as a potential precursor to 1,8-AQ (*vida infra*).

Cleavage of the two acetoxy groups in **30** with methyllithium, quenching with chlorotrimethylsilane, and oxidizing as before (equation 10, cf. equation 4) gives the parent pale yellow 1,5-AQ; PCC, DDQ and *p*-chloranil have all proven effective for the final oxidation.



(**30**) (**32**) 1,5-AQ (10)

Still other routes to the parent 1,5-AQ have also been explored. Equation 11 illustrates two variations on the intramolecular carbene addition reaction described above (equation 2). Both the *meta*-substituted anisole (**33**)[32, 33] and the acetanilide (**34**)[34] cyclize to mixtures of 1,5- and 1,7-difunctionalized hydroazulenes; however, difficulties in the subsequent transformations of these bicyclic trienones caused both routes to be abandoned.



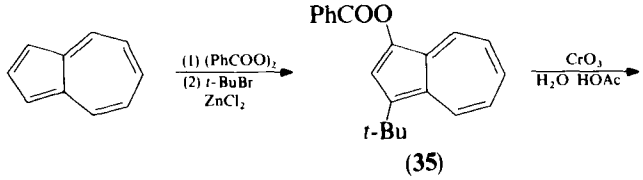
(11)

(**33**, X = OMe)
(**34**, X = NHAc)

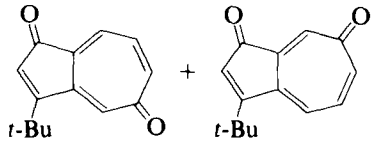
A remarkably short synthesis of 3-*t*-butyl-1,5-AQ, starting from azulene itself, has been developed by Scott and Gingerich (equation 12)[35]. Direct oxygenation of azulene with benzoyl peroxide followed by Friedel–Crafts alkylation with *t*-butyl bromide yields the 1,3-disubstituted azulene **35**. Chromium trioxide oxidation in wet acetic acid then gives the 3-*t*-butyl derivatives of 1,5-AQ and 1,7-AQ (**36** and **37**, respectively), each in about 15% yield.

An independent synthesis (equation 13) was carried out[35] to confirm the structural assignment of **36**. Analogous confirmation was obtained[35] for the structure of **37**.

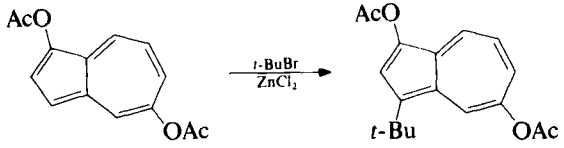
Extension of the route depicted in equation 12 to guaiazulene (**39**) gives guaiazuloquinone (**41**), albeit in low yield (equation 14)[35]. This synthesis was inspired by the discovery of guaiazuloquinone among marine natural products collected deep in the Pacific Ocean (−350 meters) by Scheuer's group in Hawaii[36]. More recently, Nozoe and coworkers have found that autoxidation of guaiazulene (**39**) at 100 °C in *N*,*N*-



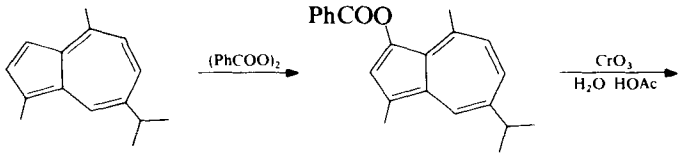
(35)



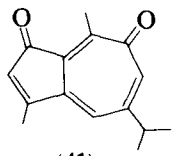
(36) (37) (12)



(30) (38) (13)

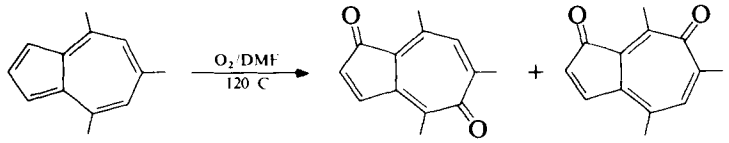


(39) (40)



(41) (14)

dimethylformamide produces guaiazuloquinone (**41**) directly in 1% yield, along with a plethora of other interesting products[37]. Under similar conditions, 4,6,8-trimethylazulene (**42**) gives the corresponding 1,5- and 1,7-AQs (**43** and **44**, respectively), each in 1.5% yield

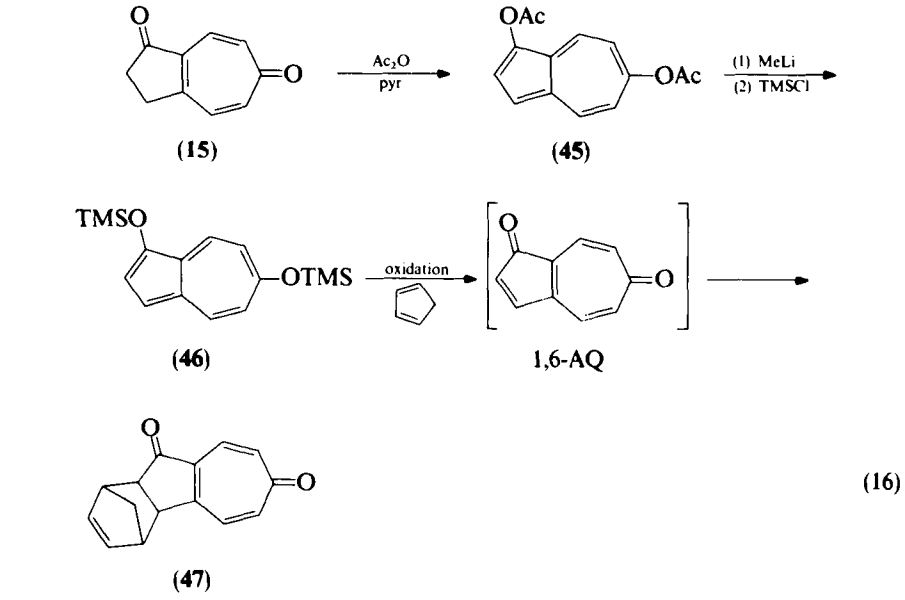


(42) (43) (44) (15)

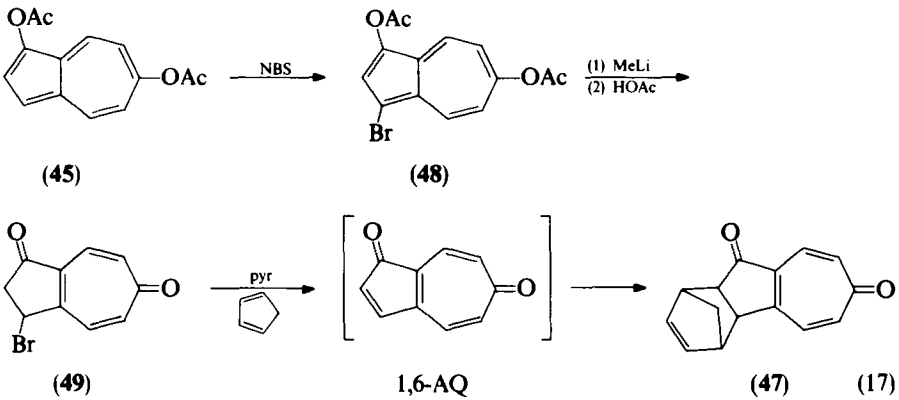
(equation 15)[38]. Somewhat higher yields can be achieved under less drastic conditions of autoxidation, but anodic oxidation shows the greatest promise (60% yield of **41** from **39**)[39].

D. 1,6-Azulene Quinone

The first two syntheses of unsubstituted 1,6-AQ were reported by Scott and coworkers in 1984[25]. Starting from tropone **15**, these routes (equations 16 and 17) employ the same chemistry as that used above to prepare the parent 1,4-AQ. Like the 1,4-AQ, this quinone also is too reactive to be isolated under ordinary laboratory conditions and must be trapped as a fleeting intermediate.

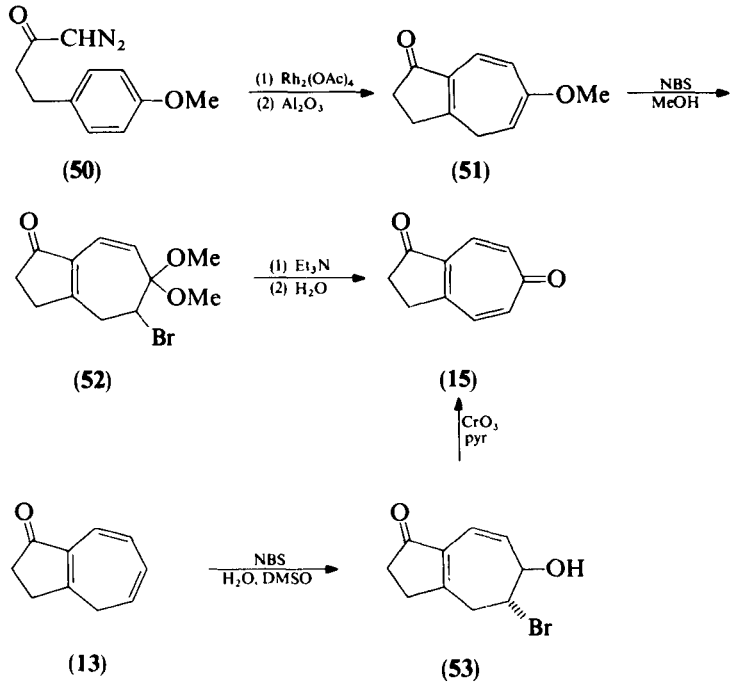


(16)



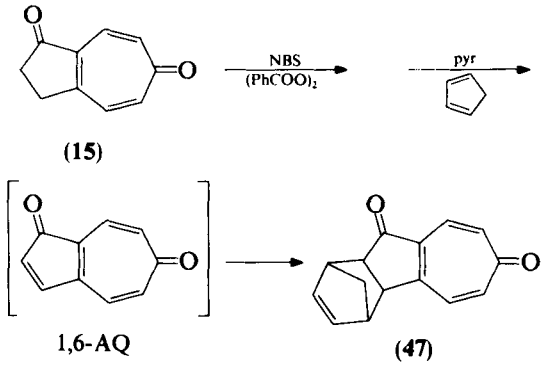
(17)

The development of high-yield routes to tropone **15** (equation 18)[25] have made this precursor to the 1,6-AQ ring system available for extensive additional experimentation. In this connection, it has been found that direct bromination of **15** with NBS and benzoyl



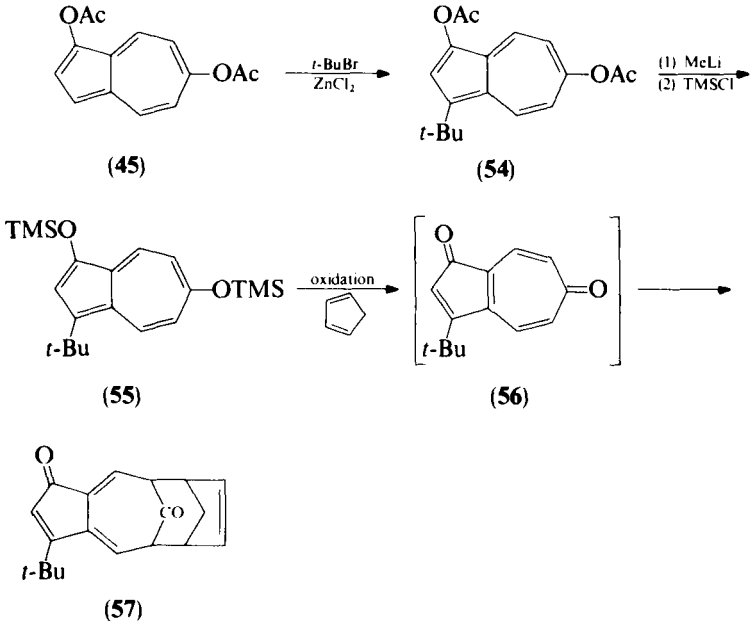
(18)

peroxide in carbon tetrachloride followed by treatment of the crude reaction mixture with excess pyridine and cyclopotentadiene also gives the Diels–Alder adduct **47**, albeit in poor yield (equation 19)[40].



(19)

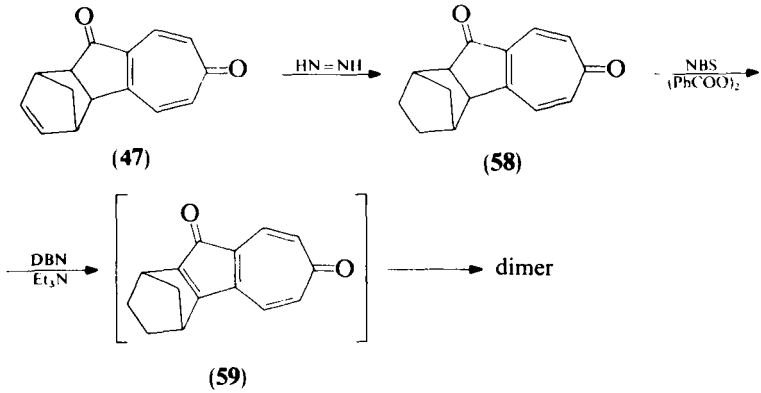
Two sterically hindered derivatives of 1,6-AQ were prepared in the hope that bulky substituents might render the quinones stable enough to survive in monomeric form. The 3-*t*-butyl derivative (**56**), synthesized as in equation 20, does in fact show greatly diminished



(20)

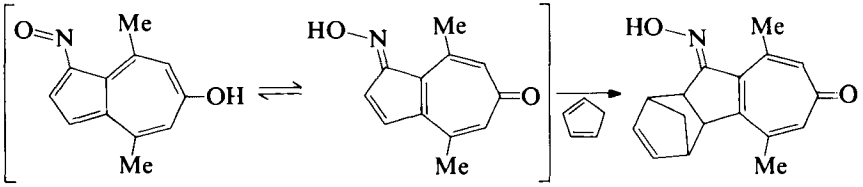
reactivity at the double bond of the cyclopentadienone ring; however, other regions of the molecule remain quite reactive, as evidenced by the efficient trapping of **56** with cyclopentadiene in a [6+4] cycloaddition reaction[40]. Unfortunately, all attempts to isolate the substituted 1,6-AQ **56** have failed.

The 2,3-disubstituted derivative **59**, prepared as in equation 21, likewise proved too reactive to be isolated[40]. In this case, however, a dimer could be obtained when the quinone was generated in the absence of trapping agents. From spectroscopic data, the gross structure of the dimer was determined to be that of a [4+2] cycloadduct formed by addition of the norbornene double bond of one molecule across a diene moiety in the tropone ring of the second molecule[40]. Although some aspects of the structure remain uncertain, it should be noted that this reaction mode simultaneously disrupts the cyclopentadienone rings in both quinones.



(21)

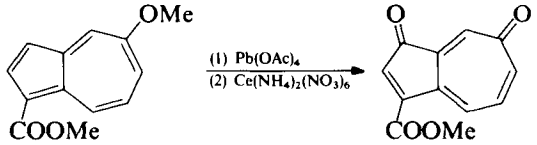
Unpublished experiments from the laboratory of Professor Hafner in Darmstadt[41] have established that compound **60**, the oxime of a 1,6-AQ obtained by nitrosation of 4,8-dimethyl-6-hydroxyazulene, behaves very much like the parent 1,6-AQ (equation 22).



(60) (22)

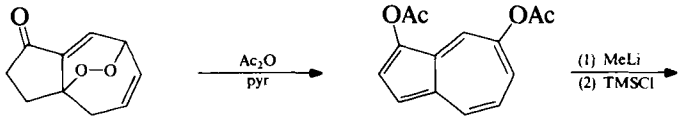
E. 1,7-Azulene Quinone

To date, all syntheses of 1,7-AQs, except that of guaiazuloquinone (equation 14), have been carried out in conjunction with syntheses of the isomeric 1,5-AQs. The 3-methoxycarbonyl derivative **61** was the first 1,7-AQ to be reported[29]. Precursor **25**, prepared as in equation 6, is converted into the quinone by the reactions indicated in equation 23 (cf. equation 7). Attempts to extend this route to a synthesis of the parent 1,7-AQ have not been successful[30].

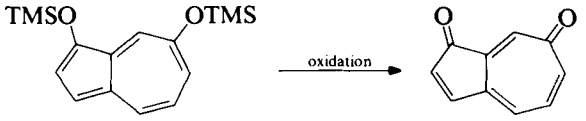


(25) **(61)** (23)

The first synthesis of the unsubstituted lemon yellow 1,7-AQ is shown in equation 24 (cf. equations 9 and 10)[26]. Preparation of endoperoxide **29** was described in equation 8.



(29) **(62)**



(63) 1,7-AQ (24)

Alternative routes to the parent 1,7-AQ have been explored, e.g. equation 11, but none has yet been carried to completion[32-34]. The 3-*t*-butyl derivative (**37**)[35] and the 4,6,8-trimethyl derivative (**44**)[38], on the other hand, have both been obtained from readily available azulenes by oxidative methods (equations 12 and 15, respectively).

F. 1,8-Azulene Quinone

This quinone is expected to exhibit reactivity comparable to that of the unstable 1,4-AQ and 1,6-AQ. Since these two quinones can be generated from diacetoxy azulenes via the corresponding bis-trimethylsilyl ethers and trapped by cyclopentadiene (equations 4 and 16), analogous reactions have been attempted[42] starting with the 1,8-diacetoxy azulene **31** (from equation 9). Cleavage of the two acetoxy groups with methyllithium and silylation of the resulting dianion with chlorotrimethylsilane proceed smoothly without any complication from *peri*-interactions of the 1,8-difunctionality (equation 25). Unfortunately, no Diels–Alder adduct could be isolated when bis-trimethylsilyl ether **64** was oxidized under a variety of conditions in the presence of cyclopentadiene; only polymers were obtained[42].

(31) (64) (25)

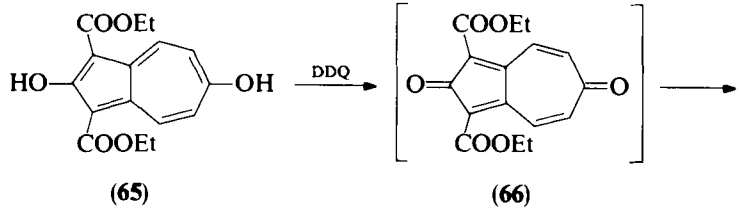
Other trapping agents, such as 1-hexyne, likewise failed to give any products arising from reactions with 1,8-AQ[43]. Thus, there is still no evidence that 1,8-AQ has ever been generated even as a transient intermediate.

G. 2,4-Azulene Quinone

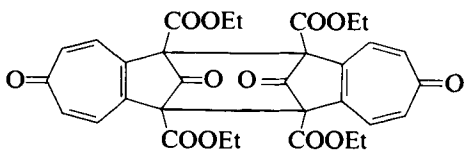
No work on the synthesis of 2,4-AQ has been reported.

H. 2,6-Azulene Quinone

The very first (bicyclic) azulene quinone ever prepared, the 1,3-diethoxycarbonyl derivative of 2,6-AQ (**66**), was reported by Morita and Takase in 1977[44]. Oxidation of the corresponding hydroquinone (**65**) with DDQ gives the substituted 2,6-AQ, which dimerizes in a [4+4] manner under the reaction conditions (equation 26). A *syn* stereochemistry has been assigned to **67** on the basis of a dipole moment measurement.



(65) (66)



(67) (26)

Regeneration of the monomeric quinone and interception by an external trapping agent has been achieved by heating a xylene solution of dimer **67** under reflux with dimethyl acetylenedicarboxylate[44].

The synthesis of unsubstituted 2,6-dihydroxyazulene was also published by Morita and coworkers in 1977, but attempted oxidations of this hydroquinone to the parent 2,6-AQ have not been reported[45a].

I. 4,5-Azulene Quinone

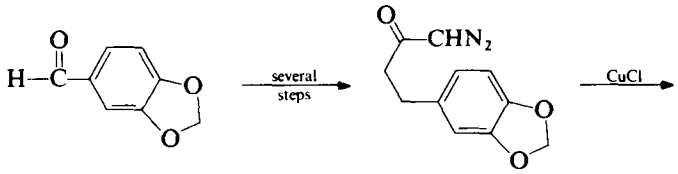
No work on the synthesis of 4,5-AQ has been reported.

J. 4,7-Azulene Quinone

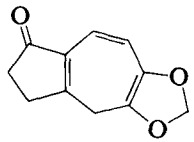
No work on the synthesis of 4,7-AQ has been reported.

K. 5,6-Azulene Quinone

Preliminary work on a potential synthesis of 5,6-AQ (equation 27) has appeared in an MS thesis from Reno[32].



(68) (69)



(70) (27)

IV. PROPERTIES

A. Chemical Properties

1. Isolability

As of mid-1987, only three of the eleven possible quinones of azulene had been isolated in monomeric form, viz. 1,2-AQ, 1,5-AQ and 1,7-AQ (see Sections III.A, III.C and III.E). Several derivatives of each of these were also parpared and characterized in the early 1980s. The parent 1,4-AQ and 1,6-AQ have been trapped as fleeting intermediates, but both have proven too reactive to be isolated under ordinary laboratory conditions (see Sections III.B and III.D). Substituted derivatives of 1,6-AQ and 2,6-AQ have likewise been generated and trapped, although none has been stable enough to be isolated (see Sections III.D and III.H). The chemical stabilities (isolability) of 1,8-AQ, 2,4-AQ, 4,5-AQ, 4,7-AQ and 5,6-AQ remain unknown.

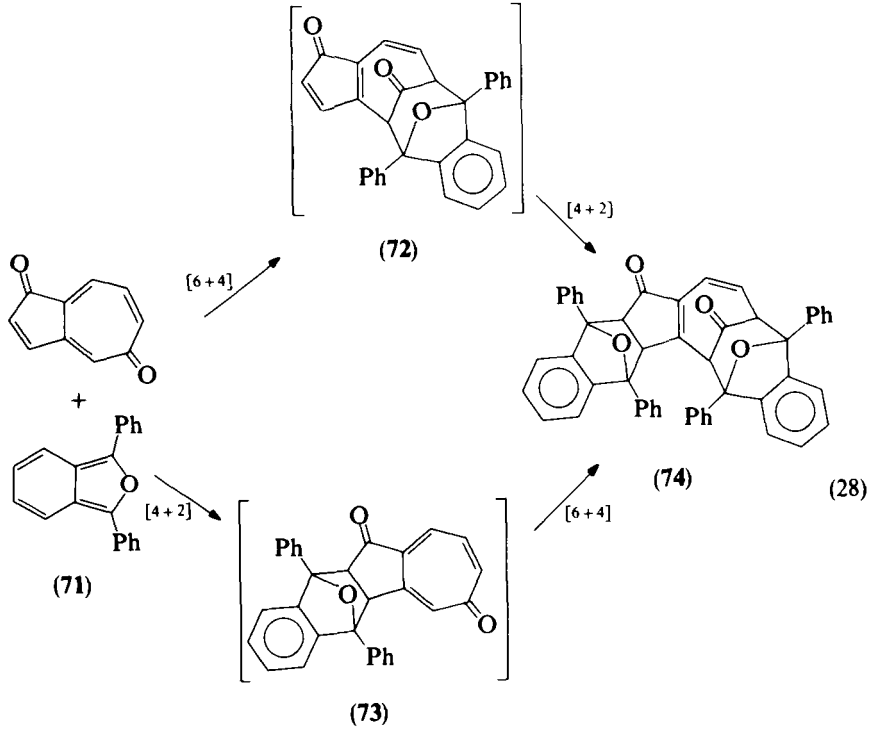
This property of the azulene quinones correlates with both the MINDO/3 π-delocalization energies and the calculated E-LUMOs (Table 1). The three isolable quinones have significantly more positive π-DEs and significantly higher-lying LUMOs than the other eight isomers, and it would be reasonable to expect difficulty in isolating any of the remaining unsubstituted quinones of azulene.

2. *Cycloadditions*

Both 1,4-AQ and 1,6-AQ exhibit high reactivity as dienophiles in the Diels–Alder reaction[25]. From the chemistry described in Sections III.B and III.D, it is evident that the cycloadditions of these quinones with cyclopentadiene at 0 °C must occur quite rapidly in order to compete so successfully with the alternative biomolecular processes that preclude their isolation. A [4 + 2] cycloaddition on the 2,3-double bond in the cyclopentadienone ring is the preferred mode of reaction, unless that site is blocked, in which case a [6 + 4] cycloaddition on the tropone ring occurs (equation 20).

In sharp contrast to these elusive quinones, both 1,5-AQ and 1,7-AQ can be recovered unchanged after mixing with cyclopentadiene[26]. These results are in complete accord with the theoretical calculations[16], which indicate that the LUMOs of 1,5-AQ and 1,7-AQ lie considerably higher in energy than those of 1,4-AQ and 1,6-AQ (Table 1); dienophilicity toward cyclopentadiene should be greatest for those quinones with the lowest-lying LUMOs[18, 19].

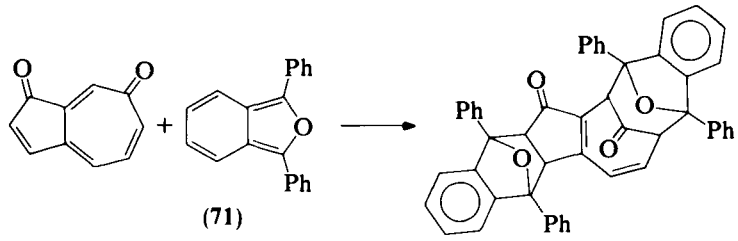
When a 1:1 mixture of 1,5-AQ and *p*-benzoquinone is treated with 1 equivalent of cyclopentadiene, only the *p*-benzoquinone reacts[45b]. This direct competition experiment demonstrates unequivocally the low dienophilicity of 1,5-AQ relative to that of *p*-



(71) (72) (73) (74) (28)

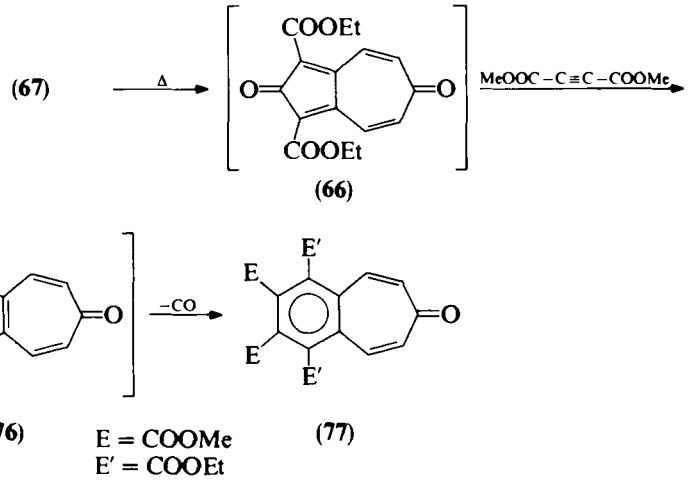
benzoquinone. The analogous experiment with 1,7-AQ and *p*-benzoquinone gave the same result[43b]. The outcome of these experiments was anticipated on the basis of the theoretical calculations, which predict that the LUMOs of 1,5-AQ and 1,7-AQ should lie even higher in energy than that of *p*-benzoquinone[16].

With diphenylisobenzofuran (DPIBF, **71**), a more reactive diene, 1,5-AQ combines to give a 2:1 adduct (equation 28)[26]. Whether the [6 + 4] cycloaddition preceeds or follows the [4 + 2] addition has not been established, since the 1:1 adduct (either **72** or **73**) reacts more rapidly with DPIBF than does the original quinone. An equimolar mixture of the two cycloaddends gives only the 2:1 adduct **74** and recovered quinone. The 1,7-quinone reacts similarly (equation 29)[26].



(71) (75) (29)

The substituted 2,6-AQ **66** (generated by cracking of the dimer, **67**, in refluxing xylene) combines with dimethyl acetylenedicarboxylate in a Diels–Alder fashion to give intermediate **76**, which spontaneously decarbonylates to yield the benzotropone **77**[44] (equation 30).

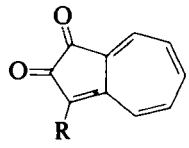


(30)

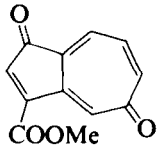
No cycloaddition chemistry has been reported for 1,2-AQ.

3. Reduction

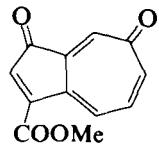
Polarographic half-wave potentials for derivatives of 1,2-AQ, 1,5-AQ and 1,7-AQ as well as those for the parent 1,2-AQ are summarized in Figure 2[24, 29]. On an absolute scale,



R	E_1	E_2
H	−0.55	−1.17
COOEt	−0.40	−1.00
CN	−0.34	−0.88



$E_1 = -0.54$



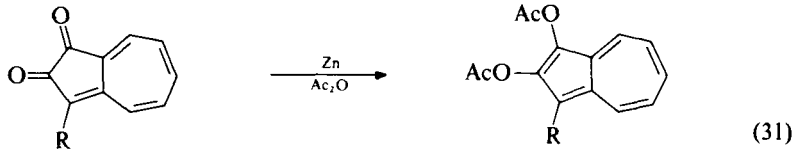
$E_1 = -0.50$

FIGURE 2. Polarographic half-wave potentials (V vs. SCE)[24, 29] in anhydrous MeCN at 25 °C, dropping-mercury electrode, supporting electrolyte 0.1 M Et_4NClO_4

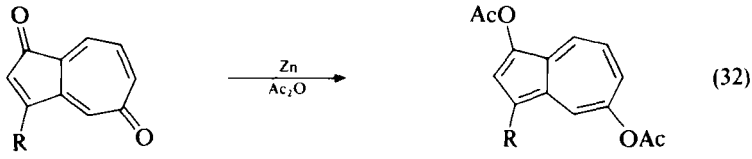
these data should be compared with the half-wave potentials for *p*-benzoquinone ($E_{1/2}$ = −0.51, −1.14 V)[46]. As predicted by theory, the parent 1,2-AQ is slightly less easily reduced than *p*-benzoquinone. A comparison of the data for the three alkoxycarbonyl derivatives further reveals that the ease of reduction of the isolable azulene quinone ring systems (1,5-AQ < 1,7-AQ < 1,2-AQ) correlates well with the calculated LUMO energies (Table 1).

As expected, electron-withdrawing groups increase the potential while donor substituents lower the potential. Nozoe and coworkers have measured the potentials for several trialkylazulene quinones[39] (V vs. SCE in anhydrous MeCN at 25°C, platinum electrode, 0.1 M Et_4NClO_4): 4,6,8-trimethylazulene-1,5-quinone **43** ($E_{1/2}$ = −1.05 and −1.46); 4,6,8-trimethylazulene-1,7-quinone **44** ($E_{1/2}$ = −1.05 and −1.5); guaiazulene-1,7-quinone **41** ($E_{1/2}$ = −1.13 and −1.52).

Although the potentials of unsubstituted 1,4-AQ, 1,5-AQ, 1,6-AQ and 1,7-AQ have not been reported, it is clear that they cannot exceed the potential of *p*-chloranil ($E_{1/2}$ = +0.01 V)[46], an oxidizing agent used to synthesize these quinones from their hydroquinone derivatives[25, 26]. By the same reasoning, the potential of 1,3-diethoxycarbonyl-2,6-azuloquinone (**66**)[44] cannot exceed that of DDQ ($E_{1/2}$ = +0.51 V)[46].

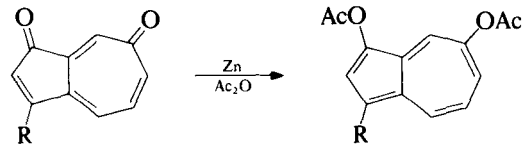


R = H, COOEt, CN (78) (31)



R = H, COOMe (79) (32)

Just as benzenoid quinones can be reduced with zinc and acetic anhydride back to the corresponding hydroquinone diacetates, so too have many of the stable azulene quinones been reduced to their corresponding diacetoxyazulenes (equations 31–33)[24, 26, 29].

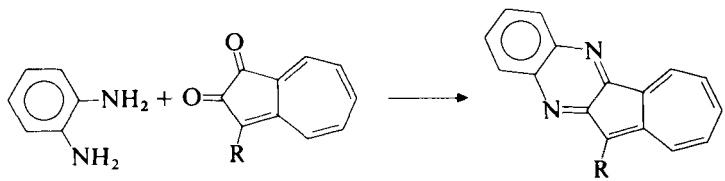


(33)

R = H, COOMe (**80**)

4. Other chemical reactions

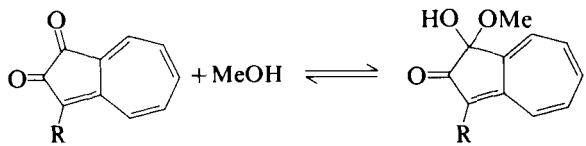
Condensation of 1,2-AQ and its derivatives with *o*-phenylenediamine gives the expected azuleno[1,2]quinoxalines **81** (equation 34)[24].



(34)

R = H, COOEt, CN (**81**)

In methanol, the parent 1,2-AQ exists in equilibrium with the hemiketal (**82**) formed by addition of solvent to the carbonyl group at the 1-position; electron-withdrawing groups at the 3-position drive this equilibrium completely over to the hemiketal (equation 35)[24].



(35)

R = H, COOEt, CN (**82**)

The stability of the residual heptafulvene moiety (a vinylogous tropone) presumably accounts for the site selectivity in this reaction[24].

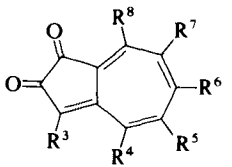
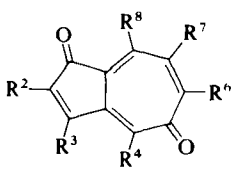
B. Spectroscopic Properties

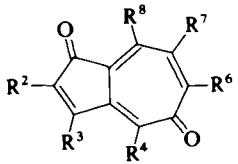
1. UV–VIS absorption spectra and color

The UV–VIS absorption spectral data available for 1,2-AQ, 1,5-AQ, 1,7-AQ and several derivatives thereof are summarized in Table 4.

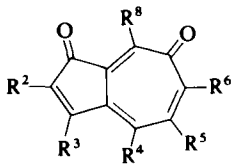
The 1,2-AQs each exhibit a maximum in the long wavelength portion of the spectrum between 565 and 595 nm, with lower intensity absorptions extending all the way out to 800 nm. From PPP calculation (Table 2, Section II), the strongest long wavelength $\pi\pi^*$

TABLE 4. UV–VIS absorption spectra of azulene quinones

Compound	R^2	R^3	R^4	R^5	R^6	R^7	R^8	Solvent	λ_{max} nm (log ε)	Reference
	—	H	H	H	H	H	H	$CHCl_3$	800 (2.05), 705 (2.63), 655 (2.74), 594 (2.79), 553 (2.74), 516 (2.71), 479 (2.68), 411sh (3.39), 386 (3.95), 361sh (3.84), 261 (4.42)[a]	24
	—	CO_2Et	H	H	H	H	H	$CHCl_3$	750 (2.21), 679 (2.53), 616 (2.76), 566 (2.82), 521 (2.76), 424sh (4.00), 397 (4.13), 371sh (4.02), 331 (3.68), 268 (4.29)[a]	24
	—	CN	H	H	H	H	H	$CHCl_3$	632 (2.55), 566 (2.66), 526 (2.63), 484 (2.63), 431 (3.84), 418 (3.84), 405 (4.00), 360sh (3.68), 305 (3.53), 279 (4.01), 263 (4.12)[a]	24
	H	H	H	—	H	H	H	MeCN	389sh (3.29), 373 (3.53), 350 (3.60), 338 (3.59), 324 (3.57), 307sh (3.54), 264 (4.27), 254 (4.36), 216 (3.89)	26
	H	H	H	—	H	H	H	EtOH	389 sh, 373, 350, 337, 322[b]	26
	H	*t*-Bu	H	—	H	H	H	MeCN	386 (3.43), 369 (3.71), 350 (3.76), 335 (3.77), 324 (3.75), 270 (4.35), 261 (4.43), 254 (4.31), 222 (4.07)	35



R^2	R^3	R^4	R^5	R^6	R^7	R^8	Solvent	λ_{max} (nm) (log ε)	Ref.
H	CO_2Me	H	—	H	H	H	$CHCl_3$	414sh (3.65), 390 (3.94), 372 (3.82)[a]	29
H	H	Me	—	Me	H	Me	MeOH	400 (3.65)[c]	38



R^2	R^3	R^4	R^5	R^6	R^8	Solvent	λ_{max} (nm) (log ε)	Ref.
H	H	H	H	H	—	H	MeCN	425sh (3.21), 401 (3.51), 384 (3.54), 345sh (3.59), 333sh (3.75), 319 (3.84), 236 (4.38)	26
H	H	H	H	H	—	H	EtOH	430sh, 399, 384, 345sh, 327sh, 319[b]	26
H	*t*-Bu	H	H	H	—	H	MeCN	391 (3.47), 375 (3.50), 328 (3.79), 317 (3.81), 270 (3.88), 235 (4.34), 226 (4.37)	35
H	CO_2Me	H	H	H	—	H	$CHCl_3$	423 (3.50), 403 (3.52), 312 (3.80)[a]	29
H	H	Me	H	Me	—	Me	MeOH	386 (3.95)[c]	38
H	Me	H	*i*-Pr	H	—	Me	MeOH	398 (3.95)[c]	37

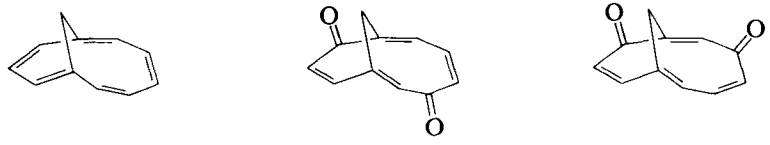
[a] Spectrum was not reported below 250 nm.
[b] Spectrum was not reported below 300 nm, sample decomposes on standing in EtOH.
[c] Only the longest wavelength absorption maximum was reported.

electronic transition for 1,2-AQ was predicted to occur at 572 nm. A second, stronger absorption in the spectrum of 1,2-AQ and its derivatives appears in the 385–405 nm region (calculated: 397 nm). The green color reported for 1,2-AQ was accurately predicted[16] on the basis of the calculations.

Also as predicted[16], the 1,5-AQs and 1,7-AQs absorb at much shorter wavelength than the 1,2-AQs and appear yellow in color. The 1,7 isomer was predicted[16] to absorb at slightly longer wavelength than the 1,5 isomer, and this too was borne out by experiment.

Especially noteworthy is the observation that these latter two quinones of azulene absorb light at significantly *shorter* wavelength than does azulene itself (λ_{max} = 579 nm). Such behavior is precisely the reverse of that which is observed for alternant systems; the quinones of benzene and naphthalene, for example, are yellow, orange and red, whereas the parent hydrocarbons are colorless. The peculiarity of the azulenic compounds is a direct consequence of the non-alternant nature of the π system and is well accounted for by the theoretical calculations[16].

In the homoazulenic series, this same peculiarity is also seen (Figure 3)[47]. Thus, quinones **84** and **85** absorb light at significantly *shorter* wavelength than does



(**83**; 484 nm) (**84**; 327 nm) (**85**; 340 nm)

FIGURE 3. Long wavelength maxima in the UV-VIS absorption spectra of homoazulene (**83**), homoazulene-1,5-quinone (**84**), and homoazulene-1,7-quinone (**85**)[47].

homoazulene itself (**83**), and in this respect they behave more like the nonalternant quinones of azulene than like quinones of a purely alternant [10]annulene. Clearly, the non-alternant homoconjugative perturbation enforced by the homoazulene skeleton[48] has a dramatic effect on the electronic properties of these bridged relatives of azulene quinones.

The success of the PPP π-electron method in predicting the long wavelength absorption maxima of 1,2-AQ, 1,5-AQ and 1,7-AQ, which range over more than 200 nm, engenders confidence in the predictions of colors for the other quinones of azulene.

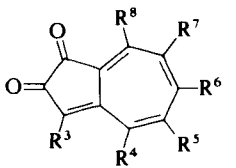
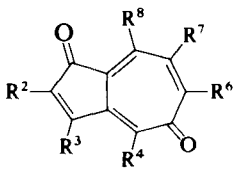
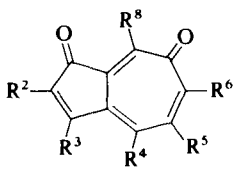
2. *Infrared spectra*

The IR spectral data available for 1,2-AQ, 1,5-AQ, 1,7-AQ and several derivatives thereof are summarized in Table 5.

The five-membered ring α-diketone and the C=C bonds of 1,2-AQ give rise to three prominent bands in the 1800–1600 cm^{-1} region of the spectrum, including a relatively high-frequency band at 1751 cm^{-1}. Derivatives of 1,2-AQ give similar IR spectra.

The IR spectra of 1,5-AQ and 1,7-AQ are very similar to one another and look much like what one would expect from the individual component rings. Tropone gives rise to two strong bands at 1643 and 1594 cm^{-1} intermingled with several weaker bands in the IR spectrum; assignment of the 1594 cm^{-1} band to the C=O stretching mode has been confirmed by an elegant ^{18}O-labeling experiment[49]. In the spectrum of 1,5-AQ, two strong bands appear at 1650 and 1590 cm^{-1}, adorned with several weak shoulders; 1,7-AQ absorbs at 1649 and 1586 cm^{-1}. Such similarities in the characteristic vibrational frequencies of these molecules indicate that the geometries and bond orders in the seven-

TABLE 5. IR spectra of azulene quinones (C=O and C=C region)

Compound	R^2	R^3	R^4	R^5	R^6	R^7	R^8	Medium	ν_{max} (cm^{-1})	Reference
	—	H	H	H	H	H	H	$CHCl_3$	1751 (m), 1687 (vs), 1643 (m)	24
	—	CO_2Et	H	H	H	H	H	$CHCl_3$	1752 (m), 1699 (vs), 1688[a], 1638 (m)	24
	—	CN	H	H	H	H	H	$CHCl_3$	1757 (m), 1707 (vs), 1693 (m)	24
	H	H	H	—	H	H	H	KBr	1706 (s), 1650 (s), 1590 (s)	26
	H	*t*-Bu	H	—	H	H	H	CCl_4	1720 (s), 1650 (s), 1605 (s)	35
	H	CO_2Me	H	—	H	H	H	KBr	1725sh, 1711, 1648, 1590	29
	H	H	Me	—	Me	H	Me	KBr	1695, 1575[b]	38
	H	H	H	H	H	—	H	KBr	1709 (s), 1649 (s), 1586 (s)	26
	H	*t*-Bu	H	H	H	—	H	CCl_4	1720 (s), 1650 (w), 1635 (w), 1605 (s)	35
	H	CO_2Me	H	H	H	—	H	KBr	1724sh, 1711, 1641, 1590	29
	H	H	Me	H	Me	—	Me	KBr	1695, 1580[b]	38
	H	Me	H	*i*-Pr	H	—	Me	KBr	1680, 1590[b]	37

[a] Assigned as the ethoxycarbonyl group by Morita and coworkers.
[b] Only the two C=O bands reported.

membered rings of 1,5-AQ and 1,7-AQ must differ very little from those in tropone. The five-membered ring C=O stretching band is seen at 1706 cm^{-1} for 1,5-AQ and 1709 cm^{-1} for 1,7-AQ.

3. ^{1}H-NMR spectra

The ^{1}H-NMR spectral data available for 1,2-AQ, 1,5-AQ, 1,7-AQ and several derivatives thereof are summarized in Table 6.

The signals for the seven-membered ring protons in 1,5-AQ and 1,7-AQ appear at slightly lower field than those in tropone (broad singlet at δ6.8), while those in 1,2-AQ appear at slightly higher field, as expected for a vinylogous tropone. The only unusual feature is the exceptionally low-field signal for the proton at position-3 in 1,5-AQ and 1,7-AQ. Substituents perturb these spectra in the anticipated manner.

The coupling constants for vicinal hydrogens in the seven-membered ring of 1,5-AQ, 1,7-AQ and their derivatives are completely consistent with a strong alternation of single and double bonds, as in tropone[50]. Unfortunately, the spectra for 1,2-AQ and its derivatives were insufficiently resolved at 100 MHz to permit the measurement of coupling constants for most of the protons in these molecules.

4. ^{13}C-NMR spectra

The ^{13}C-NMR spectral data available for azulene quinones are limited to 1,5-AQ, 1,7-AQ[26], the 3-*t*-butyl derivatives thereof[35] and the 3-methoxycarbonyl derivatives thereof[29]. For all six compounds, the resonance of C(1) appears in the region δ192–195, and the seven-membered ring carbonyl carbon absorbs at δ187–188. Morita and coworkers have pointed out[29] that the order of average chemical shift of the ring carbons in the ^{13}C-NMR spectra for the 3-methoxycarbonyl derivatives of 1,5-AQ and 1,7-AQ (δ149.1 and 148.6, respectively) agrees with the order of the polarographic half-wave potentials.

5. Mass spectra

The mass spectra of 1,2-AQ, 1,5-AQ and 1,7-AQ all show prominent molecular ions and sequential loss of two carbonyl groups to give a base peak at *m/z* 102:

1,2-AQ[24] (25 eV) *m/z* (relative abundance) 158 (M^+, 30), 130 (M–CO, 11), 102 (M–2CO, 100).

1,5-AQ[26] (70 eV) *m/z* (relative abundance) 158 (M^+, 20), 130 (M–CO, 85), 102 (M–2CO, 100), 76 (24).

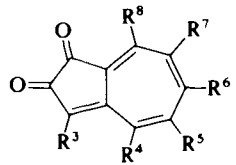
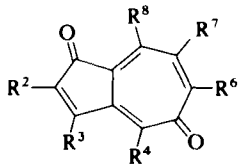
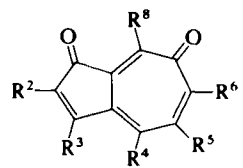
1,7-AQ[26] (70 eV) *m/z* (relative abundance) 158 (M^+, 38), 130 (M–CO, 71), 102 (M–2CO, 100), 76 (31).

Similar fragmentation patterns are observed for the 3-alkoxycarbonyl derivatives of these quinones and for the 3-cyano derivative of 1,2-AQ, although the substituents do complicate the picture to some extent[24,29]. Mass spectra of the trialkylazulene 1,5- and 1,7-quinones **41**, **43** and **44** show base peaks for the molecular ions but otherwise fragment normally[37–39].

C. Biological Properties

A number of azuloquinone and hydroquinone derivatives have been found to exhibit significant cytotoxic activity. In the standard KB cell culture screen, compounds with an $ED_{50} < 4\ \mu g\ ml^{-1}$ are considered significantly cytotoxic by the US National Cancer

TABLE 6. ^{1}H-NMR spectra of azulene quinones in $CDCl_3$

Compound	R^2	R^3	R^4	R^5	R^6	R^7	R^8	MHz	δ (ppm from $SiMe_4$)	Reference
	—	H	H	H	H	H	H	100	6.24–6.04 (m, H^4–H^8), 5.78 (s, H^3)	24
	—	CO_2Me	H	H	H	H	H	100	8.29 (complex d, J = 12 Hz, H^4), 7.12–6.72 (m, H^5–H^8), 4.36 (q, J = 7.0 Hz, CH_2), 1.40 (t, J = 7.0 Hz, Me)	24
	—	CN	H	H	H	H	H	100	7.20 (dd, J = 10, 1.4 Hz, H^4), 7.08–6.42 (m, H^5–H^8)	24
	H	H	H	—	H	H	H	360	7.78 (d, J = 5.9 Hz, H^3), 7.31 (dd, J = 7.8, 1.1 Hz, H^8), 7.11 (dd, J = 12.2, 7.8 Hz, H^7), 6.94 (ddd, J = 12.2, 2.6, 1.1 Hz, H^6), 6.82 (d, J = 2.6 Hz, H^4), 6.56 (d, J = 5.9 Hz, H^2)	26
	H	*t*-Bu	H	—	H	H	H	100	7.35–6.80 (m, H^4–H^8), 6.36 (s, H^2), 1.40 (s, *t*-Bu)	35
	H	CO_2Me	H	—	H	H	H	200	7.81 (H^4), 7.43 (H^8), 7.19 (H^7), 7.09 (H^2), 7.03 (H^6), 3.98 (COOMe)	29
	H	H	Me	—	Me	H	Me	200	7.94 (d, J = 6.0 Hz, H^3), 7.04 (s, H^7), 6.25 (d, J = 6.0 Hz, H^2), 2.60 (s, Me^8), 2.31 (s, Me^4), 2.24 (s, Me^6)	38
	H	H	H	H	H	—	H	360	7.84 (d, J = 5.8 Hz, H^3), 7.24 (d, J = 2.8 Hz, H^8), 7.04 (dd, J = 12.4, 8.0 Hz, H^5), 6.82 (dd, J = 12.4, 2,8 Hz, H^6), 6.76 (d, J = 8.0 Hz, H^4), 6.50 (d, J = 5.8 Hz, H^2)	26
	H	*t*-Bu	H	H	H	—	H	100	7.30–6.70 (m, H^4–H^8), 6.33 (s, H^2), 1.42 (s, *t*-Bu)	35
	H	CO_2Me	H	H	H	—	H	200	7.83 (H^4), 7.35 (H^8), 7.20 (H^5), 7.02 (H^2), 6.95 (H^6) 3.99 (COOMe)	29
	H	H	Me	H	Me	—	Me	200	8.06 (d, J = 6.0 Hz, H^3), 7.09 (q, J = 1.5 Hz, H^5), 6.38 (d, J = 6.0 Hz, H^2), 2.65 (s, Me^8), 2.33 (s, Me^4), 2.27 (d, J = 1.5 Hz, Me^6)	38
	H	Me	H	*i*-Pr	H	—	Me	200	6.76 (d, J = 2.0 Hz, H^6), 6.63 (dd, J = 2.0, 0.5 Hz, H^4), 6.23 (qd, J = 1.5, 0.5 Hz, H^2), 2.76 (sept, J = 7.0 Hz, $CHMe_2$), 2.64 (s, Me^8), 2.29 (d, J = 1.5 Hz, Me^3), 1.26 (d, J = 7.0 Hz, $CHMe_2$)	37

Institute. More than half of the compounds submitted for testing by Scott and coworkers have proven active at this level or below (Figure 4), and the parent 1,5-AQ and 1,7-AQ exhibit 100% activity at the lowest dosage measured (1.0 $\mu g\ ml^{-1}$)[51].

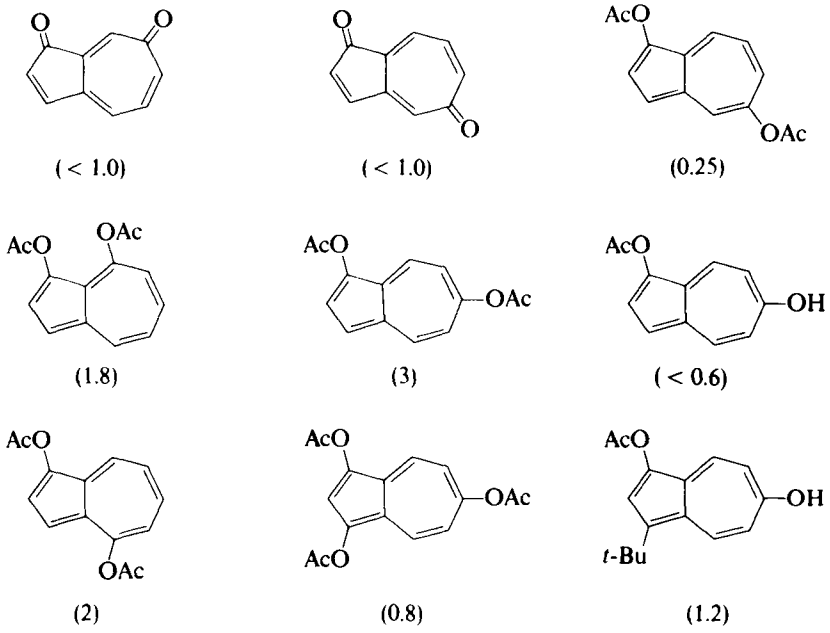


FIGURE 4. KB cell cytotoxicity (ED_{50} $\mu g\ ml^{-1}$)[51]

The hydroquinone derivatives presumably owe their activity to an *in vivo* oxidation which generates reactive quinones within the cell. In agreement with this hypothesis, several of the most active hydroquinone derivatives were found to produce a dramatic stimulation of O_2 uptake in Sarcoma 180 whole cell respiration[51]. Also, those hydroquinone derivatives with a free OH group show greater activity than the corresponding doubly acetylated hydroquinones, while the methyl ethers exhibit little activity[51].

Seven of the most cytotoxic compounds have been tested against P-388 leukemia in mice[51]. All seven compounds exhibit pronounced biological activity at relatively low dosages; however, no dosages have yet been found which effect remission (T/C > 125) for any of the compounds. The parent 1,5-AQ and 1,7-AQ are toxic in mice (T/C < 100) at a level of 1.0 $mg\ ml^{-1}$.

V. NON-KEKULÉ QUINONES

In addition to the eleven possible Kekulé quinones of azulene illustrated in Figure 1, five non-Kekulé quinones can be derived from the azulene framework (Figure 5, cf. *meta*-benzoquinone). None of these has ever been isolated or even trapped as a reactive intermediate, but the entire family warrants attention in light of the growing interest in non-Kekulé benzenoid quinones[52] (cf. Chapter 10 of this volume).

As expected, MINDO/3 calculations[16] predict the non-Kekulé azulene quinones all to have less favorable heats of formation, lower-lying LUMOs, larger LUMO coefficients,

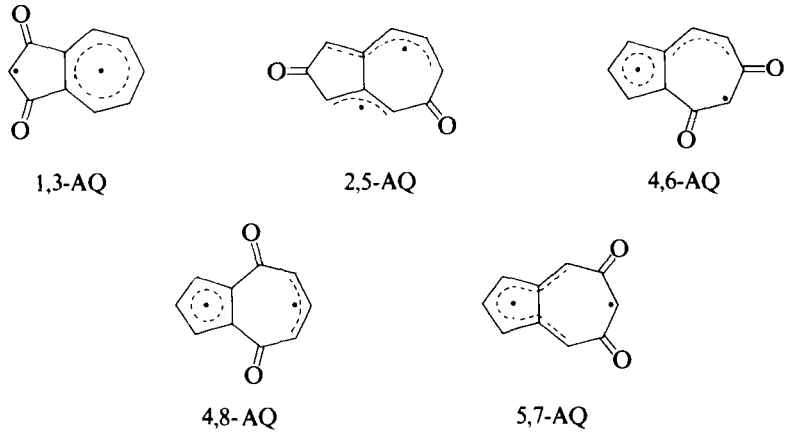
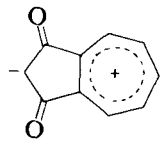


FIGURE 5. The five possible non-Kekulé quinones of azulene

and smaller HOMO–LUMO energy gaps than the isomers shown in Figure 1. Thus, all the non-Kekulé quinones of azulene are predicted to suffer easy dimerization, polymerization, nucleophilic addition and reduction. The 2,5-AQ is actually not even a minimum on the MINDO/3 energy surface but collapses to a cyclopropanone by formation of a bond between C(1) and C(3).

Of these hypothetical quinones, however, 1,3-AQ stands out as a particularly intriguing compound. Inspection of the calculated geometry and charge density pattern[16] suggests that this isomer can best be represented as



1,3-AQ

It is difficult to conceive of *any* non-Kekulé quinone (non-benzenoid or benzenoid) with a more stabilized zwitterionic form than this one. Compared to the other quinones in Figure 5, 1,3-AQ is predicted to have, by far, the most favorable heat of formation, the highest-lying LUMO, the smallest LUMO coefficients, and the largest HOMO–LUMO energy gap. Of the five possible non-Kekulé azulene quinones, this one should have the best chance for survival.

VI. FUTURE PROSPECTS

It is inevitable that all of the remaining Kekulé quinones of azulene will sooner or later become known, but it now seems unlikely that any of the parent quinones other than 1,2-AQ, 1,5-AQ and 1,7-AQ will be isolable under ordinary laboratory conditions. Direct spectroscopic study of the more reactive quinones in solid matrices should be possible, even for the non-Kekulé quinones, and some of the Kekulé isomers may even survive in dilute solution at low temperatures. Judiciously positioned bulky alkyl substituents could stabilize some of the more reactive quinones sufficiently to permit studies of their chemical

and spectroscopic properties. This ploy might even render the non-Kekulé 1,3-AQ observable in solution. Clearly there is still much work to be done on azulene quinones.

VII. ACKNOWLEDGEMENTS

The author is deeply indebted to all of the principal investigators in this field during the last decade for their free communication of new results and information prior to publication. The warm hospitality of K. Takase and T. Morita (Sendai), T. Nozoe (Tokyo) and K. Hafner (Darmstadt) during visits by the author was especially appreciated. Most of the research conducted on azulene quinones in Reno was supported by the US National Institutes of Health and the National Science Foundation.

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CHAPTER **25**

Extended quinones

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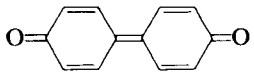
I. INTRODUCTION

Extended quinones are those quinones which bear the quinonoid carbonyl groups in different rings. Three major classes may be envisaged: first compounds which are treated in Chapter II and in which the two carbonyl groups are present in rings or ring systems connected by a double bond, cumulene bonds, or conjugated double bonds. The parent quinones are called diphenoquinones (**1**), cumulenoquinones or diquinoethylenes (**2**) and (with two conjugated double bonds) stilbenoquinones (**3**), respectively.



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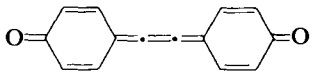

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(3)

Many members of this group of compounds are known. Publications until 1978 have been reviewed in detail, including some benzo-annelated homologues[1]. No important developments in this field have since been published with the exception perhaps of the oligoquinocycloalkanes (which may be considered as substituted stilbenoquinones) and the cumulenoquinones. Therefore only these two classes are reviewed in Section II.

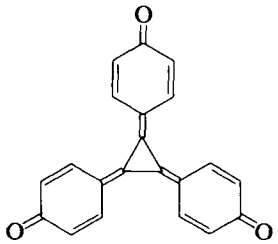
Another large class of extended quinones are derived from polycyclic aromatic compounds. Some of them have been known for about 70 years and many have attained technical importance as vat dyes. To my knowledge no modern, comprehensive review of this interesting class of quinones has been published. They are treated in Section III.

Section IV is dedicated to perhaps the most exciting class of extended quinones. They may be regarded as non-classical quinones, because they are related to non-classical aromatic systems such as azulene or the annulenes. They have been synthesized and studied within the last two decades, many of them within the last few years.

II. POLYQUINOCYCLOALKANES AND DIQUINOETHYLENES

A. Polyquinocycloalkanes

This class of quinones has been explored by West and coworkers[2-7]. The strongly coloured, dye-like polyquinocycloalkanes of type **4** or **5** may be regarded as substituted



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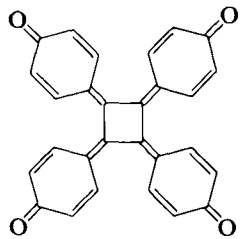

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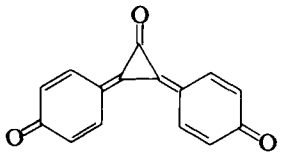

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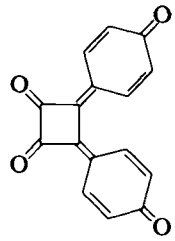
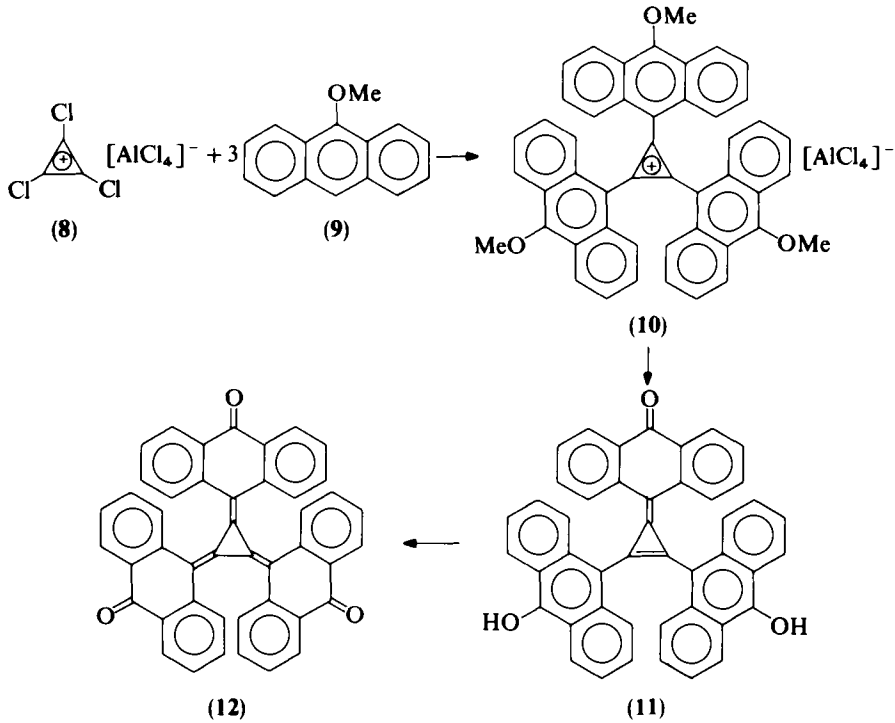
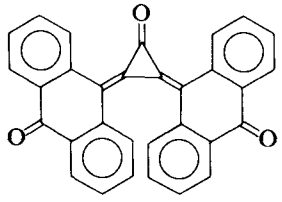


(7)

stilbenoquinones. The same is true for the isolable but unstable diquinocyclopropanone **6**, and the rather labile 1,2-diquinocyclobutanedione **7**. The last step of the preparation is usually the oxidation of the conjugate hydroquinone. Thus for the preparation of tris(9-anthron-10-ylidene)cyclopropane (**12**), the hydroquinone is typically prepared by Friedel–Crafts reaction of 9-methoxyanthracene (**9**) with trichloropropenylium tetrachloroaluminate (**8**), followed by demethylation of the resulting **10**. The bis(9-hydroxy-10-anthryl)cyclopropylideneanthrone (**11**) thus formed, a stilbene derivative, is finally oxidized to **12**.

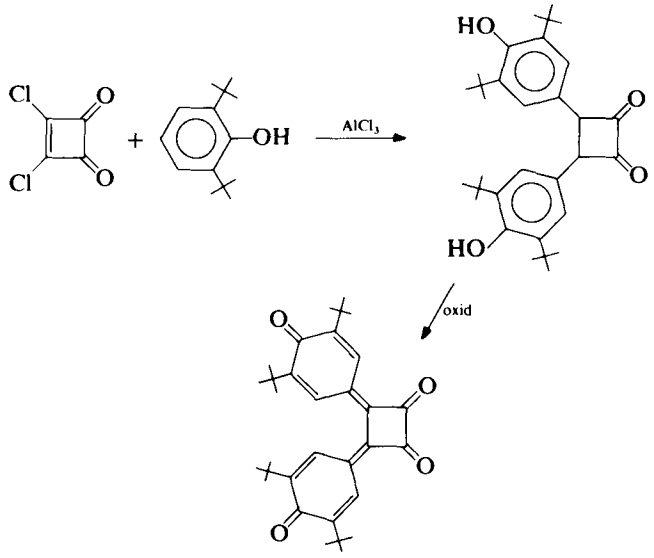


Reaction of two equivalents of 9-methoxyanthracene results after ether cleavage, hydrolysis and oxidation in the formation of 2,3-bis(9-anthron-10-ylidene)cyclopropanone (**13**)[2]. An analogous procedure has been used for the preparation



(13)

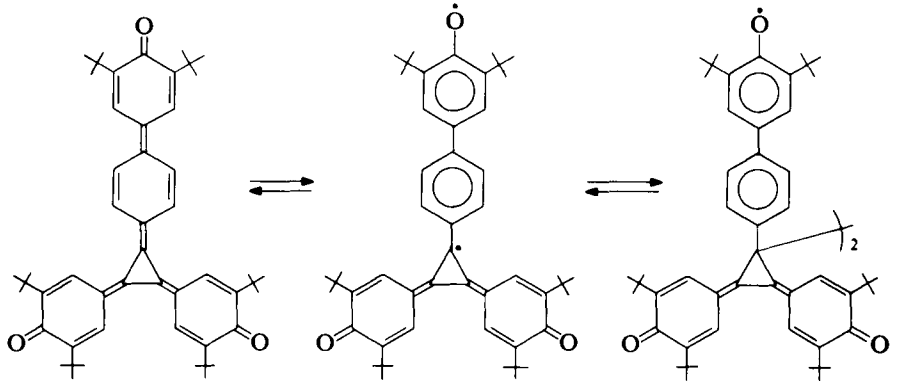
of 1,2-diquinocyclobutanediones, as shown in the reaction scheme for the synthesis of 1,2-bis(3,5-di-*t*-butyl-4-oxo-2,5-cyclohexadien-1-ylidene)cyclobutanedione (**14**)[3]:



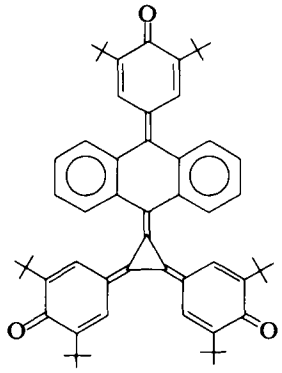
(14)

A variety of diquinocyclopropanones and triquinocyclopropanes has been synthesized by this method[2~4]. An outstanding example is **15**[4] with a remarkable electronic excitation absorption at 1300 nm[5]. This absorption is well into the near-infrared region, an area approaching molecular bond vibrational energy and not often seen for electronic excitation. The ESR spectrum suggests that **15** exists predominantly in the diradical form **16**, which dimerizes to give the diradical dimer **17**. **18** was found to be a little more stable than **15**. It could be isolated in crystalline form whereas **15** has a half-life time of 92 min in solution at room temperature. **18** exhibits very strong absorption at 672 nm and no other bands are observed up to 2000 nm.

Another synthetic method to a quinocycloalkane has been used in the case of the bright purple tetraquinocyclobutane **20**[6], which was obtained by heating the cumulenoquinone **19** in cyclooctane for 3–4 hours. X-ray analysis showed that **20** is not planar and exists in a propeller-like conformation with an average twist angle of 36°. The central four-membered ring is also distorted from planarity. The reduction of **20** to the hydroquinone **21** is not accomplished easily. Although **20** is stable indefinitely in hydrocarbon



(15) (16) (17)



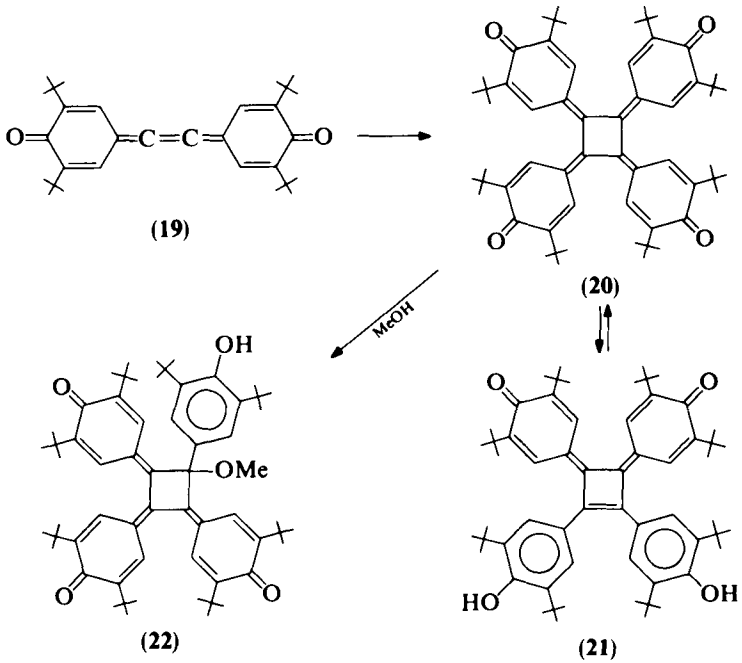
(18)

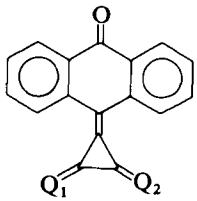
solutions, it reacts with nucleophiles. Solution in methanol results in the addition of one mole of methanol to give **22**, and conventional reduction techniques fail because of this reactivity with nucleophiles. However, on refluxing with benzopinacol in cyclooctane the diaryldiquinocyclobutene **21** is formed and is readily reoxidized to **20** by atmospheric oxygen.

The redox behaviour of the triquinocyclopropanes **23a** and **b**, **12**, and of **13** has been examined using cyclic voltammetry[7]. Two-wave redox cycles were observed for each compound corresponding to the formation of the semiquinone radical and the dianion. Compounds **23a** and **b**, **12**, and **13** are powerful oxidizing agents with first reduction waves at $+0.02$–$+0.05$ and second waves at about -0.27 V (vs. saturated calomel). The ESR spectra of the semiquinone anions has been measured. The hyperfine splitting constants are in accoordance with that predicted by MO calculations.

B. Diquinoethylenes

West[8] proposed the name diquinoethylenes for compounds containing quinone nuclei connected by cumulated double bonds. They are genuine quinones since they are reduced



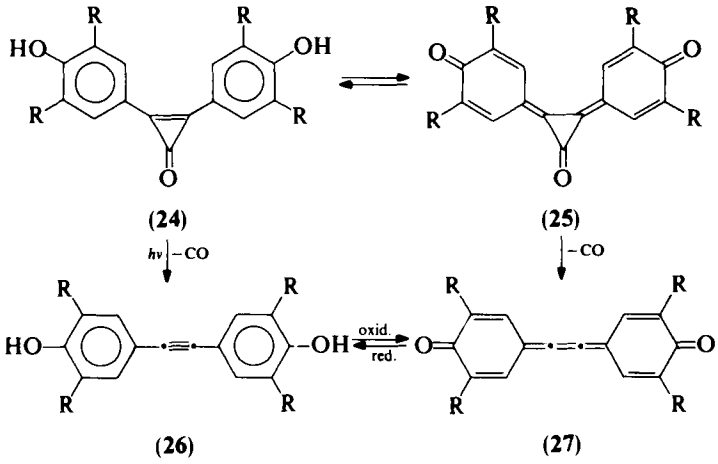


a: $Q_1 = Q_2$ = 4-oxo-3,5-di-*t*-butyl-2,5-cyclohexadien-1-ylidene
b: Q_1 = 4-oxo-3,5-di-*t*-butyl-2,5-cyclohexadien-1-ylidene;
Q_2 = 9-anthron-10-ylidene

reversibly to the conjugate hydroquinones with two aromatic nuclei connected by an acetylene moiety (see e.g. **26** and **27**).

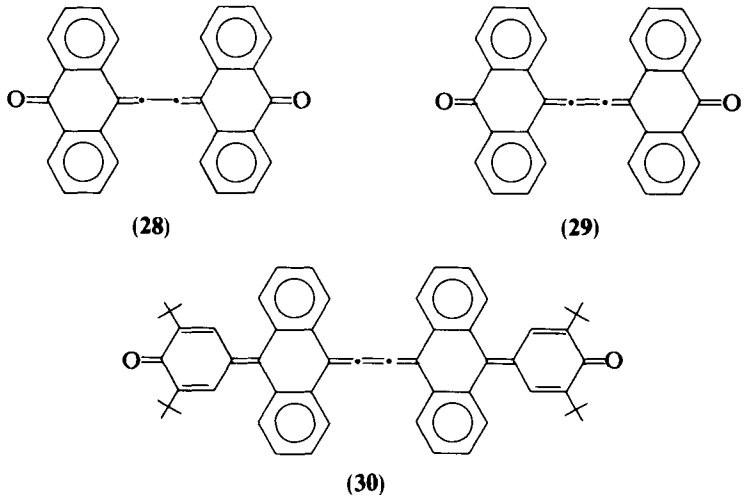
Diquinoethylenes are formed by the spontaneously proceeding decarbonylation of diquinocyclopropanones **25** at room temperature or by photochemical-induced decarbonylation of their conjugate hydroquinones, the bis(*p*-hydroxyaryl)cyclopropenones (**24**, R = H) to the alkynes **26**, with subsequent oxidation[8].

The diquinoethylenes are magenta-coloured solids. Their stability depends on the alkyl groups: **27c** (R = *t*-butyl) is stable and unreactive, **27b** (R = isopropyl) is isolable but reacts with water, and **27a** (R = methyl) was so reactive that it could not be isolated and was detected only by its UV–VIS spectrum in solution.



a: R = Me **b**: R = *i*-Pr **c**: R = *t*-Bu

In the same way dianthraquinoethylene (**29**)[2] and compound **30**[4] have been synthesized. the latter could not be isolated, but its existence was indicated by the UV–VIS spectrum of the blue-green solution.



In contrast **29** is a stable and long-known bordeaux-red dye, which has also been prepared from anthrone. By treatment with glyoxal sulphate, the stilbenoquinone **28** is easily formed and can be oxidized by heating with ethanolic potassium hydroxide to **29**, forming a cherry-red vat dye[9]. The reversible reduction of **29** has been investigated by cyclic voltammetry[8]. Two wave cycles were observed in alkaline solution, corresponding to the semiquinone anion and to the dianion with $E_{(1/2)1} = -0.42$ V and $E_{(1/2)2} = -0.61$ V. The ESR spectrum of the semiquinone anion has been measured.

III. QUINONES OF POLYCYCLIC AROMATIC HYDROCARBONS

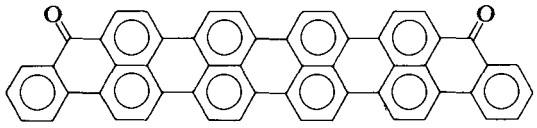
A. General Aspects

Extended quinones of condensed aromatics have some synthetic importance as precursors for the conjugate aromatic hydrocarbon itself[10], since the quinones having carbonyl groups are more readily available by syntheses.

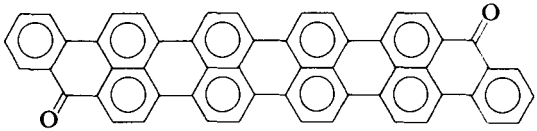
Commercially, some extended quinones have gained importance as dyes[11]. They have been used as vat dyes for many decades to dye cotton and other cellulose fibres. Despite their high cost and not so brilliant colours these dyes are extremely important because of their superior fastness. Because of their low solubility they can be used also as pigments, but in this case they have to possess a high degree of purity and certain physical properties of the particles. Their relatively high cost restricts their use to special applications, e.g. with high requirements for fastness.

The reactivities of extended quinones with nucleophiles, electrophiles and free radicals[12], their ground-state properties and electronic structure[13] as well as heats of atomization, dipole moments, carbonyl stretching frequencies, and reduction potentials[14] have been calculated.

With some quinones of the highly condensed aromatic hydrocarbons the question arises, whether the compound is a quinone or a simple aromatic diketone. 'Violongthrone'[15] (**31**), e.g. may be viewed as quinone insofar as on reduction a 54 π-electron system with cyclic conjugated double bonds is formed, and is formally a Hückel aromatic with $4n + 2$ electrons, $n = 13$. However, the quinone itself represents a very stable aromatic ketone, which forms no vat with alkaline dithionite. In contrast, iso-violongthrone[16] (**32**) forms an (unstable) dark-blue vat dye on treatment with pyridine and alkaline dithionite.



(**31**)

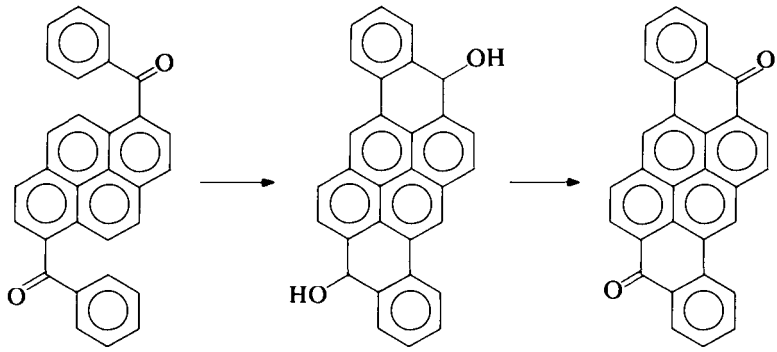


(**32**)

The formation of a vat with alkaline dithionite is no unambiguous proof of a quinonoid character. It may be that the redox potential in the case of **31** was insufficient, or that in the case of **32** not the alkali salt of the conjugate hydroquinone was formed but overreduction took place. This is observed in some cases[10a]. The investigation of the electrochemical behaviour, if possible with cyclic voltammetry, seems to be a more reliable method to answer the question, whether a certain compound is a quinone, i.e. whether it possesses reversible redox properties or not. Little is known about the photochemistry of the extended quinones with the exception of their photosensitizing ability, which has practical importance in the use of some vat dyes[17].

The most important method for the synthesis of extended quinones of condensed aromatics seems to be the 'Scholl cyclization' of benzoyl or naphthoyl derivatives of

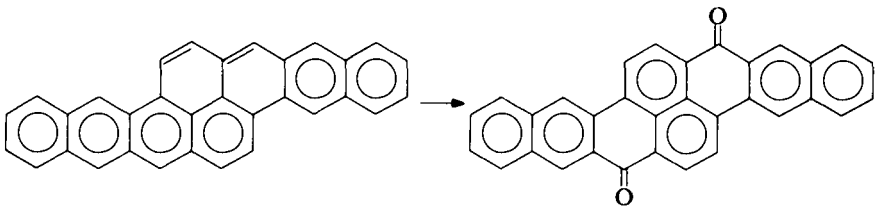
condensed aromatics which in an aluminium chloride melt yield quinones[18]. Later this method was improved by introducing dry oxygen into the well-stirred melt[19] when, e.g. 1,6-dibenzoylpyrene (**33**) gives pyranthrone (**35**) in 80% yield. Other oxidants such as nitrates have also been used.



(**33**) (**34**) (**35**)

Attention should be given to the fact that under the conditions of Scholl cyclization migrations of the aroyl substitutents are sometimes observed.

Another route to extended quinones is oxidation of the condensed aromatic hydrocarbon with chromic acid or selenium dioxide, for example, of **36** to **37**[20].



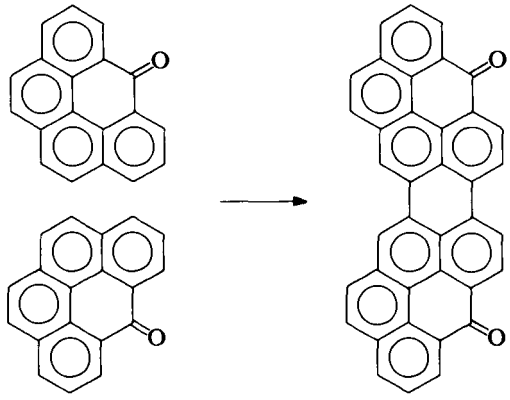
(**36**) (**37**)

The products may be predicted by the simple rule of thumb that a maximum number of intact benzene and/or naphthalene rings should be retained in the process. The ease of oxidation increases with increasing annelation.

The synthetic value of this method is limited because, as mentioned, the aromatic hydrocarbons themselves are synthesized very often by reduction of the conjugate quinones[10].

Benzanthrone, its derivatives and homologues with free 6- and 7-positions can be dimerized by melting with potassium hydroxide, with or without melting-point reducing additives. Thus naphthanthrone (**38**) gives, in a potassium hydroxide/potassium acetate melt at 240°C, the quinone **39**[21]. Benzanthrone and its derivatives are therefore important initial products for technical syntheses of vat dyes.

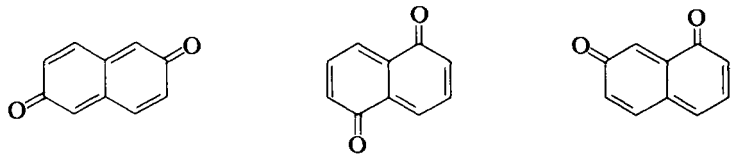
In the following sections the quinones are classified according to number of rings they contain.



(38) (39)

B. Two-ring Quinones

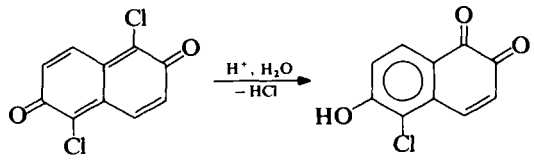
The extended naphthoquinones **40**–**42** are unstable and the only known one is the 2,6-quinone **40**, which was prepared by oxidation of the conjugate hydroquinone with lead



(40) (41) (42)

dioxide[22]. The yield was improved later by the use of active lead dioxide[23]. The 2,6-quinone is stable in absence of water but reacts quickly with traces of moisture.

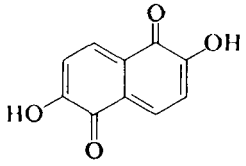
1,5-Disubstituted derivates of **40**, such as 1,5-dichloro-2,6-naphthoquinone (**43**), are more stable. **43** can be prepared by oxidation of the conjugate hydroquinone with chromic acid[1a, 22]. Prolonged treatment with an excess of sodium bichromate yields **44**.



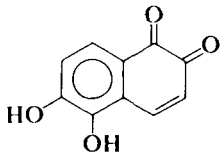
(43) (44)

For the oxidation product of 1,2,5,6-tetrahydroxynaphthalene structure **45** was claimed[24], but the prototropic structure **46** seems to be more stable. In contrast the structure of 1,5-diamino-2,6-naphthoquinone seems to be well established[25].

Attempts to prepare 1,5-naphthoquinone (**41**) in the same manner as **40** failed, even in the absence of water[26]. The reason is probably that **41** possesses conjugated double bonds

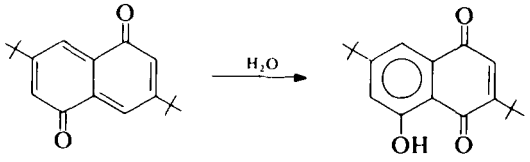


(45)



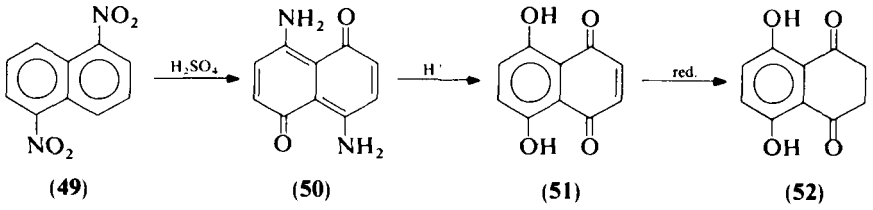
(46)

with a *s-cis* partial structure and, unlike **40**, it can undergo Diels–Alder addition reactions with itself. Only by shielding the molecule with two *t*-butyl groups in the 3- and 7-positions is the sufficiently stable 1,5-quinone **47** obtainable[27]. In the presence of water it is converted slowly to **48**.

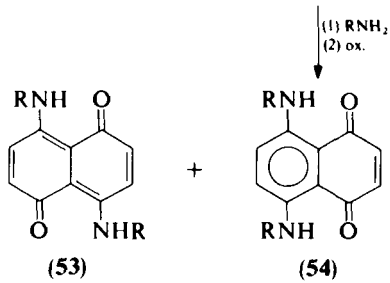


(47) (48)

The stable 4,8-diamino-1,5-naphthoquinone (**50**) is an intermediate in the conversion of 1,5-dinitronaphthalene (**49**) to naphthazarin (**51**) with fuming sulphuric acid and sulphur[28].



(49) (50) (51) (52)

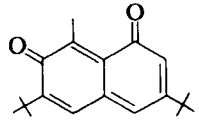


(53) (54)

For naphthazarin (**51**) a 1,5-quinonoid structure was proposed, but the 1,4-quinonoid structure is now well established[27]. However, compound **50** clearly has the 1,5-quinonoid structure, as shown[29].

50 or *N*,*N*′-dialkyl derivates (**53**) can generally be prepared starting with **51**, which is reduced to the leuco form **52** and then treated with an amine. The substances are then reoxidized with atmospheric oxygen. The 5,8-dialkylamino-1,4-naphthoquinones (**54**) are sometimes formed as by-product[29].

PMO/MNDO calculations suggested that 1,7-naphthoquinones should undergo Diels–Alder reactions with themselves as easily as 1,5-naphthoquinones[30]. On the basis of PMO calculations and by comparison with analogous cases, *t*-butyl groups in the 3,6-positions should ensure sufficient kinetic stability with respect to reactions with nucleophiles, such as water or Diels–Alder self-condensations. Nevertheless, 3,6-di-*t*-butyl-8-methyl-1,7-naphthoquinone (**55**) showed an unexpected low stability. According to MNDO calculations the alkyl groups, especially the methyl group, cause a high steric strain in the molecule that is possibly responsible for the low stability of **55**. But the 8-methyl group proved to be indispensible, since in its absence the corresponding hydroquinone underwent an oxidative coupling reaction in the 8-position[30].



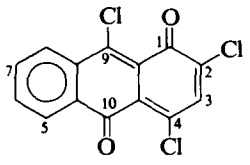
(**55**)

C. Three-ring Quinones

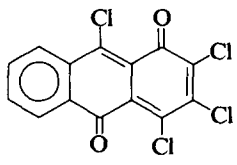
1. Anthraquinones

Of the possible nine anthraquinones only those with the quinone carbonyl groups in one ring are known, i.e. the 1,2-, 1,4- and 9,10-quinones. The reason is the inherent instability of the extended quinones. On the basis of PMO/MNDO calculations it has been predicted that the reactivity of the extended anthraquinones toward water[27], and in some cases the dimerization tendency[30], should be very high. 1,10-Anthraquinones are known with chlorine, and/or amino groups, as well as alkyl groups as stabilizing substituents.

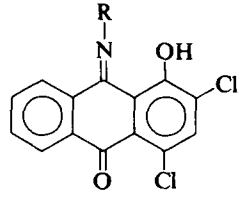
Boiling of 1,4-dihydroxyanthraquinone with thionyl chloride in the presence of bases yielded 2,4,9-trichloro-1,10-anthraquinone (**56**) and 2,3,4,9-tetrachloro-1,10-anthraquinone (**57**). Both compounds can also be obtained from other 1-hydroxy-anthraquinones, such as 1-hydroxyanthraquinone, 4-chloro-1-hydroxyanthraquinone,



(**56**)



(**57**)

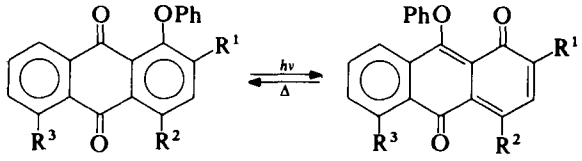


(**58**)

2,4-dichloro-1-hydroxyanthraquinone and 2-chloro-1,4-dihydroxyanthraquinone. This reaction is evidently common to compounds containing a hydroxy group in the 1-position[31].

With ammonia, aliphatic and aromatic primary amines **56** gives 2,4-dichloro-1-hydroxyanthraquinone-9-imines (**58**)[32]. Derivatives of 1-phenoxyanthraquinone containing amino-, methylamino-, or benzoylamino groups at positions 2, 4 and 5 show photochromism, which involves the reversible photoisomerization of the 9,10-quinonoid structure (**59**) to the 1,10-quinonoid structure (**60**). The ability of the compounds **59** to

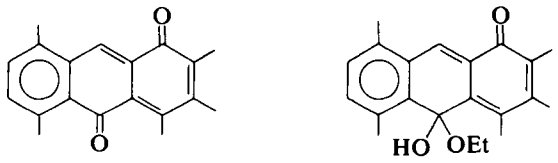
undergo photoisomerization depends on the position and electronic nature of the substituents. 4-Amino-9-phenoxy-1,10-anthraquinone (**60a**) was obtained in pure crystalline form by irradiation of **59a**[33].



(59) **(60)**

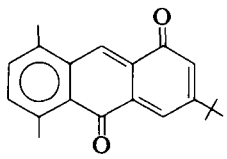
a: $R^1 = R^3 = H$; $R^2 = NH_2$

Attempts were made to synthesize the 1,10-anthraquinone (**61**) shielded with methyl groups, but only the hemiketal **62** could be isolated in pure form[34], probably due to overcrowding at the 10-carbonyl group.



(61) **(62)**

The 3-*t*-butyl-5,8-dimethyl-1,10-anthraquinone (**63**) could be prepared in a five-step synthesis and was stable enough to be isolated. Despite the shielding of the *meso*- position by the 1-carbonyl and 8-methyl groups **63** reacts rapidly with water and oxygen to give 3-*t*-butyl-1-hydroxy-5,8-dimethyl-9,10-anthraquinone (**64**)[35]. Stable derivatives of 2,6-anthraquinone, 3,7-dihydroxy-9,10-dimethylanthraquinone (**65**)[36] and 3,7-di-*t*-butyl-9,10-dimethyl-2,6-anthraquinone (**66**)[37] are also described. The latter has been prepared by oxidation of the conjugate hydroquinone with a mixture of nitrogen oxides.



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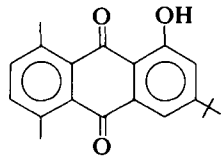

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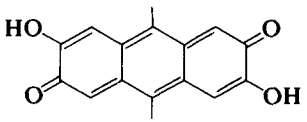

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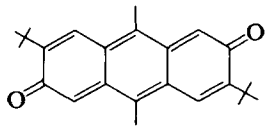
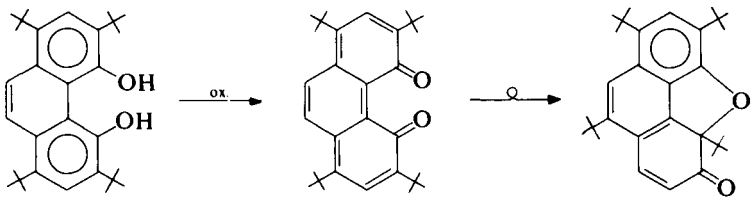


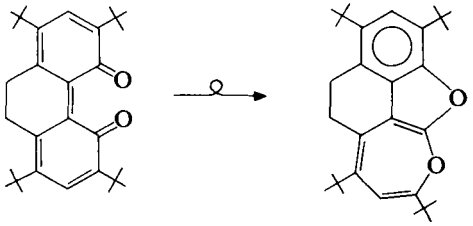
(66)

2. *Phenanthrenequinones*

As with the anthracene system only phenanthrenequinones with the carbonyl groups in the same ring are known. Newman and Childers[38] have synthesized and oxidized several 4,5-phenanthrenediols, most giving 1,4-phenanthrenequinone derivatives. 4,5-Dihydroxy-1,3,6,8-tetramethylphenanthrene gave an apparently polymeric product[39]. Only 1,3,6,8-tetra-*t*-butyl-4,5-phenanthrenequinone (**68**) has been detected as a short-lived species in solution: 1,3,6,8-tetra-*t*-butyl-4,5-dihydroxyphenanthrene (**67**), prepared in a five-step synthesis starting with 2,4-di-*t*-butyl-5-methylphenol, gave on oxidation with lead dioxide in benzene a fleeting green solution containing **68**, which rapidly rearranges to the dienone **69**. The corresponding 9,10-dihydro compound **70**, prepared in a similar way, crystallizes as its oxepine valence isomer **71**[40].



(67) (68) (69)

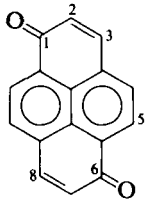


(70) (71)

D. Four-ring Quinones

1. *Pyrenediones*

A mixture of the 1,6-pyrenequinone (**72**) and 1,8-pyrenequinone (**73**) was obtained more than one hundred years ago by chromic-acid oxidation of pyrene[41]. The ratio 1,6/1,8-quinone was determined to be 1:2[19]. Since then several methods for the preparation of pyrenequinones by oxidation of the parent hydrocarbon have been described, especially



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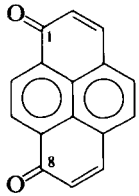
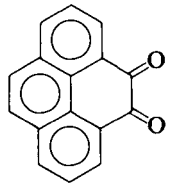


(73)

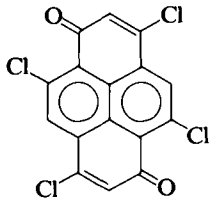


(74)

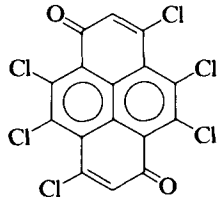
vapour-phase oxidation with oxygen over vanadium and/or titanium oxide catalysts[42]. The 4,5-pyrenequinone (**74**) was obtained as by-product. The addition of ammonia in this oxidation increases the yields of the 1,6- and 1,8-quinones while the yields of the 4,5-quinone **74** and of higher oxidation products were unaffected. This effect is probably caused by shielding those active centres of the catalyst that were responsible for the oxidation of the 4–5 and 9–10 bonds of pyrene[43].

Especially under basic conditions, the quinones are oxidized further to yield mainly aromatic carboxylic acids. Thus a mixture of 1,6- and 1,8-pyrenequinone with 1.5 mole of aqueous potassium hydroxide at 140°C was completely oxidized by air within 1 hour. The main product (37%) proved to be naphthalene-1,4,5,8-tetracarboxylic acid[44]. 1,6-Dibenzoylpyrene gives 3,8-dibenzoyl-1,6-pyrenequinone on cautious oxidation with chromic acid in acetic acid[19].

Chloro derivatives of pyrenequinones can be obtained by oxidation of chloropyrenes: a mixture of 3,8-dichloro-1,6-pyrenequinone and 3,6-dichloro-1,8-pyrenequinone was obtained by treatment of 1,3,6,8-tetrachloropyrene with 20% oleum at 85°C[19] and 3,5,8,10-tetrachloro-1,6-pyrenequinone (**75**) could be synthesized by treatment of 1,3,5,6,8,10-hexachloropyrene with nitric acid at room temperature. In the same way 3,4,5,8,9,10-hexachloro-1,6-pyrenequinone (**76**) and 2,3,4,5,7,8,9,10-octachloro-1,6-pyrenequinone (**77**) are formed from the corresponding octa- and deca-chloropyrenes[19].



(75)



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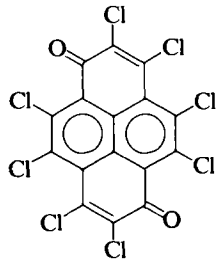


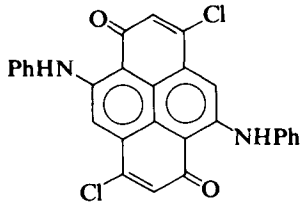
(77)

Chloro derivatives of 1,6-pyrenequinone can also be prepared by chlorination of 1,6-pyrenequinone with chlorine in trichlorobenzene at 100°C. 2,7-Dichloro-1,6-pyrenequinone, and under more vigorous conditions 2,3,7,8-tetrachloro-1,6-pyrenequinone, is formed[19].

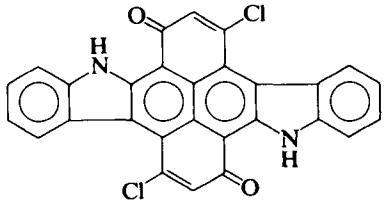
The reactivity for the substitution of chlorine atoms by amines[19] depends strongly on the position of the chlorine in 1,6-pyrenequinone. Chlorine in the *peri*-position (5,10-position) is exchanged very easily, followed by chlorine in the 3,8-position. But it was not possible, even under drastic conditions, to substitute chlorines in the 2,7-position. Thus 2,3,7,8-tetrachloro-1,6-pyrenequinone is converted by heating with arylamines to 3,8-diarylamino-2,7-dichloroquinone and in 3,5,8,10-tetrachloro-1,6-pyrenequinone (**75**) the chlorine can be substituted stepwise by aniline, at first in the 5-position (60°C) and at higher temperature and in the presence of bases also in the 10-position. Boiling with an excess of aniline under copper salt catalysis leads in high yield, via the trianilino derivative, to 3,5,8,10-tetraanilino-1,6-quinone. Other amines react similarly, and several unsymmetrically substituted 1,6-pyrenequinones have been synthesized in this way.

3,5,8,10-Tetrachloro-1,6-pyrenequinone (**75**) is converted to the 10-hydroxy derivate by heating with potassium acetate in nitrobenzene. Other compounds with active hydrogens, such as phenols and thiophenols, also substitute easily the reactive chlorines in 1,6-pyrenequinone[19,45].

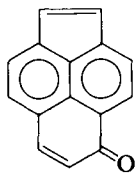
Characteristic of the 5,10-diarylamino-1,6-pyrenequinones is the cyclization reaction with sulphuric acid or aluminium chloride/pyridine or in an aluminium chloride/sodium chloride melt. The cyclization product is oxidized by air. Thus 5,10-dianilino-3,8-dichloro-1,6-pyrenequinone (**78**) forms the dicarbazole (**79**)[19].



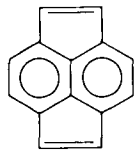
(**78**)



(**79**)



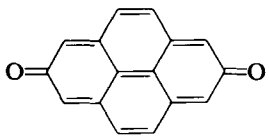
(**80**)



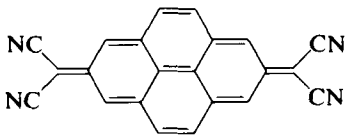
(**81**)

Vacuum flow pyrolysis of 1,6- and 1,8-pyrenedione (**72** and **73**) at 1100°C leads to stepwise decarbonylation under formation of 5*H*-cyclopent[*cd*]phenalen-5-one (**80**) and, finally, cyclopent[*fg*]acenaphthylene (**81**, pyracyclene)[46]. The use of pyrenequinones as sensitizers in photoresist compositions for reproduction techniques has been proposed[47].

The remarkable conductive properties of the tetrathiofulvalene/7,7,8,8-tetracyanoquinodimethane complex led to a search for further 'organic metals'. In this connection INDO and π-SCF calculations were performed on the electronic properties of the unknown 2,7-pyrenequinone (**82**), its quinodimethane, and the 13,13,14,14-tetracyano-2,7-pyrenoquinodimethane (**83**)[13]. The synthesis of **83** and its electrical properties have been described by Cowan and coworkers[48].



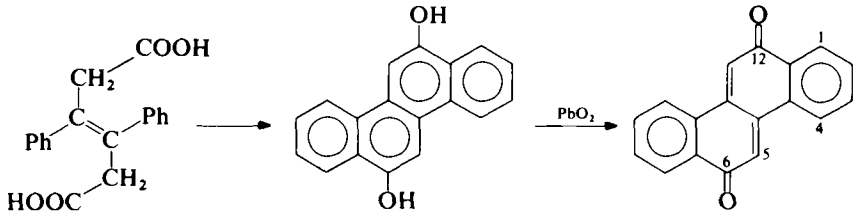
(**82**)



(**83**)

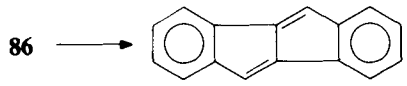
2. *Chrysene-6,12-dione*

The only known extended quinone of chrysene is the 6,12-dione (**86**). An interesting synthesis was performed via the dicarboxylic acid **84**, which can be synthesized by Reformatzky reaction of benzil with bromoacetic acid. Cyclization gave the hydroquinone **85**, which gave **86** on treatment with lead dioxide[49, 50]. **86** is converted in alkaline solution in the presence of oxygen to the 12-hydroxy-5,6-chrysenequinone[49].



(84) (85) (86)

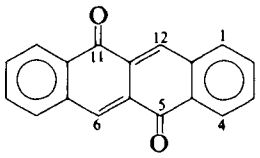
Pyrolysis of **86** at 900°C leades to decarbonylation and formation (15%) of indeno [2, 1-*a*] inden (**87**), which was not easily accessible previously. This and other aromatic carbonyl compounds were chosen, because they readily lose carbon monoxide in the mass spectrometer[51].



(87)

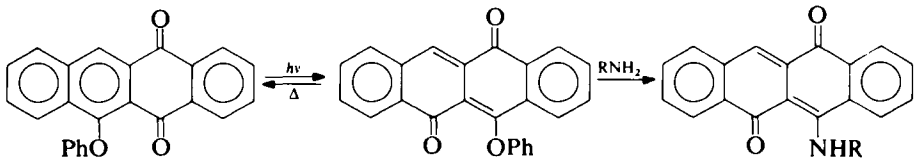
3. Naphthacene-5,11-dione

The 5,11-naphthacenequinone (**88**) is the only known extended naphthacenequinone. It is prepared by heating 5,11-dibromonaphthacene with 88% sulphuric acid[52].



(88)

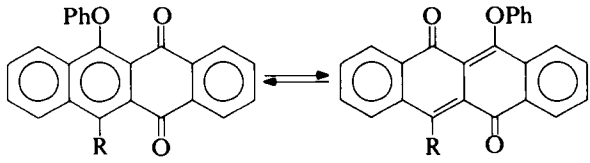
The photochromism of 6-phenoxy-5,12-naphthacenequinone (**89**) is due to the formation of 12-phenoxy-5,11-naphthacenequinone (**90**)[53]. Orange crystals of **90** are converted to the original quinone merely on melting. In benzene, **90** was readily converted under the influence of ammonia or aniline into the 12-amino-5,11-naphthacenequinones (**91a, b**), earlier synthesized by an alternative method[54-56].



(89) (90) (91)

a: R = Ph
b: R = H

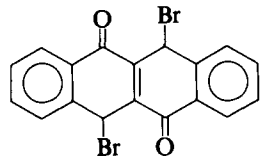
The 5,12-naphthacenequinones **92a** and **b** are converted under the influence of concentrated sulphuric acid or aluminium chloride (in benzene) into mixtures with the tautomeric 5,11-naphthacenequinone derivatives **93a** and **b**. With substituents **a** the 5,11-quinonoid form **93** dominates, and with substituents **b** the 5,12-quinonoid form (**92**)[57].



(**92**) (**93**)

a: R = NH_2, NHMe, NHPh, NHAc
b: R = H, OPh, OMe, Cl

With bromine 1,4-addition to positions 6 and 12 takes place giving **94**, and no substitution reaction is observed[54].

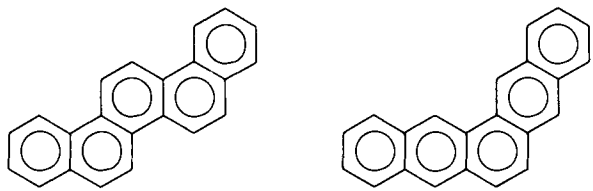


(**94**)

5,11- and 5,12-naphthacenequinone and 5,6,11,12-diquinone have been proposed for use as cathode material for a battery with alkali metals or alkali earth metals as anode[58a].

E. Five-ring Quinones

Of the common five-ring aromatics no extended quinones are known of picene (**95**) and pentaphene (**96**).



(**95**) (**96**)

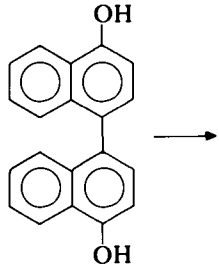
Extended quinones of perylene, pentacene, benzopyrene and benzochrysene are treated below.

1. Perylenediones

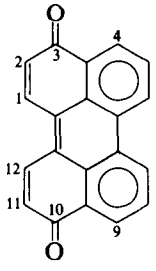
At the present time four quinones of perylene are known, the perylene-3,10-, 3,9-, 1,12-diones and perylene-3,4,9,10-tetraone (**98**, **99**, **100** and **102**, respectively). Most important

is 3,10-perylenequinone (**98**), which can be obtained by oxidation of perylene with aqueous chromic acid[58b] or by heating 3,10-dihalogenoperylene with sulphuric acid[59, 60].

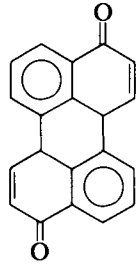
4,4'-Dihydroxy-1,1'-binaphthyl (**97**) is also converted to 3,10-perylenequinone by heating with aluminium chloride/manganese dioxide and subsequent oxidation[61] or by heating with concentrated sulphuric acid containing a little nitric acid and iron(II) salt[62]. 3,10-Perylenequinone forms a red vat.



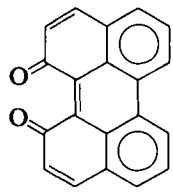
(**97**)



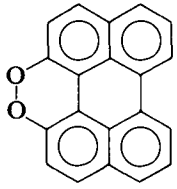
(**98**)



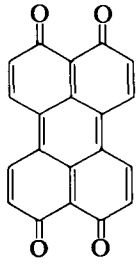
(**99**)



(**100**)

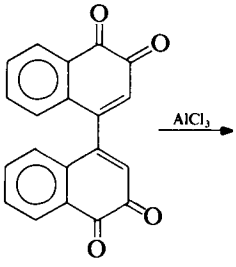


(**101**)

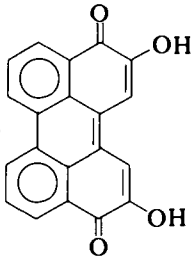


(**102**)

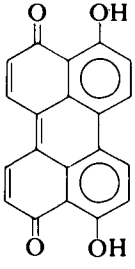
2,11-Dihydroxy-3,10-perylenequinone (**104**) has been synthesized in a similar way by treating 1,1'-binaphthyl-3,4,3',4'-diquinone (**103**) with aluminium chloride[61]. **104** cannot be oxidized to the diquinone.



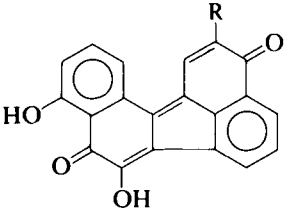
(**103**)



(**104**)



(**105**)



(**106**, R = OH)
(**107**, R = H)

4,9-Dihydroxy-3,10-perylenequinone (**105**) was found as a component of the fruiting bodies of the fungus *Daldinia concentrica*[63]. It has been established that perylene derivates

can also be produced in nature by oxidative coupling of naphthalene derivatives[64] and 4,5,4',5'-tetrahydroxy-1,1'-binaphthyl is considered to be the precursor of **105** in *Daldinia concentrica*[63]. It seems reasonable to assume that similar precursors are involved in the formation of bulgarhodin (**106**) and bulgarein (**107**), two other extended quinones found together with **105** in the fruiting bodies of *Bulgaria inquinans*[65]. This fungus grows, e.g. on the bark of freshly felled oaks. In order to produce the benzo[*j*]fluoranthene nucleus of **106** and **107**, a *para,meta* coupling of a binaphthyl precursor would be required. This is unlikely in 4,5,4',5'-tetrahydroxy-1,1'-binaphthyl itself but should be possible if further hydroxy groups are introduced into the 3- and 3'-positions.

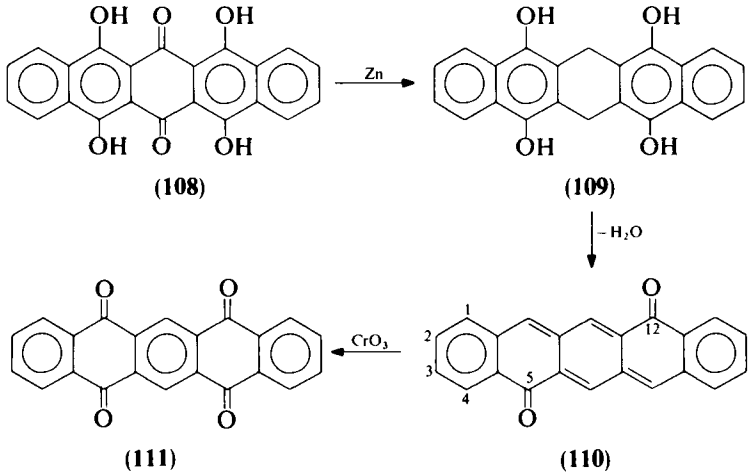
3,9-Perylenequinone (**99**) can be obtained by heating 3,9-dibromo- or 3,9-dichloroperylene with sulphuric acid[66]. Dehydrogenation of 1,2,7,8-tetrahydroperylene-3,9-quinone also yields (**99**)[67]. (**99**) is very easily oxidized to 3,4,9,10-diquinone **102**. It forms a red vat.

1,12-Perylenequinone (**100**) is obtained by oxidation of the conjugate hydroquinone in alkaline solution with air. The hydroquinone is formed by heating 2,2'-dihydroxy-1,1'-binaphthyl[68]. **100** is an isomer of perylene-1,12-peroxide (**101**), which is formed from 1,12-dihydroxyperylene with zinc chloride[69]. In contrast to **100**, **101** is not reduced with dithionite or hydrogen iodide.

3,4,9,10-Perylene-diquinone (**102**) is obtained by heating 3,9-dichloro-4,10-dinitro-, 3,4,9,10-tetranitro-, or 3,10-dinitroperylene with sulphuric acid[70]. It gives a dark-red vat dye with alkaline dithionite.

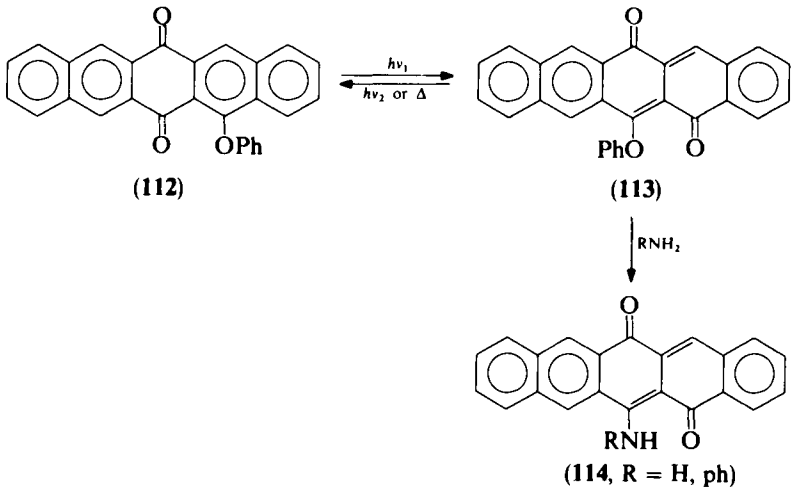
2. *Pentacenediones*

5,12-Pentacenequinone (**110**) has been synthesized starting with 5,7,12,14-tetrahydroxy-6,13-pentacenequinone (**108**)[71], which was reduced with zinc powder in acid or alkaline medium to 5,7,12,14-tetrahydroxy-6,13-dihydropentacene (**109**), which in turn loses water to form **110**. Oxidation of **110** with chromic acid yields the diquinone **111**.



The phenoxy derivative of 5,13-pentacenequinone **113** can be prepared from 5-phenoxy-6,13-pentacenequinone (**112**) by UV irradiation[72]. On exposure of a solution of **113** to visible light or on keeping it in the dark, the reverse isomerization takes place. These

reactions are paralleled by those of *peri*-aryloxyanthraquinone (see Section III.C.1) and naphthacenequinone (see Section III.D.3).



(112) (113)

(114, R = H, ph)

On account of the slow thermal isomerization of **113** it was possible to isolate it in the crystalline state. With amines, nucleophilic substitution of the phenoxy group by an amino group occurs at room temperature with formation of **114**.

3. Benzo[def]*chrysenediones (benzo*[a]*pyrenediones)*

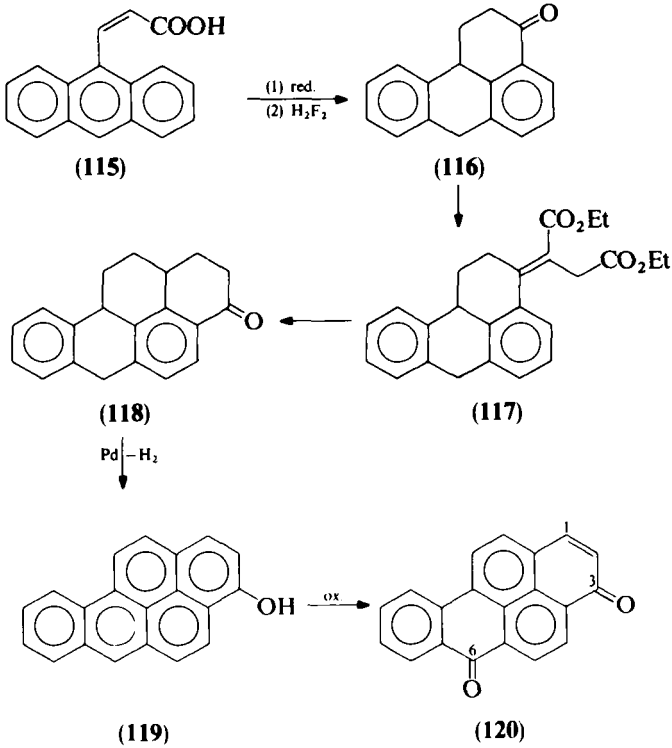
The IUPAC nomenclature prescribes benzo[*def*]chrysene instead of benzo[*a*]pyrene for the conjugate hydrocarbon. Since the name benzo[*a*]pyrene (or formerly 3,4-benzopyrene) has always been used in the literature this name is retained in this chapter.

3,6-benzo[*a*]pyrenequinone (**120**) has been synthesized starting with the 9-anthracene aldehyde which, on Knoevenagel condensation with malonic ester, yielded **115**. Reduction and cyclization with hydrogen fluoride gave **116**. Knoevenagel condensation of **116** with ethyl succinate led to **117** which, after saponification, was decarboxylated, reduced, and cyclisized to **118**. Dehydrogenation by heating with palladium gave 3-hydroxy-benzo[*a*]pyrene (**119**), which was easily oxidized to 3,6-benzo[*a*]pyrenequinone (**120**)[73].

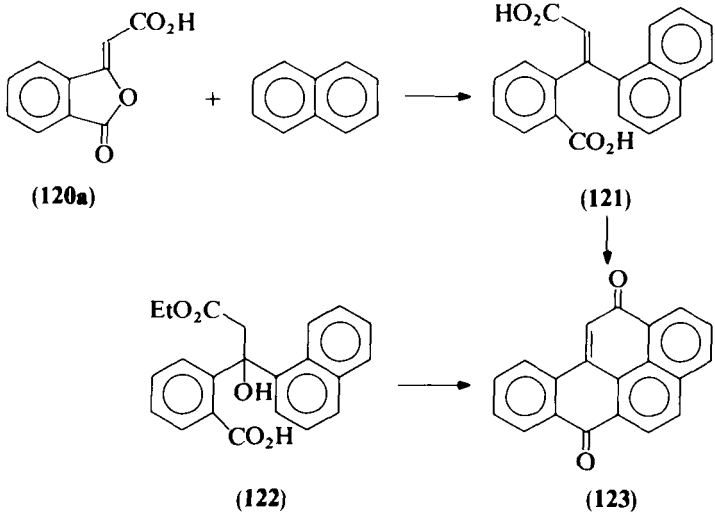
The synthesis of 6,12-benzo[*a*]pyrenequinone (**123**) was effected by condensation of the phthalidene acid **120a** with naphthalene in anhydrous hydrogen fluoride, probably with **121** as an intermediate[74]. A similar synthesis has been described by Norman and Waters[75]. Attempts to use the equivalent synthon **122** or its lactone for the synthesis of **123** have also been successful (77% yield)[76]. The first synthesis gave appreciable yields only with naphthalene, while the latter was more versatile also in the synthesis of derivatives.

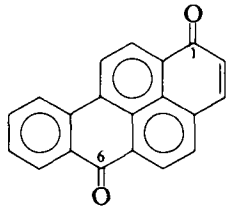
Oxidation of benzo[*a*]pyrene always gave mixtures of benzo[*a*]pyrenequinones. As with pyrene itself chromic acid attacks the 3,6- and 1,6-positions and 3,6-benzo[*a*]pyrenequinone (**120**) and 1,6-benzo[*a*]pyrenequinone (**124**)[19] are formed. The same is probably true for 10-azabenzo[*a*]pyrene, but only the 1,6-quinone **125** has been isolated[19].

Pure 3,6-benzo[*a*]pyrenequinone (**120**) is also obtained by oxidation of benzo[*a*]pyrene-1-carboxylic acid followed by decarboxylation[76].

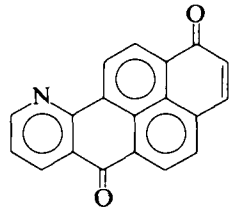


An important aspect of the oxidation of polycyclic aromatic compounds is the removal of these potential carcinogens from tap water or other sources. The $NaClO_2$ oxidation products of benzo[*a*]pyrene were separated by thin-layer chromatography and identified

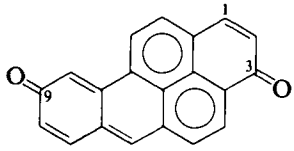




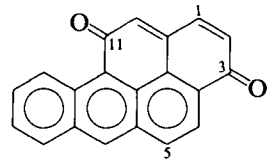
(124)



(125)



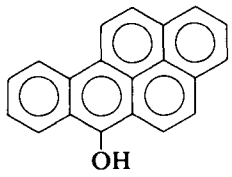
(126)



(127)

as 3,6-benzo[*a*]pyrenequinone (**120**), 3,9-benzo[*a*]pyrenequinone (**126**), and 3,11-benzo[*a*]pyrenequinone (**127**)[77]. The products of the chlorine dioxide treatment of benzo[*a*]pyrene have been investigated. Three of the eight isolated derivatives were again identified as **120**, **126** and **127**, which represent about 90% of the products and are considered inactive with respect to carcinogenesis. The other products are chloro derivates of benzo[*a*]pyrene. Accordingly, the treatment of drinking water with chlorine dioxide seems to be a method to reduce the possible carcinogenic danger[78]. For the same reason, the oxidation of benzo[*a*]pyrene with iron(III) chloride/hydrogen peroxide has been investigated. Oxidation in nitromethane and acetone as solvent yielded, among other products, 1.8% of **126**, 0.7% of **120**, and 1.4% of **127**[79].

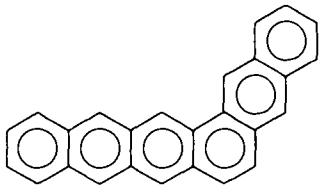
The destruction of benzo[*a*]pyrene by light and oxygen or ozone has been studied[80], using the hydrocarbon in low concentrations and an excess of ozone. From about eight products detected in these experiments three have been identified as 1,6-, 3,6- and 6,12-quinones (**124**, **120** and **123** respectively). Considerable evidence has been accumulated in support of the hypothesis that cellular metabolism is a prerequisite for the carcinogenic activity of the polycylic aromatic hydrocarbons. Hence much effort has been directed to the elucidation of the metabolism of the carcinogenic hydrocarbons. Often found metabolic products of benzo[*a*]pyrene are **123**, **124** and **120**. A common precursor seems to be 6-hydroxybenzo[*a*]pyrene (**128**), which is indeed oxidized in rat liver homogenate and is autoxidized in aqueous buffer–ethanol solution to produce the three quinones in yields of 36%, 27% and 29%, respectively. Thus the carcinogenic activity of benzo[*a*]pyrene seems to be connected with 6-hydroxybenzo[*a*]-pyrene (**128**) and its cellular oxidation[81]. The mechanism of the formation of **128** and two alternative pathways for the oxidation to the three quinones are discussed[82].



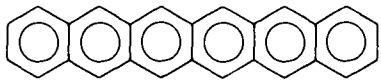
(128)

F. Six-ring Quinones

No extended quinones of hexaphene (**128a**) and hexacene (**129**) seem to have been described.



(**128a**)

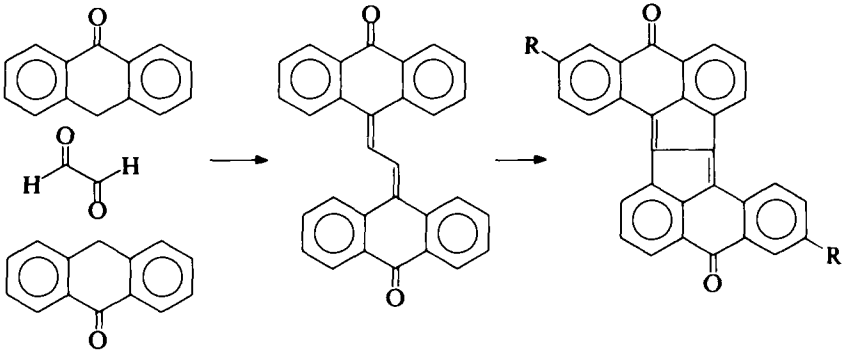


(**129**)

The known extended quinones with six rings are derived from aceanthreno[1,2:2',1']aceanthrene, anthanthrene, zethrene, benzoperylene, dibenzochrysene, dibenzopyrene and dibenzonaphthacene, which are reviewed below.

1. Aceanthrono[1,2:2',1']aceanthrone (acedianthrone)

Aceanthrono[1,2:2',1']aceanthrone, usually called acedianthrone (**133**), can be synthesized easily starting with anthrone (**130**). Condensation with glyoxal sulphate[82a] generates the stilbene-quinone **131**, which yields on alkaline oxidation[83] or on heating with nitrobenzene and organic acid chlorides **132**[84, 85].



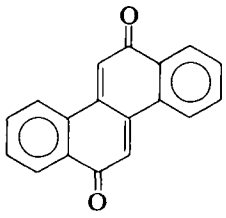
(**130**) (**131**) (**132**, R = H)
(**133**, R = Cl)

This process is used in industry for the synthesis of the vat dye Indanthrene Red Brown RR (**133**) from 2-chloroanthrone[11b]. In a similar manner many other derivatives of **132** have been synthesized[86].

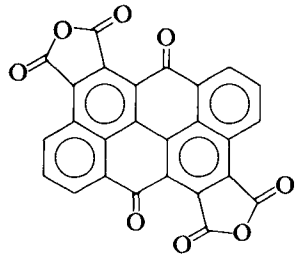
2. Anthanthrone

Quinones may undergo Diels–Alder reactions acting either as dienophiles or as dienes. Therefore an interesting path to polycyclic quinones could be a Diels–Alder reaction of angular anellated quinones with dienophiles. Indeed 6,12-chrysenedione (**134**) reacts in

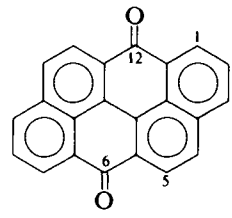
boiling maleic anhydride in the presence of chloroanil as dehydrogenating agent to give anthanthronetetracarboxylic acid-(5,6,12,13)-dianhydride (**135**), which in turn was decarboxylated to anthanthrone (**136**) (overall yield about 35%).



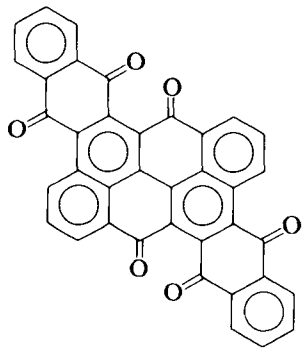
(**134**)



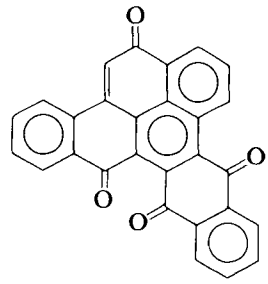
(**135**)



(**136**)

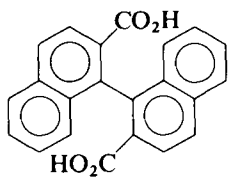


(**137**)



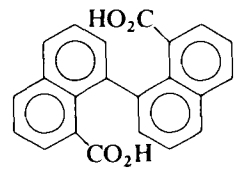
(**138**)

With nitrobenzene as solvent and dehydrogenating agent the addition reaction of maleic anhydride probably gave only the mono-addition product (as the hydroquinone) whereas naphthoquinone yielded both the mono- and di-adducts (**137**, **138**)[87].

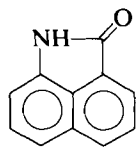


(**139**)

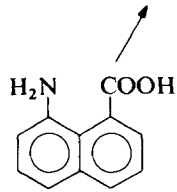
136



(**140**)



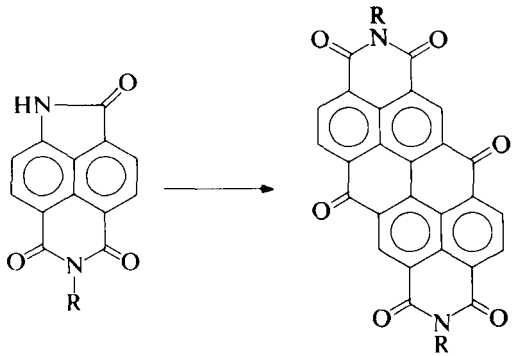
(**141**)



(**142**)

A synthesis of **136** starting with acenaphthene and the preparation of some derivatives has been described[88]. **136** was first synthesized by a double ring-closure of either 1,1'-binaphthyl-2,2'-dicarboxylic acid (**139**), or of the 8,8'-dicarboxylic acid **140** with sulphuric acid, or of the dichlorides with aluminium chloride[89]. This procedure is used for commercial syntheses. The starting material is naphthostyril (**141**), which is hydrolyzed to the amino acid **142**, diazotized, and dimerized, losing nitrogen[90]. The ring-closure is effected by sulphuric acid.

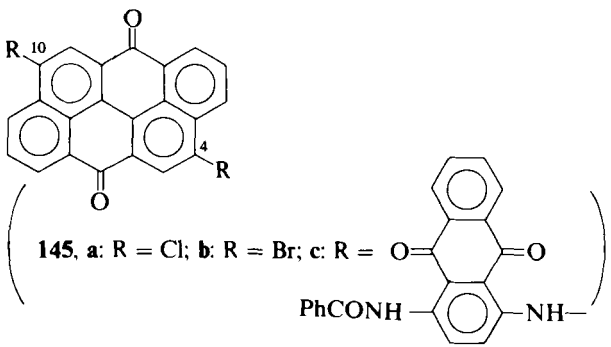
In the same way the novel vat dyes, such as 6,12-anthanthrenedione-3,4,9,10-tetracarboxylic diimides (**144a–c**), have been prepared from **143**[91].



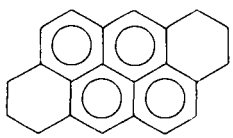
(**143**) (**144**)

a: $R = H$
b: R = Et
c: R = Ph

Anthanthrone is an intensely coloured orange vat dye, but has only little fibre affinity. By halogenation, 4,10-dichloroanthanthrone (**145a**) and 4,10-dibromo-anthanthrone (**145b**) are formed in high yield[92] and show greater affinity to fibres and possess brighter, more intense red shades.



145, **a**: R = Cl; **b**: R = Br; **c**: R =



(**146**)

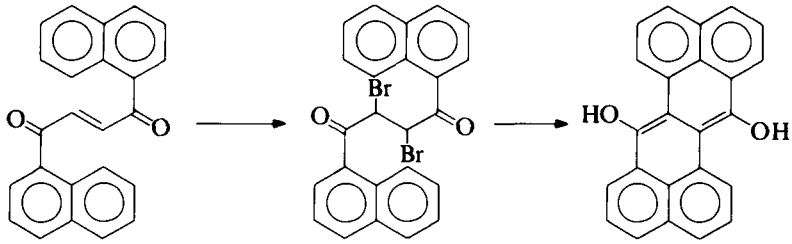
The bromine atoms in the 4- and 10-positions undergo nucleophilic substitution: heating of **145b** with 1-amino-4-benzoylaminoanthraquinone gives, e.g. another valuable

vat dye, **145c** (Indanthren Grey BG)[93]. For the reduction of anthanthrone to anthanthrene the zinc powder melt is, as usual, the simplest and best procedure[94].

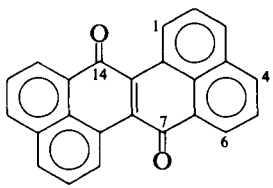
Hydroiodic acid/red phosphorous reduces anthanthrone **136** to 1,2,3,7,8,9-hexahydrodibenzo[*def, mno*]chrysene (**146**), with replacement of the oxygen atoms and partial hydrogenation of the aromatic rings[95]. The electrochemical behaviour of anthanthrone has been examined and it was found that ion pairs with divalent metal ions were absorbed at the surface of mercury electrodes. This phenomenon is not observed with gold electrodes. The possible structure and orientation of the ion pairs on the surface has been discussed[96].

3. Dibenzo[hi:qr]*naphthacene-7,14-dione (7,14-zethrenequinone)*

Of the derivatives of zethrene, the 7,14-quinone **150** has been described[10b].



(147) **(148)** **(149)**



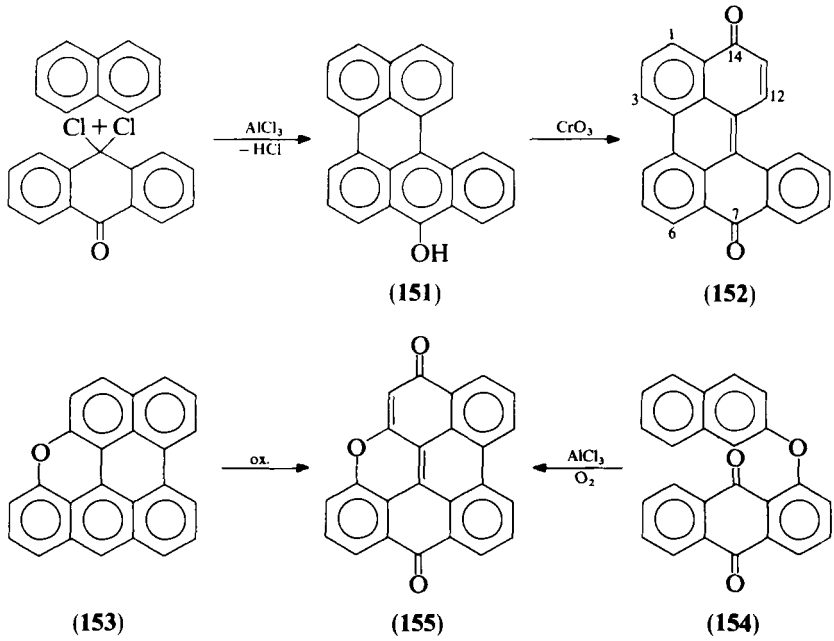
(150)

The diketone **147** is obtained by Friedel–Crafts condensation of fumaryl chloride with naphthalene. **147** adds bromine to yield **148**, which cyclizes to **149** in an aluminium chloride/sodium chloride melt. When oxygen is passed in during melting, **150** is formed immediately. 7,14-Zethrenequinone gives a blue vat on short reduction with alkaline sodium dithionite.

4. Benzo[a]*perylene-7,14-dione*

Benzo[*a*]perylene-7,14-quinone (**152**) has been synthesized in two steps, starting with an aluminium chloride catalysed condensation of 10,10-dichloroanthrone with napthalene to 7-hydroxybenzo[*a*]perylene (**151**), which gives the quinone **152** on oxidation with chromic acid[97]. **152** forms a greenish-blue vat.

The quinone with an oxygen bridge between the 11- and 12-positions, **155**, is obtained by oxidation of the conjugate hydrocarbon **153** or by heating 1-(*β*-



(151) (152)

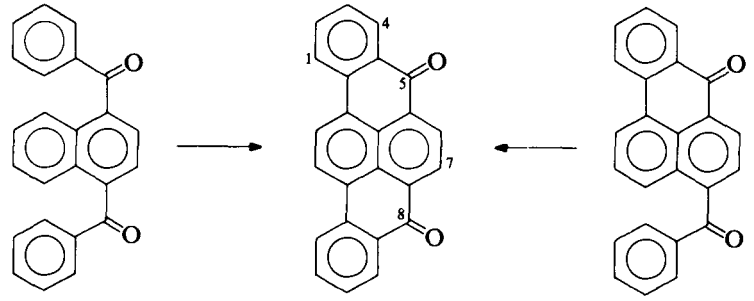
(153) (155) (154)

naphthoxy)anthraquinone (**154**) in an aluminium chloride/sodium chloride melt passing in oxygen[98].

5. *Benzo*[rst]*pentaphene-5,8-dione (dibenzo*[a,i]*pyrene-5,8-quinone)*

The correct IUPAC name is the first one, but the second is mostly used in the literature and is therefore retained here.

Dibenzo[*a*, *i*]pyrene-5,8-quinone (**157**) can be easily synthesized by Scholl cyclization of 1,4-dibenzoylnapthalene (**156**)[99] or 4-benzoylbenzanthrone (**158**)[100]. Also chromium trioxide[99] and selenium dioxide oxidation of dibenzo[*a*, *i*]pyrene leads to **157**[101]. Ozonolysis of dibenzo[*a*, *i*]pyrene yielded in low yield (17%) the 5,8-dione. 56% of the starting material has been recovered[102].



(156) (157) (158)

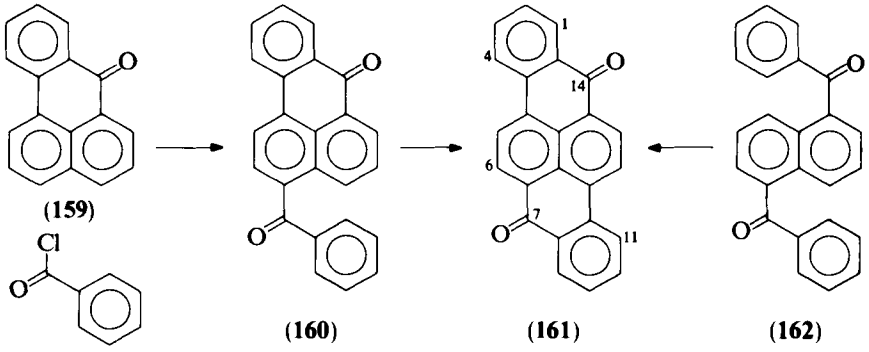
Oxidation of certain condensed aromatic carcinogenic hydrocarbons with chlorine dioxide to quinones has been recommended as a possible procedure to purify tap water (see also Section III.E.3). The quinones are considered as not dangerous. It has even been claimed that **157**, which was found in cigarette-smoke condensates, stops the progress of already established cancer in mice[103].

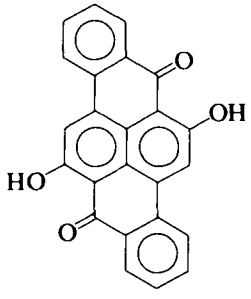
157 was formed in an attempt to perform a Diels–Alder condensation between *trans*-1,2-dibenzoylethylene and diethyl muconate. The product was not the expected one but **157**. A mechanistic explanation for this surprising result has been given[104]. **157** gives a yellow-red vat dye. In contrast to the dibenzo[*b*, *i*]pyrene-7,14-quinone (Section III.F.6) **157** is not used commercially as a vat dye.

The synthesis of 1,2-diazadibenzo[*a*, *i*]pyrene-5,8-quinone has also been described[105]. **157** is attacked by bromine to yield a dibromo compound. Though this compound was used as vat dye, the constitution has not been published[11c].

6. *Dibenzo*[b,def]*chrysene-7,14-dione (dibenzo*[b,i]*pyrene-7,14-quinone)*

The IUPAC name is the first one. However dibenzo[*b*, *i*]pyrene-7,14-quinone (**161**) and some of its derivatives are of technical interest as vat dyes, and the conventional name will be retained here. The quinone (**161**) is used as golden-yellow dye (Indanthren Goldgelb-GK or Cibanongelb-GK). It was first synthesized by heating benzanthrone (**159**), benzoyl chloride, and aluminium chloride in the presence of oxidants or oxygen. **160** is an intermediate[106]. This synthesis is now obsolete. The commercially used synthesis is a Scholl cyclization of 1,5-dibenzoylnaphthalene (**162**)[107] which can be performed also without oxygen or other oxidants[108], although an improvement was achieved by addition





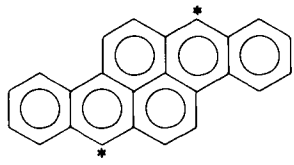
(163)

of m-$O_2NC_6H_4SO_3K$ as hydrogen acceptor to the aluminium chloride/sodium chloride melt[109]. The reaction was also performed with aluminium chloride in chlorobenzene, in the presence of 2,4-dinitrobenzene and melting-point reducing agents such as alkali chlorides, organic amines or amides (urea)[110].

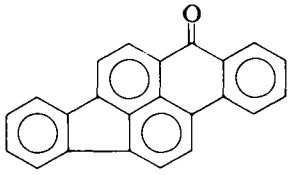
Many derivatives of **161** have been synthesized by Scholl cyclization or by direct substitution reactions. 8-Bromodibenzo[*b*, *i*]pyrene-7,14-quinone, another vat dye (Indanthren Goldgelb-RK or Cibanongoldgelb-RK), is prepared by bromination of **161** in the melt[111]. 6,13-Dihydroxydibenzo[*b*, *i*]pyrene-7,14-quinone (**163**) is formed (70%) from 2,6-dihydroxy-1,5-dibenzoylnaphthalene by Scholl cyclization[19]. It is converted by phosphorus pentachloride to 6,13-dichlorodibenzo[*b*, *i*]pyrene-7,14-quinone, which in turn reacts with aniline to give 6-anilino-13-chloroquinone and, on further heating, yields 6,13-dianilinoquinone.

The same product can be obtained by methylating the hydroxyquinone and heating the dimethyl ether with aniline. The methoxy groups are substituted as easily as the chlorine atoms[19]. **161** was also used for the synthesis of dibenzo[*b*, *def*]chrysene-7,14-^{14}C (**164**). The radioactive carbon was introduced via Grignard reaction of 1,5-dibromonaphthalene with [^{14}C]carbon dioxide. The dicarboxylic acid was converted to 1,5-dibenzoylnaphthalene by Friedel–Crafts reaction with benzene. For the Scholl cyclization of the dibenzoylnaphthalene in an aluminium chloride/sodium choride melt *m*-dinitrobenzene was used as oxidant. Reduction of the quinone to the dibenzochrysene was effected as usual by zinc dust in a sodium chloride/zinc chloride melt at 210° C with about 70% yield[112].

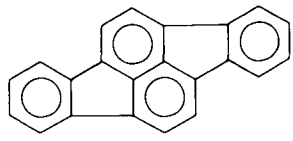
161 on vacuum flow pyrolysis successively eliminates two molecules of carbon monoxide and forms 13*H*-naphtho[3,2,1-*cd*]fluoranthene-13-one (**165**) and indeno[1,2,3-*cd*]fluoranthene (**166**)[113].



(**164**)



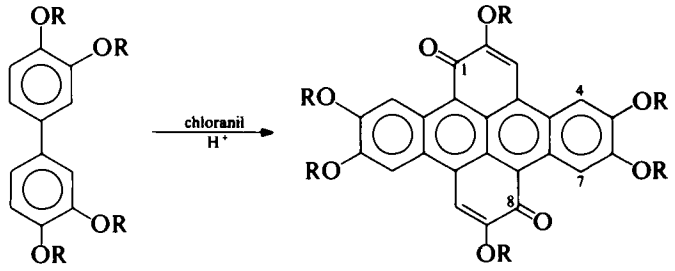
(**165**)



(**166**)

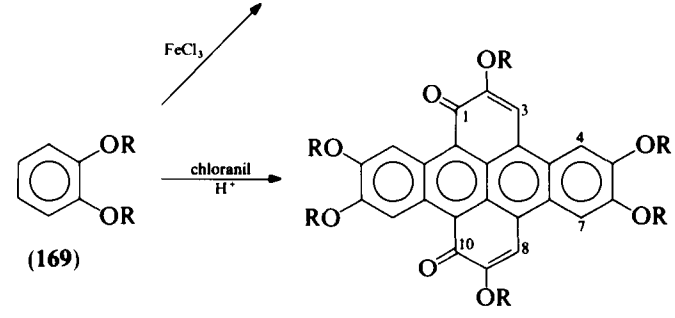
7. *Dibenzo*[fg,op]*naphthacenediones*

A surprising, elegant and effective synthesis of dibenzopyrene quinones was possible by oxidation of 3,3',4,4'-tetraalkoxydiphenyl (**167**) and of 1,2-dialkoxybenzenes (**169**), respectively, with chloranil in aqueous sulphuric acid. 2,5,6,9,12,13-Hexamethoxydibenzo[*fg*, *op*]naphthacene-1,8-dione (**168a**) was formed from the tetramethoxydiphenyl (**167**) in 76% and the isomeric 1,10-dione (**170a**) from 1,2-dimethoxybenzene in 72% yield[115]. Though **168** and **170** may be regarded as derived from dibenzopyrene, the IUPAC notation as dibenzonaphthacene derivatives is used here. Ethers with other alkyl groups (**168b, c** and **170b**) have also been synthesized.



(167) (168)

a: R = Me; **b**: R = CD_3; **c**: R = Et



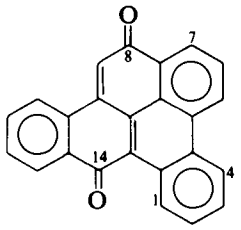
(169) (170)

a: R = Me; **b**: R = Et

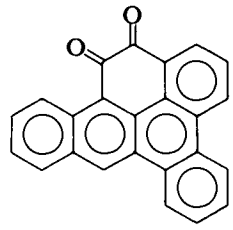
The mechanism of the reactions has been discussed[114, 115]. The ability of chloranil to abstract hydride ions, i.e. the oxidative power, seems to be enhanced considerably by protonation. Moist iron(III) chloride transforms 1,2-dimethoxybenzene to **168a**. The 1,8-dione **168** dyes cotton to a dull violet which lacks fastness.

8. Naphtho[1,2,3,4,-def]chrysene-8,14-dione

The 5-methyl derivative of naphtho[1,2,3,4-*def*]chrysene-8,14-dione (**171**) has been obtained by chromic acid oxidation of the corresponding hydrocarbon[116]. This reaction seems to be remarkable because, e.g. the formation of the *o*-quinone **172** would retain a larger aromatic system. Indeed Zincke and coworkers supposed falsely that **172** was formed[117].



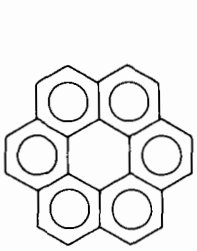
(171)



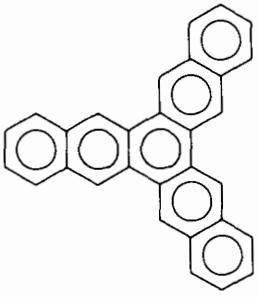
(172)

G. Seven-ring Quinones

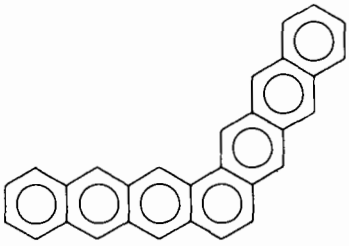
Extended quinones of the common seven-ring aromatics coronene (**173**), trinaphthylene (**174**), heptaphene (**175**) and heptacene (**176**) have not yet been described. The quinones of the other seven-ring aromatics are treated in alphabetical order.



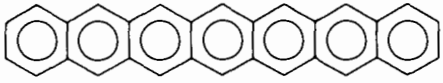
(**173**)



(**174**)



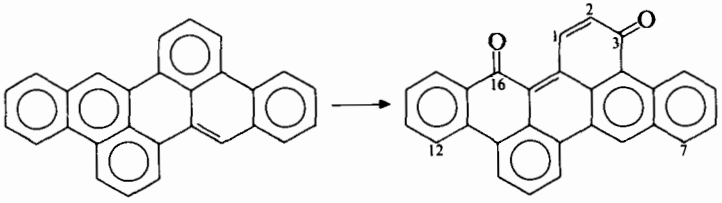
(**175**)



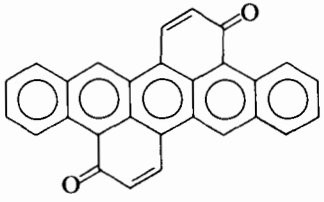
(**176**)

1. Dibenzo[hi:st]*pentacenedione*

Oxidation of dibenzo[*hi*:*st*]pentacene (**177**) yields a quinone of uncertain structure which contains three oxygen atoms[114]. On reduction with alkaline dithionite and reoxidation with air a compound with two oxygens is formed[115], very probably **178**. Structure **179**[115] should be excluded[10c]. **178** gives with alkaline dithionite an orange-red vat.

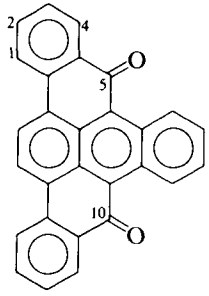


(**177**) (**178**)

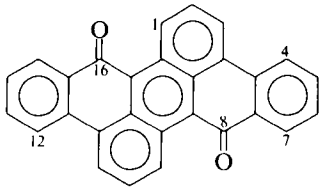


(**179**)

At fusion of 9,10-dibenzoylanthracene with aluminium chloride a red violet or bluish condensation product is formed[116]. Its constitution can be the dibenzo [*h*:*rst*]pentaphene-5,10-dione (**180**) or the dibenzo[*hi*:*st*]pentacene-8,16-dione (**181**) or a mixture of both, and since migrations of benzoyl groups are sometimes observed in the aluminium chloride melt, other structures cannot be excluded.



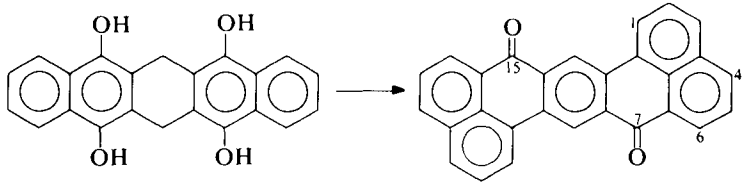
(**180**)



(**181**)

2. *Dibenzo*[jk:uv]*pentacene-7,15-dione*

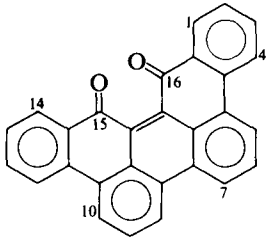
Dibenzo[*jk*:*uv*]pentacene-7,15-dione (**183**) has been synthesized simply by heating 5,7,12,14-tetrahydroxy-6,13-dihydropentacene (**182**) with glycerol and sulphuric acid[117]. In a zinc dust melt **183** yields a hexahydro derivative of the conjugate hydrocarbon. With alkaline dithionite **183** gives no vat.



(**182**) (**183**)

3. *Dibenzo*[fg:ij]*pentaphene-15,16-dione*

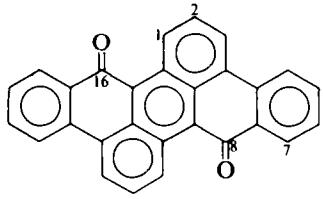
On oxidation of dibenzo[*fg*:*ij*]pentaphene a quinone is formed which probably possesses the constitution **184**. With hydrazine it forms an azine[118].



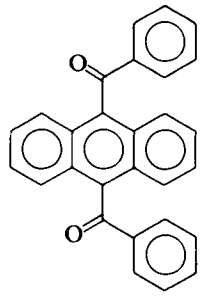
(**184**)

4. *Dibenzo*[h:rst]*pentaphene-5,10-dione*

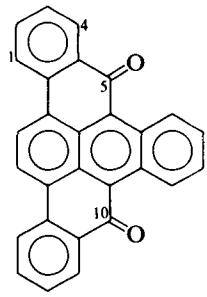
On fusion of 9,10-dibenzoylanthracene (**186**) with aluminium chloride a red violet or bluish condensation product is formed[119]. The constitution is not clear. It may be the dibenzo[*h:rst*]pentaphene-5,10-dione (**187**) or the dibenzo [*hi:st*]pentacene-8,16-dione (**185**) or a mixture of both and yet other structures.



(**185**)



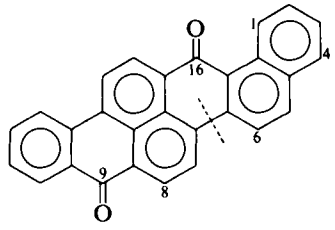
(**186**)



(**187**)

5. *Dibenzo*[b:tuv]*picene-9,16-dione*

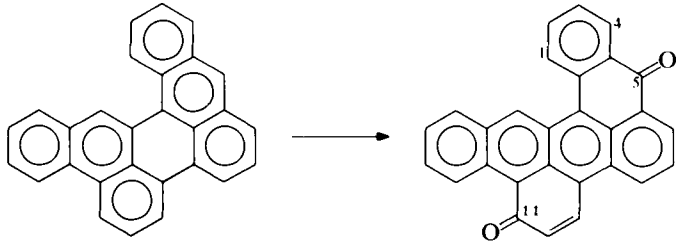
The dibenzo[*b:tuv*]picene-9,16-dione (**188**) is formed by Scholl cyclization of 3-(1-naphthoyl)-benzanthrone in an aluminium chloride melt[120]. The position of the ring-closure is marked by a dotted line. **188** dyes cotton in brown-orange hues.



(**188**)

6. *Dibenzo*[a,n]*perylene-5,11-dione*

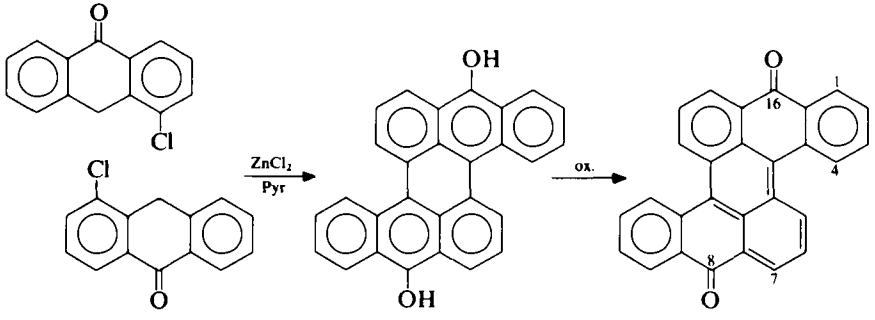
A compound with the tentative structure of a dibenzo[*a, n*] perylene-5,11-dione (**190**) is formed at oxidation of dibenzo[*a, n*]perylene (**189**) with selenium dioxide in acetic acid. The quinone forms a blue-green vat with alkaline dithionite[121,122].



(**189**) (**190**)

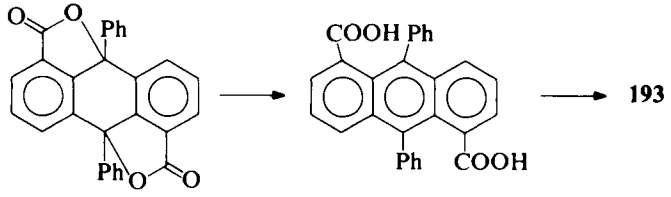
7. *Dibenzo*[a,j]*perylene-8,16-dione (hetero-coerdianthrone)* (**193**)

In the older literature the name hetero-coerdianthrone is used for structure **193**. Several syntheses have been described. The simplest seems to be heating of 1-chloroanthrone-(10) (**191**) with zinc chloride and pyridine at 245°C. The first-formed hydroquinone **192** is oxidized to **193** during working up[123].



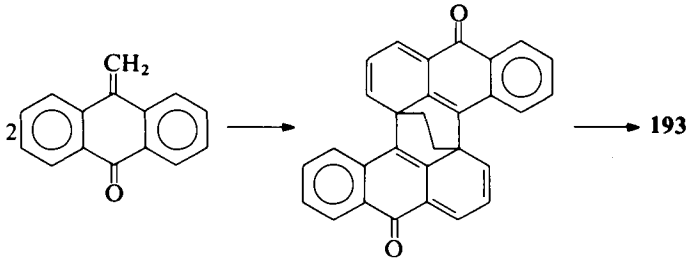
(**191**) (**192**) (**193**)

An interesting synthesis has been described by Scholl and coworkers starting with anthraquinone-1,5-dicarboxylic acid. The dichloride reacts with aluminium chloride in benzene to the dilactone **194**, which can be reduced with hydroiodic acid and phosphorous to 9,10-diphenylanthracene-1,5-dicarboxylic acid (**195**). On treatment with sulphuric acid **195** gives **193**[124].



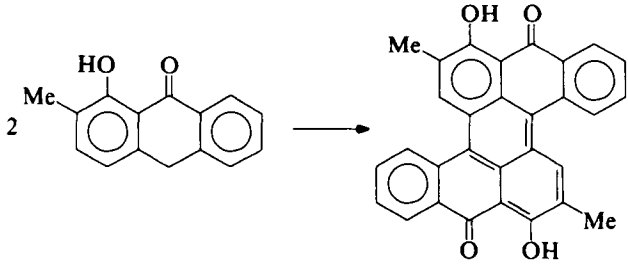
(**194**) (**195**)

Another very simple synthesis is achieved by melting methyleneanthrone (**196**) with aluminium chloride. In the first step the endocyclic ring system **197** is formed which, on heating with aluminium chloride or alone, splits off ethylene in a retro-Diels–Alder reaction and forms **193**[124].



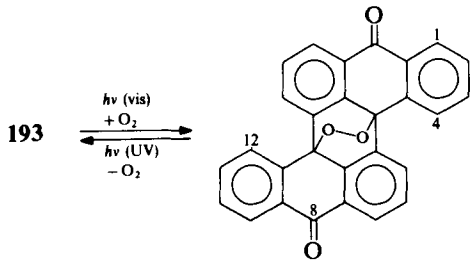
(**196**) (**197**)

The Scholl cyclization was also used for the synthesis of **193**, starting with 1,5-dibenzoylanthracene. As oxidant in the aluminium chloride melt manganese dioxide was used[125].



(198) **(199)**

The described syntheses have also been used to prepare some derivatives of **193**[126]. **199** was synthesized by mild oxidation of 1-hydroxy-2-methyl-9-anthrone (**198**) with iodine in pyridine[127]. **193** is easily reduced to the corresponding hydrocarbon with zinc in pyridine/acetic acid[123], when it forms in organic solvents a red-violet solution with strong red fluorescence. On irradiation with visible light in the presence of oxygen the extraordinary thermally stable 4*b*,12*b*-endoperoxide **200** is formed[128, 129]. This is split



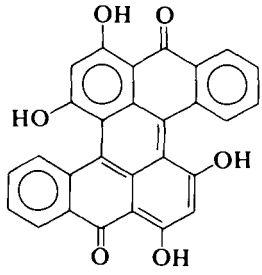
(200)

with light of wavelength between 248 and 334 nm to the parent compounds[129]. These high-quantum-yield processes are very selective with only one subordinate side-reaction (quantum yield 0.005)[130]. The system is proposed as a new reusable liquid chemical actinometer in the UV region[129–131]. The quantum yield for the splitting reaction in the mentioned wavelength range is nearly wavelength-independent. The system has high reproducibility and accuracy and can be used without loss of accuracy in more than 100 repeated actinometric cycles[129]. The kinetics of the self-sensitized photo-oxidation with visible light[131] and the photolysis of the *endo* peroxide[132] have been investigated.

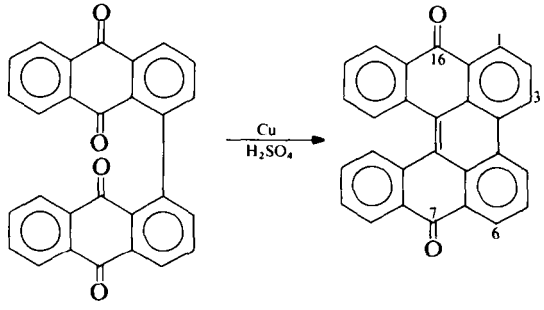
A further derivative of **193**, 5,8,13,15-tetrahydroxy-7,16-dibenzo[*f*, *n*]perylene-7,16-dione (**201**), is formed (29%) at prolonged heating of an alkaline solution of 1,3-dihydroxy-9,10-anthraquinone under nitrogen in the presence of hydroquinone[133].

8. Dibenzo[a, o]*perylene-7,16-dione (helianthrone, ms-benzodianthrone)* (**203**)

203 is formed easily by reduction of 1,1′-dianthraquinonyl (**202**) with copper powder in concentrated sulphuric acid. Other reducing agents, such as zinc/acetic acid, tin(II)

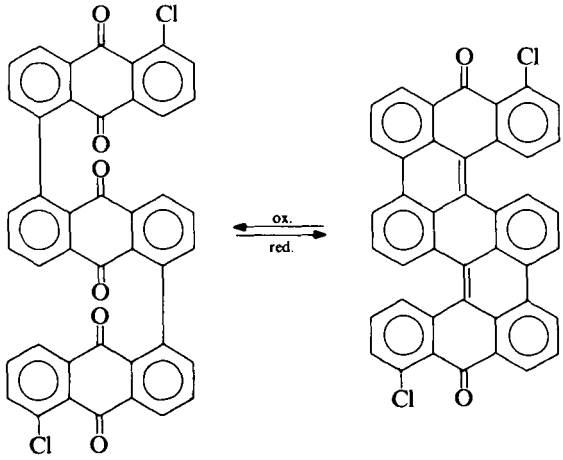


(201)

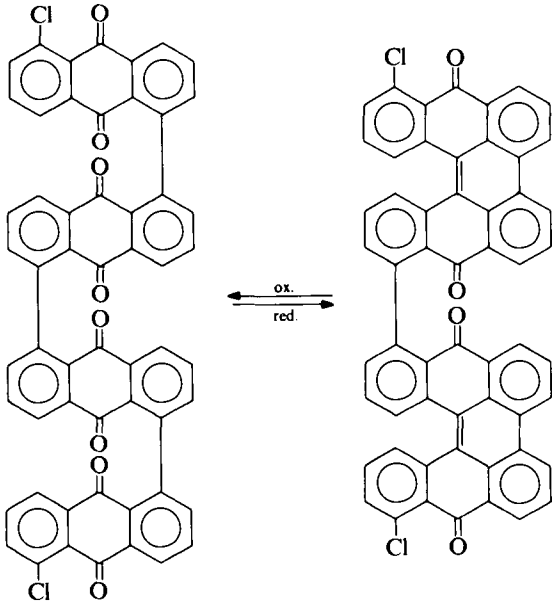


(202) (203)

chloride/alcoholic hydrochloric acid, and zinc in a zinc chloride melt or with alcoholic potassium hydroxide, can be used[134]. The formation of **203** is obviously facilitated by the proximity of the anthraquinone nuclei in **202** and its derivatives. It seems especially remarkable that the two helianthrone homologues **203a** and **203b** are not stable. They revert to **202a** and **202b**, respectively, even in the solid state[135].

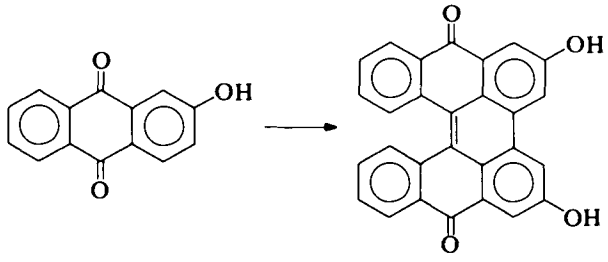


(202a) (203a)



(202b) (203b)

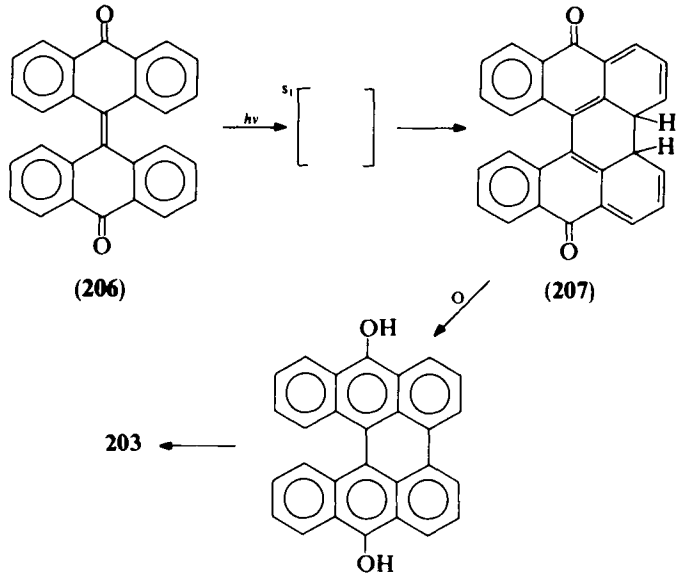
Alkyl, carboxy[136], chloro[137], and hydroxy derivatives[138] have been synthesized by reductive cyclization. Hydroxy derivatives of **203**, e.g., **205**, can also be obtained by reduction of hydroxyanthraquinones, directly[139] or by oxidation of hydroxyanthrones[140].



(204) (205)

An elegant synthetic access to helianthrones is the irradiation of dehydrodianthrones. On irradiation in the presence of oxygen **206** forms the hydroquinone **208**. This is oxidized *in situ* to the quinone **203**[141]. The irreversible photochemical primary process is a ring connection to **207** in the 4,4'-position starting from the S_1 state. The aromatization under formation of the hydroquinone is a solvent-dependent secondary reaction. Below $-130°C$ the triplet state seems to be involved in the primary reaction[142].

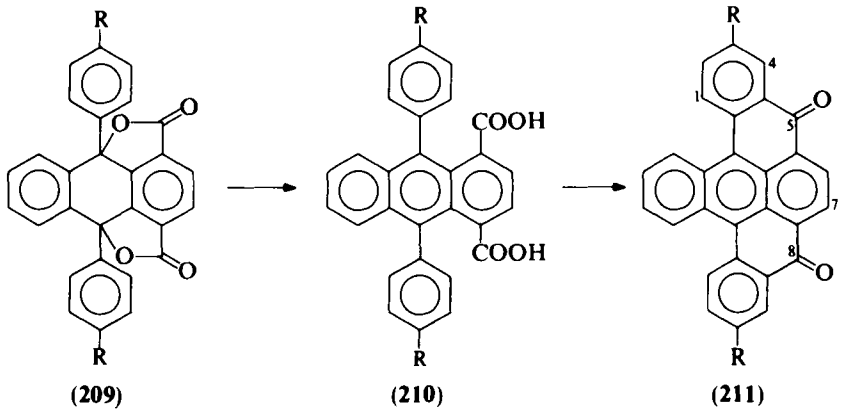
The results of Pariser–Parr–Pople calculations suggest that the intermediate **207** is the most probable structure of the green photochromic form of dehydrodianthrone (**206**)[143]. Finely grounded **203** yields with alkaline dithionite a green vat.



(206) (207) (208)

9. *Naphtho[1,2,3-rst]pentaphene-5,8-dione*

The 3,10-dimethyl- and 3,10-dimethoxy-naphtho[1,2,3-*rst*]pentaphene-5,8-dione (**211a** and **b**) are accessible by Friedel–Crafts reaction of anthraquinone-1,4-dicarboxylic acid with toluene or anisole to the dilactone **209**. **209** can be reduced by hydroiodic acid to **210**, which gives with concentrated sulphuric acid a double ring-closure to **211**[144]. **211a** is a blue and **211b** a green vat.

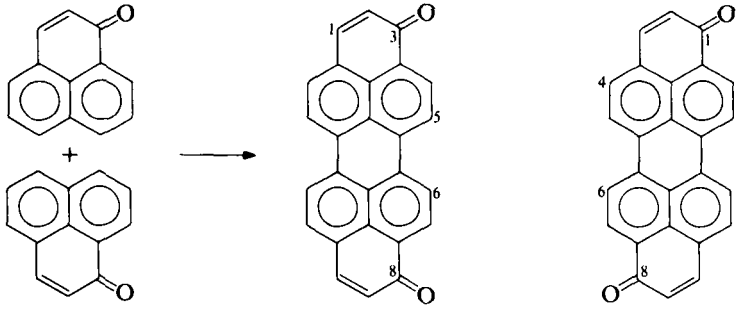


(209) (210) (211)

a: R = Me; **b**: R = OMe

10. Dibenzo[cd,lm]*perylenediones (peropyrenequinones)*

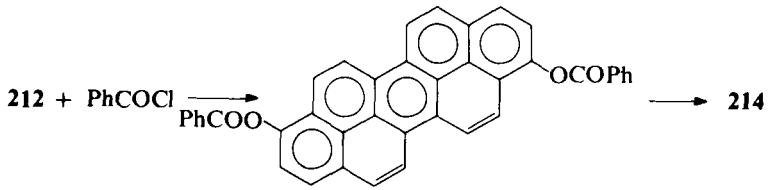
Dibenzo[*cd, lm*]perylene-3,8-dione (**213**) is formed by melting 1-phenalenone (**212**) with methanolic potassium hydroxide[145]. It is possible that the 1,8-dione **214** is also formed. **213** (or **214**) is a purple-red vat dye. Several derivatives have been prepared by



(212) (213) (214)

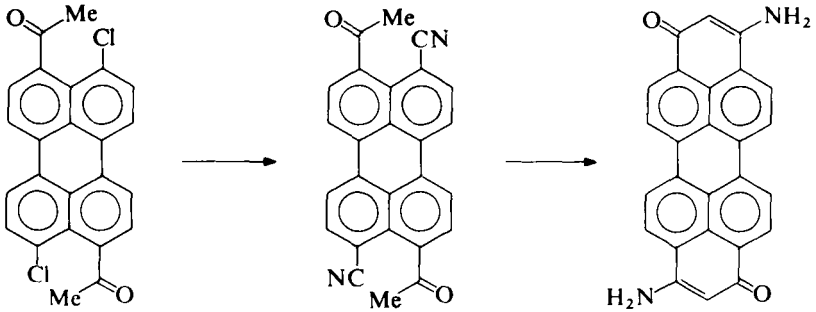
using substituted 1-phenalenones[146]. The corresponding hydrocarbon is sometimes also named peropyrene, but the IUPAC nomenclature is preferred.

An unequivocal two-step synthesis of the dibenzo[*cd, lm*]perylene-1,8-dione (**214**) started with 1-phenalenone (**212**) which, on heating with benzoyl chloride, gave 3,10-dibenzoyloxydibenzo[*cd, lm*]perylene (**215**). Saponification of **215** with concentrated sulphuric acid yielded the quinone **214**[147].



(215)

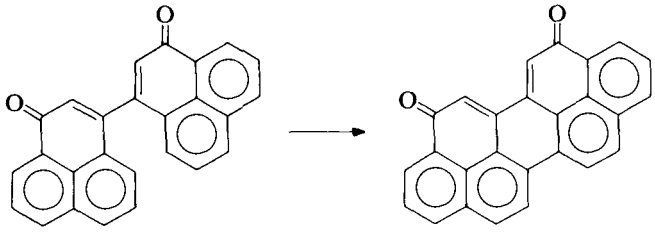
The 3,10-diamino derivative (**218**) of the 1,8-dione **214** has been obtained by heating 3,9-diacetyl-4,10-dichloroperylene (**216**) with copper(I) cyanide in quinoline. The dinitrile **217**



(216) (217) (218)

should be an intermediate. The reaction is also possible with other acyl groups in 3,9-positions[148].

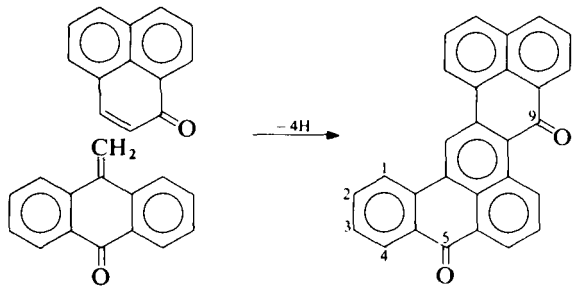
3,3'-Biphenalene-1,1'-dione (**219**) gives, on Scholl cyclization, the dibenzo [*cd*, *lm*]perylene-4,7-dione (**220**). The hydroquinone of **220** is formed readily on reduction. Several ethers of the hydroquinone and the diacetate have been described[149].



(219) (220)

11. Tribenzo[a:de:mn]*naphthacene-5,9-dione (***221***)*

The synthesis of **221** involved a Diels–Alder condensation between 1-phenalenon and methyleneanthrone in boiling nitrobenzene[10d]. Reduction of **221** in a zinc powder melt leads to the corresponding aromatic hydrocarbon, showing the instability of the central double bonds in naphthacene. Nevertheless it is possible to generate an unstable green vat from **221** with alkaline dithionite.



(221)

H. Eight-ring Quinones

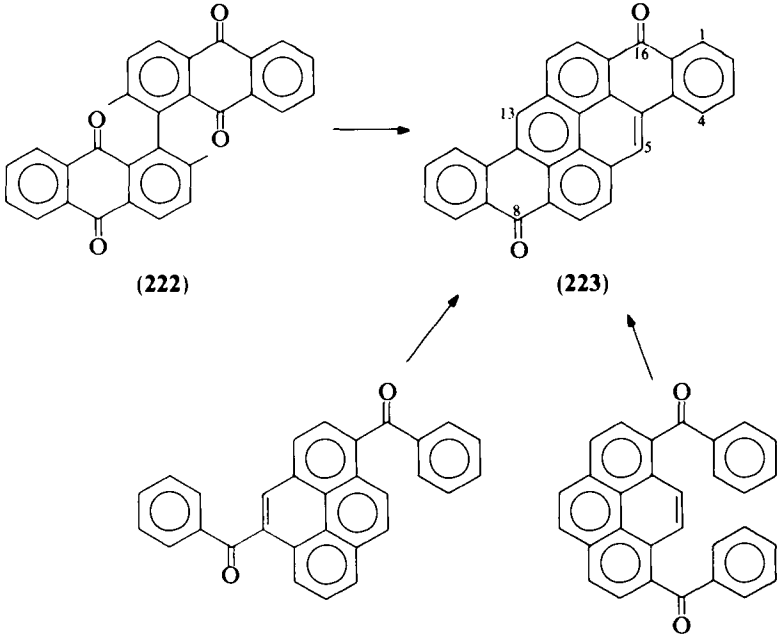
The most important eight-ring quinones which are derived from pyranthrene and *meso*-naphthodianthrene are treated first. The others follow in alphabetical order.

1. Pyranthrenediones (pyranthrones)

Two pyranthrenediones, the 8,16- and 5,13-isomers, are known. Only the 8,16-dione, also named pyranthrone, and some of its derivatives are of technical importance as fast vat dyes.

Pyranthrone (**223**) is prepared commercially by a Knoevenagel-type double ring-closure of 2,2'-dimethyl-1-1'-bianthraquinonyl (**222**), which is produced by Ullmann reaction of 1-chloro-2-methylanthraquinone[150]. The ring-closure is effected by alkali, e.g. by heating

222 at 105°C with potassium hydroxide/isobutanol, but it is also possible by heating **222** alone, with zinc chloride or with potassium hydroxide/sodium acetate. Some process improvements have been described in patents[151].

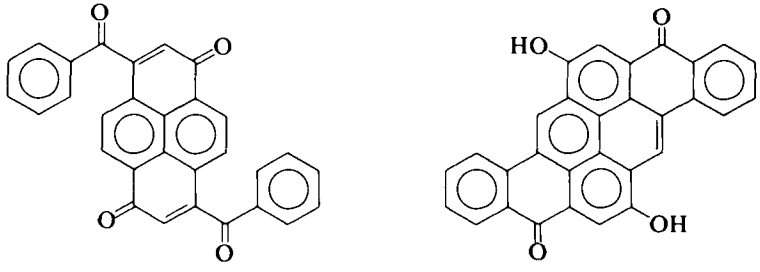


(222) **(223)**

(224) **(225)**

Scholl cyclization of 1,6-dibenzoylpyrene (**224**) also yields pyranthrone (**223**) (85%)[19, 152] which is formed in addition from 3,6-dibenzoylpyrene (**225**), but the yield is lower (30%) and decomposition is observed[19]. This result shows that rearrangements of the aryl ketones can occur under the reaction conditions and that the course of Scholl cyclization is not always unambiguous.

It is possible to synthesize pyranthrone also in a one-step reaction of pyrene, aluminium chloride and benzoyl chloride[153]. 1,6-Dibenzoyl-3,8-pyrenequinone (**226**) on melting with aluminium chloride/sodium chloride forms 6,14-dihydroxypyranthrone (**227**)[19].



(226) **(227)**

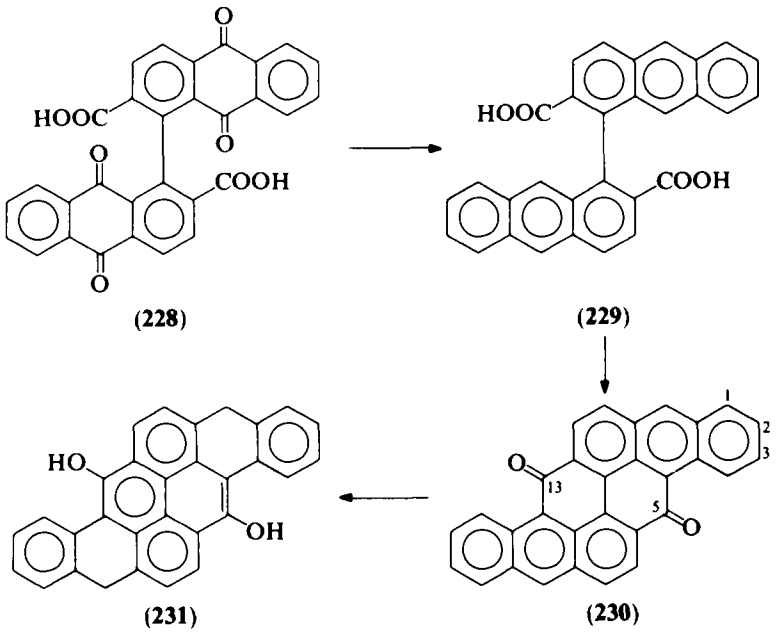
Pyranthrone forms a purple red vat and the salt of tetrahydropyranthrone is formed on reduction of **223** with alkaline dithionite[154].

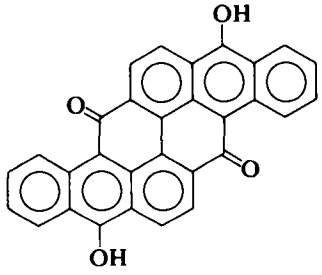
Since pyranthrone is a valuable vat dye (Indanthren Goldorange G, Caledon Goldorange-G), there were many attempts to synthesize its derivatives. Alkyl homologues have been synthesized starting from the corresponding 1,1'-bianthraquinonyls[155 156] and 1,3-diarylpyranthrones are obtained by reduction of 2,2'-diaroyl-l,l'-bianthraquinonyls. Pyranthrone itself is formed from the 1,1'-bianthraquinonyl-2,2'-aldehyde already at vatting[157]. Halogen derivatives of **223** can be obtained by synthesis[158] or direct halogenation[159]. It is also possible to introduce nitro groups by mixed acid or with nitric acid in nitrobenzene[160]. A dibenzoylpyranthrone is obtained by heating tetrachlorotetrabenzoylpyrene with potassium hydroxide in quinoline[161].

4-Bromopyranthrone (Caledon Goldorange-2RTS), 4,7-dibromopyranthrone (Indanthren Orange RRTS, Caledon brilliantorange-4R), and a mixture of a di- and tribromo derivatives (Indanthren Orange 4R) are of technical interest as vat dyes. They are prepared by bromination of pyranthrone in chlorosulphonic acid in the presence of iodine or sulphur[11b]. For the reduction potentials of the pyranthrone dyes see Marshall and Peters[162] and Gupta[163].

On oxidation with chromic acid pyranthrone gives the dicarboxylic acid **228**, which can be reduced with ammonia/zinc to the bianthracene **229**. Heating **229** with zinc chloride or phosphorous pentachloride yields pyranthrene-5,13-dione (**230**)[164]. **230** forms with alkaline dithionite[230] a blue-green vat at room temperature the blue salt of the conjugate hydroquinone, at elevated temperatures the green salt of the tetrahydro derivative **231**[154].

230 can be dihydroxylated directly in the 8,16-position to **232**. The tautomeric 5,13-dihydroxypyranthrone **233** is obtained by hydroxylation of pyranthrone[165].





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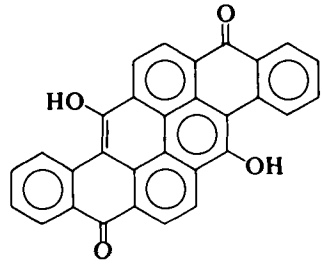
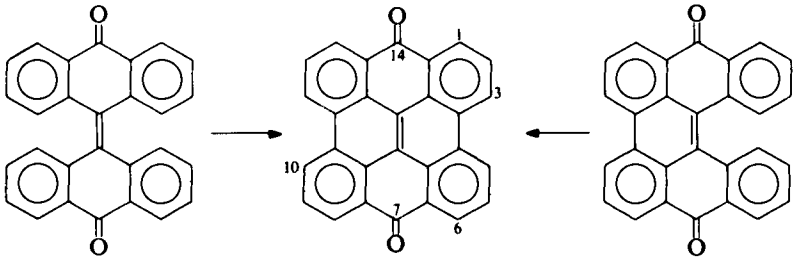


(233)

2. Phenanthro[1,10,9,8-opqra]perylene-7,14-dione(meso-naphthodianthrone) (235)

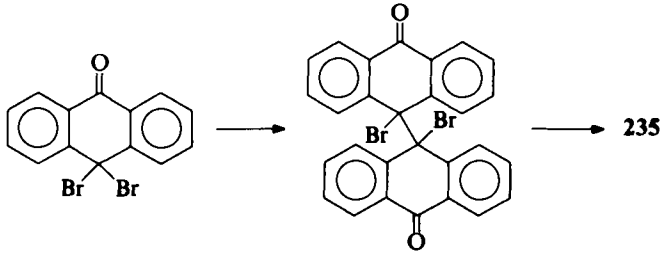
235 and its derivatives are synthesized mostly from helianthrones (**236**) or dehydrodianthrone (**234**) and the corresponding derivatives, respectively. The ease of formation of **235** from **234** and **236** seems to be influenced by the close proximity of the



(234) (235) (236)

two anthraquinone ring systems. **236** is converted to **235** by Scholl cyclization or by oxidation with chromic acid in sulphuric acid[166]. Irradiation in the presence of oxygen also converts **236** and even **234** to **235**[141,167].

235 is also formed in a one-step synthesis by irradiation of 9-bromo-, 9,9-dichloro-, or 9,9-dibromo-anthrone (**237**). On short exposure to light the 9,9'-bianthrones are formed, in the case of **237** 9,9'-dibromodianthrone (**238**) via dimerization of 10-anthryloxy radicals involving triplet states, followed by the conversion of the dianthrone **238** to *meso*-naphthodianthrone (**235**) at prolonged irradiation[168,169].

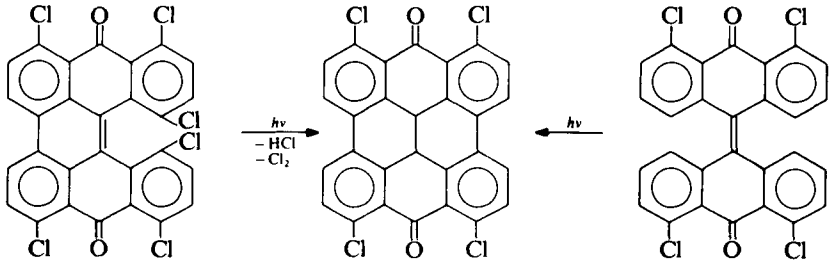


(237) (238)

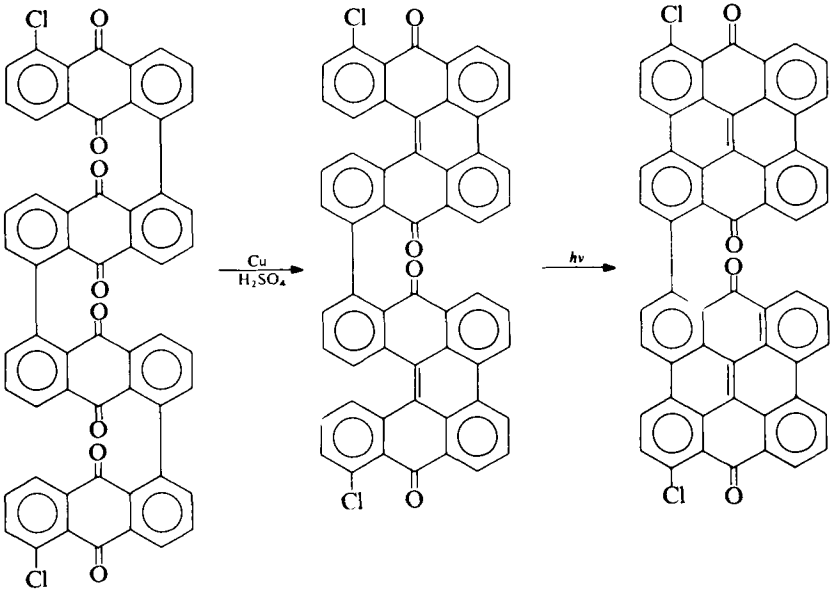
Formation of **235** from 1,1'-dianthraquinonyl on zinc powder distillation should also be mentioned[170]. **235** yields *meso*-naphthodianthrene on reduction with zinc in pyridine/acetic acid[171]. With alkaline dithionite **235** forms only a vat dye if zinc powder is added.

Finally, it is of interest that thin films of **235** exhibit semiconductivity[172] with two activation energies at 0.74 and 0.43 eV. In the presence of oxygen the conductivity associated with the lower activation energy is decreased[173].

Halogen derivatives of **235** have been synthesized mostly via Scholl cyclization of halogenated helianthrones[137,174]. Another route includes photochemical reactions; however, if the positions in bianthrone (**234**) or helianthrone (**236**) where the photochemical cyclization has to take place are occupied by chlorine atoms, no reaction occurs on irradiation in organic solvents. On irradiation in concentrated sulphuric acid, even in these cases ring-closure to *meso*-naphthodianthrones is observed under elimination of hydrochloric acid[135]. Thus, 1,4,5,8,10,15-hexachlorohelianthrone (**239**) is unchanged, e.g.



(239) **(240)** **(241)**



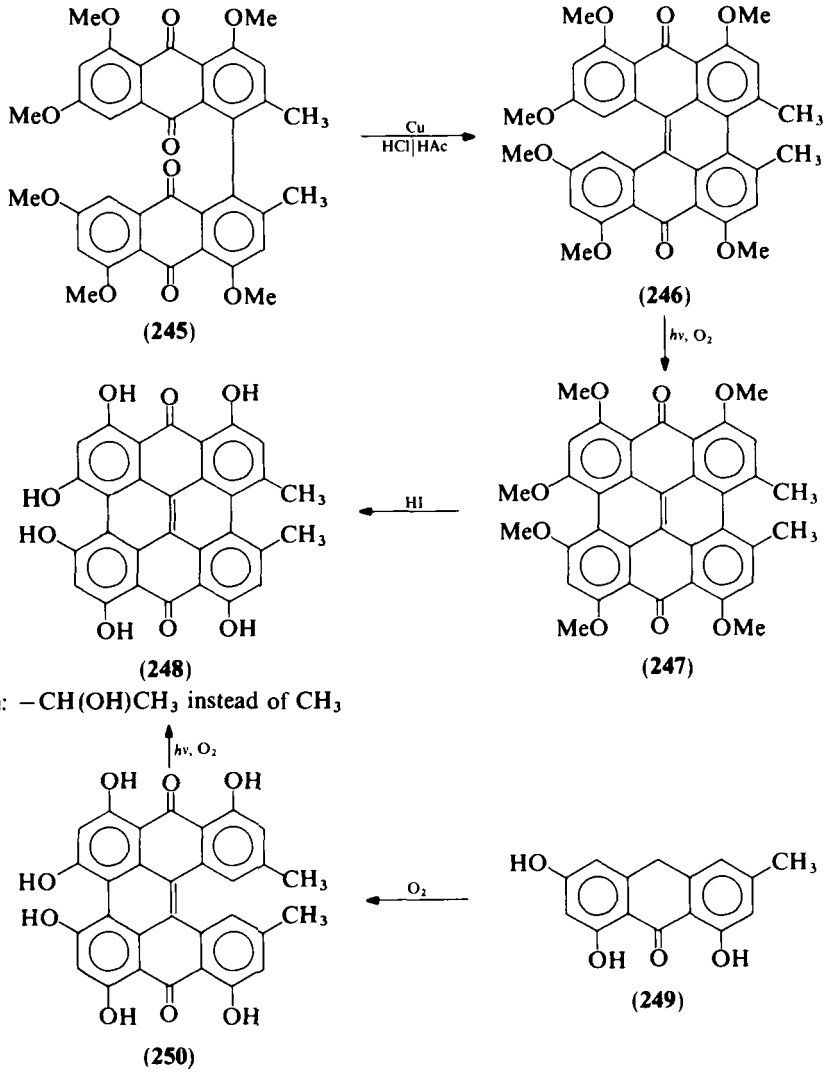
(242) **(243)** **(244)**

by irradiation in nitrobenzene, but gives 1,6,8,13-tetrachloro-*meso*-naphthodianthrone (**240**), eliminating hydrochloric acid and subsequently chlorine on irradiation in sulphuric acid.

Irradiation of the tetrachlorobianthrone **241** also leads to **240**. Many other derivatives of **235** are known, e.g. methyl[136, 175, 176] and hydroxy derivatives[177] as well as carboxylic acids[136].

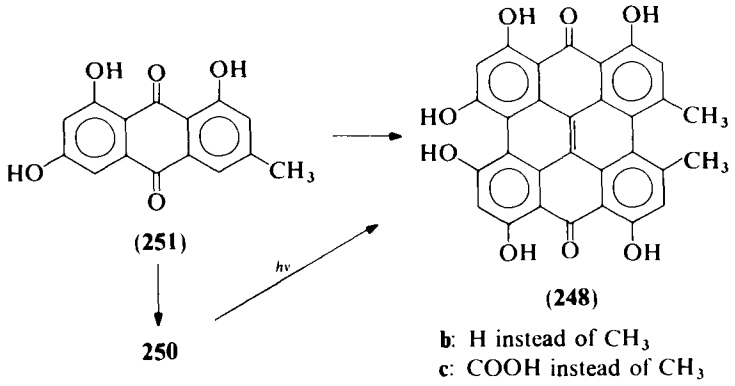
The dimeric *meso*-naphthodianthrone **244** has been synthesized by reduction of the tetra-anthraquinonyl **242** with powdered copper in sulphuric acid to the dimeric helianthrone **243**, followed by irradiation of **243** to give by further cyclization **244**[135].

Derivatives of special interest are hypericine (**248**) and pseudohypericine (**248a**), which occur in nature[178]. A mixture of both are found in *Hypericum perforatum* (St. John's-wort),



(245) (246) (247) (248) (249) (250)

a: $-CH(OH)CH_3$ instead of CH_3



the former in *Hypericum hirsutum*. From St. John's-wort the red quinones may be set free by pressing and rubbing the buds or yellow blossoms between two fingers. The hypericines are responsible for a light illness of sheep, cows, goats and horses with fair coat that have eaten St. John's-wort (hypericism).

Two main approaches have been used for the synthesis of hypericine and related compounds, the 1,1'-dianthraquinonyl route and the dianthrone route, respectively. In the first case 4,5,7,4',5',7'-tetramethoxy-2,2'-dimethyldianthraquinonyl-(1,1') (**245**) was heated with copper powder in acetic acid/hydrochloric acid to yield the corresponding helianthrone derivative **246**. The third ring connection to yield **247** could be effected by irradiation with visible light in the presence of oxygen. In the absence of oxygen a second helianthrone molecule serves as an oxidant and is reduced to the conjugate hydroquinone. The last step was ether cleavage by heating with potassium iodide in phosphoric acid. A similar synthesis of 2,2'-dimethyl-*meso*-naphthodianthrone was possible. The second, biomimetic route starts from emodine-9-anthrone (**249**), which is oxidized by air to give the helianthrone **250** directly via the dianthrone. The latter is also a precursor of hypericine in the plant and was named protohypericine. The ring-closure to hypericine was effected again by photochemical dehydrogenation.

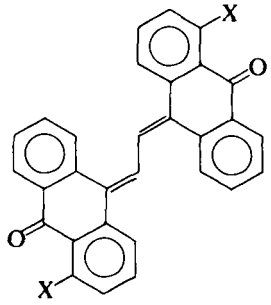
In further biomimetic synthesis[179], hypericine (**248**) is formed (29%) on prolonged heating of an alkaline solution of emodine (**251**) under nitrogen and in the presence of hydroquinone. Similar yields are obtained for the syntheses of bisdesmethylhypericine (**248b**) and hypericine dicarboxylic acid (**248c**).

It was shown[180] that protohypericine (**250**) is formed under these conditions. Ring-closure to **248** occurs on working up by light.

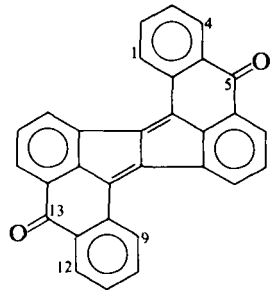
3. *Aceanthryleno[2,1-a]aceanthrylene-5,13-dione (acedianthrone)* (**253**)

For the sake of brevity, we will use the name acedianthrone. Anthrone can be condensed with glyoxal sulphate in acetic acid or with chloral and tin(II) chloride to 1,2-bis(10-oxo-10*H*-[9]anthrylidene)ethane (**252**)[181,182]. With aluminium chloride in the presence of diluents and oxidants[182,183], or on heating a nitrobenzene solution with benzoyl chloride or other acid chlorides[184], **252** gives cyclization to acedianthrone (**253**).

Several derivatives of **253** have been synthesized[183,184]. Despite two five-membered rings in the molecule, **253** has the properties of a real quinone. With alkaline dithionite it is reduced to a yellow-brown vat, which dyes cotton to a red-brown. **253** can be regarded as stilbenoquinone. The stilbenoquinone **252** and its 4,4'-dichloro derivative (**252a**) are also vat dyes[185].



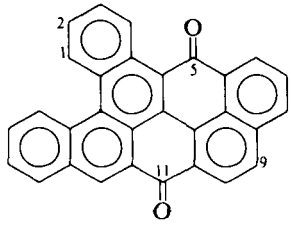
(252, X = H)
a: X = Cl



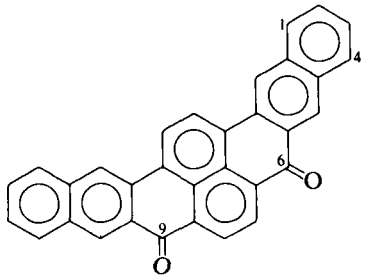
(253)

4. *Benzo[3,4]anthraceno[2,1,9,8-aopqr]naphthacene-5,11-dione* (**254**)

254 has been prepared by selenium dioxide oxidation of benzo[3,4]anthraceno[2,1,9,8-*aopqr*]naphthacene[186].



(254)



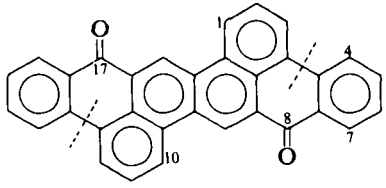
(255)

5. *Dibenzo[b:vwx]hexaphene-6,9-dione* (**255**)

255 has been prepared by selenium dioxide oxidation of dibenzo[*b*:*vwx*]hexaphene in refluxing nitrobenzene. It gives a violet vat with alkaline dithionite[187].

6. *Dibenzo[jk:wx]hexacene-8,17-dione* (**256**)

256 is obtained by Scholl cyclization of 5,11-dibenzoylchrysene. The newly formed bonds are marked with a dotted line in the structure. The blue-green colour of the seems to justify structure **256**[188].



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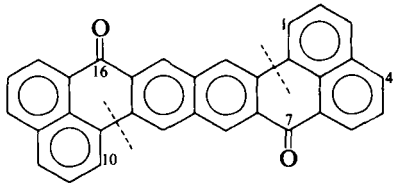


(257)

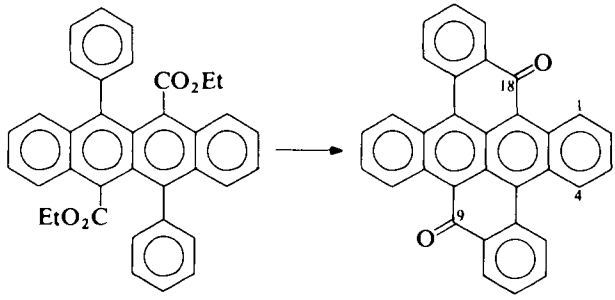
7. *Dibenzo*[lm:yz]*hexacene-7,16-dione (octacethrene-7,16-dione)* (**257**)

257 has been prepared by heating the easily accessible 2,6-bis(1-naphthoyl) naphthalene in a sodium chloride–aluminium chloride melt at 140°C under passing in oxygen (40%)[189]. The bonds formed in this Scholl cyclization are marked with a dotted line in structure **257**. Other quinones could possibly be formed, but the structure **257** has been proved by oxidative degradation.

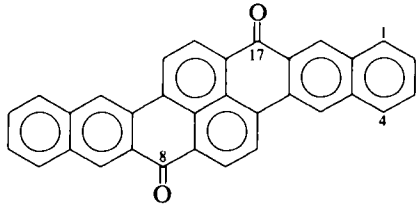
Zinc powder melt of **257** yielded not the corresponding aromatic hydrocarbon but the 7,16-dihydro derivative.

8. *Dinaphtho*[1,2,3-fg:3,2,1-op]*naphthacene-9,18-dione* (**259**)

259 could be synthesized by heating the ester of 6,12-diphenylnaphthacene-5,11-dicarboxylic acid (**258**) with concentrated sulphuric acid[190].



(**258**) (**259**)



(**260**)

9. *Naphthaceno*[2,1,12-aqr]*naphthacene-8,17-dione* (**260**)

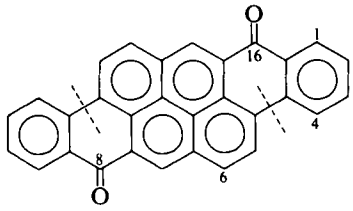
260 has been synthesized by selenium dioxide oxidation of naphthaceno(2,1,12-*aqr*)naphthacene[87] and it forms a brownish olive-red vat.

10. *Naphthaceno*[2,1,12,11-aopqr]*naphthacene-8,16-dione* (**261**)

Scholl cyclization of 4,9-dibenzoylpyrene gives quickly and almost quantitatively **261**[19,191]. The formed bonds are marked with a dotted line in the structure. **261** is a bluish-red vat dye.

11. *Tetrabenzo*[a:de:j:mn]*naphthacene-5,14-dione* (**264**)

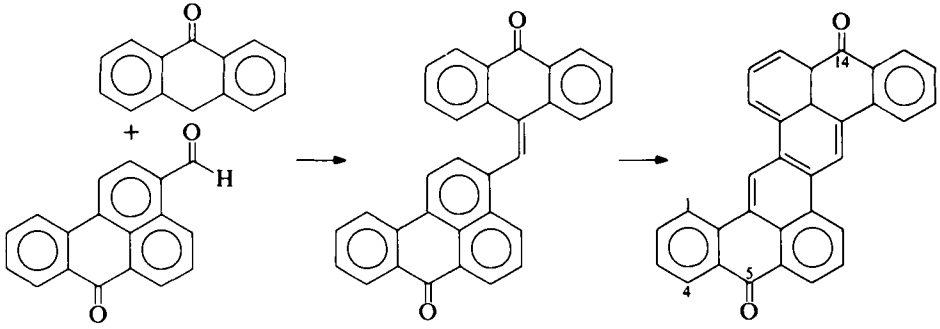
Condensation of benzanthrone-3-aldehyde (**262**), obtainable from methyleneanthrone and acrolein, with anthrone in pyridine/piperidine gives **263**, which on Scholl cyclization



(261)

forms **264**[192]. With alkaline dithionite a ruby vat is formed, obviously derived from a tetrahydro derivative of **264**, since judging from similar compounds the vat of **264** should be coloured deep green.

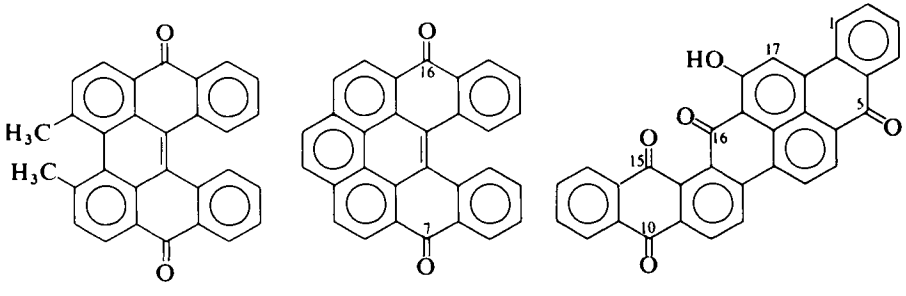
Halogen derivatives of **264** can be prepared starting with halogenated methyleneanthrones or by direct halogenation[192].



(262) (263) (264)

12. Tribenzo[a:ghi:o]*perylene-7,16-dione* (**266**)

266 is formed by boiling 3,4-dimethylhelianthrone (**265**) with barium hydroxide in nitrobenzene or on melting with a mixture of potassium hydroxide and aniline[193]. **266** forms a vat with alkaline dithionite.



(265) (266) (267)

13. Tribenzo[b:n:tu]*picene-5,10,15,16-tetraone*

The 17-hydroxy derivative of tribenzo[*b:n:tu*]picene-5,10,15,16-tetraone (**267**) is obtained by oxidation of violanthrone. Alkylation of **267** leads to orange-red vat dyes[194].

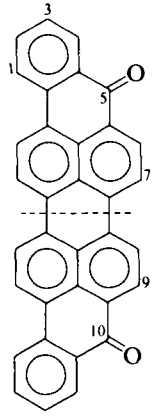
I. Nine-ring Quinones

The two most important compounds of this group are violanthrone and isoviolanthrone. These are treated first, followed by the others in alphabetical order.

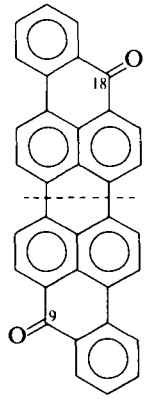
*1. Violanthrone (**268**) and isoviolanthrone (**269**)*

The correct IUPAC notation for **268** is anthra[9,1,2-*cde*]benzo[*rst*]pentaphene-5,10-dione and for **269** benzo[*rst*]phenanthro[10,1,2-*cde*]pentaphene-9,18-dione. In the literature the names violanthrone and isoviolanthrone are used almost exclusively.

268 and **269** are formed formally by symmetrical or unsymmetrical condensations of two benzanthrone molecules. The dotted lines in the structures show the place of connection of the two benzanthrone halves.



(**268**)



(**269**)

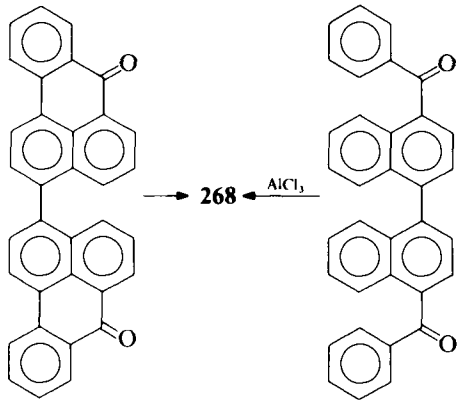
a. Violanthrone

Symmetrical condensation with generation of **268** takes place in potassium hydroxide or alcohol/potassium hydroxide melt of benzanthrone at 230–240°C[195]. 3,3'-Dibenzanthrone (**270**) is an intermediate[196] and is the main product at lower temperatures. Indeed **268** can be synthesized in especially pure form and in 96% yield by heating **270** at 430°C for 15 min[127]. Only small amounts of **268** are formed by Ullmann reaction of 3-halobenzanthrones[198].

The amounts of side products, such as 4-hydroxybenzanthrone or isoviolanthrone, can sometimes be considerable in the potash melt of benzanthrone. Several processes have been developed to decrease the amounts of undesirable side products or to purify the intermediate **270** or the crude violanthrone[199, 200]. Effective and high-yield syntheses from benzanthrone are possible by adding to the melt, chlorates or nitrites, glycol- or polyglycol-ether and surfactants[201, 202].

Another interesting but technically unimportant synthesis of **268** is by heating 4,4'-dibenzoyl-1,1'-binaphthyl (**271**) with aluminium chloride[152]. **271** is easily obtained by Friedel–Crafts reaction of benzoyl chloride with 1,1'-binaphthyl.

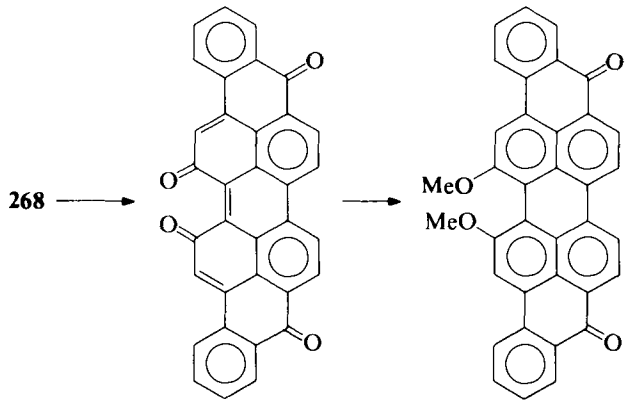
Violanthrone is a blue compound which dyes cotton to a fast violet. It is an important vat dye and is marketed as Indanthrene Dark Blue BOA. For the redox potential of violanthrone see Gupta[163]. Violanthrone as well as its corresponding aromatic hydrocarbon are semiconductors[172, 203].



(270) (271)

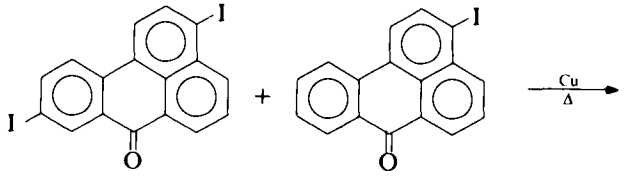
Many derivatives of **268** have been synthesized in order to obtain other hues such as 3,12,16,17-tetrachloroviolanthrone (Indanthren Navy Blue RB), a monobromo (Indanthren Navy Blue BRF) and a dibromo derivative (Indanthrene Navy Blue BF). The halogen derivatives are prepared by direct halogenation of violanthrone in chlorosulphonic acid or in organic solvents, sometimes in the presence of sulphur or antimony[204]. 15,16,17-Trichloroviolanthrone is obtained, besides other products, by treating 16,17-dihydroxyviolanthrone with phosphorous pentachloride[205]. Nitro derivatives can be prepared by direct nitration of violanthrone[206]. The dinitro compound can be reduced to a green diamino compound, which in turn yields on oxidation with hypochlorite on the fibre a valuable black[207].

Of technical importance is the oxidation of violanthrone with manganese dioxide in sulphuric acid in the presence of boric acid[208]. Violanthrone-16,17-dione (**272**) is formed and, on reduction, gives 16,17-dihydroxyviolanthrone and, after methylation, 16,17-dimethoxyviolanthrone (**273**). **273** is a valuable green vat dye (Indanthren Brilliant Green FFB, Caledon Yade Green).

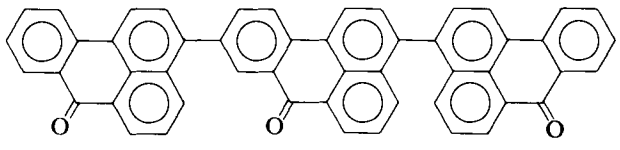


(272) (273)

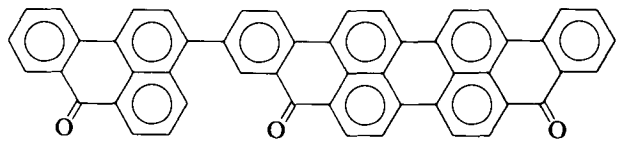
Syntheses of homologues[209], of 6,9-diphenylviolanthrone[210], and of hydroxy and alkoxy derivatives[211] have been described. 3-(3-Benzanthranyl)violanthrone (**277**) was synthesized by Ullmann condensation of 3,9-diiodobenzanthrone (**274**) with 3-iodobenzanthrone (**275**). The Ullmann product (**276**, 16%) was quantitatively converted to **277** by alkaline condensation[212].



(**274**) (**275**)

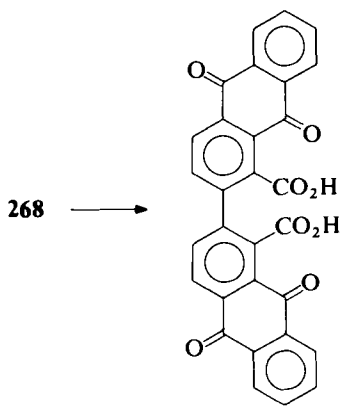


(**276**)



(**277**)

Violanthrone is oxidized by chromic acid in sulphuric acid to 2,2'-dianthraquinonyl-1,1'-dicarboxylic acid (**278**)[213]. Reduction of violanthrone in a zinc dust melt leads in



(**278**)

high yield to anthra[9,1,2-*cde*]benzo[*rst*]pentaphene, the corresponding aromatic hydrocarbon[214].

b. Isoviolanthrone

Isoviolanthrone (**269**) and some of its derivatives are of importance as vat dyes. When melting benzanthrone (**279**) with alcoholic potassium hydroxide[195] at 170–175°C the portion of **268** is at maximum, but both below and above this temperature range more **269** is formed[196]. **269** is also formed predominantly at low temperatures with potassium hydroxide in the presence of solvents as benzene or trichlorobenzene[215] or with metal anilides as condensating agents[216].

The separation of violanthrone and isoviolanthrone in the raw product is possible since the reduced form of violanthrone is insoluble in 4% sodium hydroxide[196].

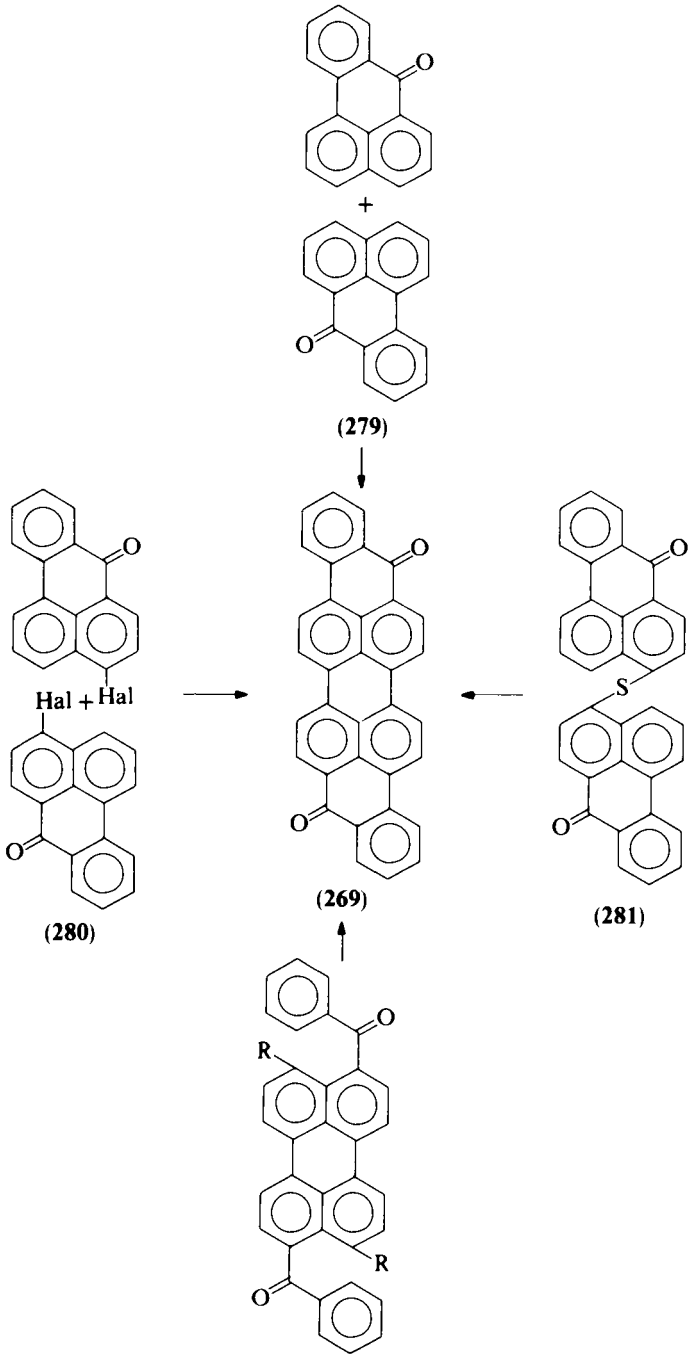
Pure **269** can be synthesized by heating 4-chloro- or 4-bromo-benzanthrone (**280**) with alcoholic potassium hydroxide to 120–140°C[217]. Also, mixtures of 4-halogenobenzanthrones with benzanthrone[218] and the thioether **281**[219,220] give **269** under alkaline conditions. The thioether route is the nowadays applied technical synthesis of isomer-free isoviolanthrone[221]. A synthesis starting from perylene has been described by Zincke and coworkers[59]. 4,10-Dibenzoylperylene (**282a**) is converted in low yields to **269** by heating with aluminium chloride. The yield can be raised (45%) by adding manganese dioxide[222]. Very pure isoviolanthrone has been obtained by heating 4,10-dibenzoyl-3,9-dibromoperylene (**282c**) with aluminium chloride[59]. The same condensation is also possible under alkaline conditions. In the case of the **282c** boiling with powdered potassium hydroxide is sufficient; with **282b**, boiling quinoline is needed[222]. Benzo[*rst*]phenanthro[10,1,2-*cde*]pentaphene, the aromatic hydrocarbon corresponding to **269**, can be prepared in high yield (85%) from isoviolanthrone in a zinc dust melt[214]. Isoviolanthrone and the hydrocarbon are both semiconductors[172,203].

Isoviolanthrone is marketed as Indanthren violet R Extra. Other important vat dyes are 6,15-dichloroisoviolanthrone (Indanthren Brilliant Violet RR and 4R) and tribromoisoviolanthrone (Indanthren brilliantviolet 3B and F3B). Chlorination of isoviolanthrone is effected with sulphuryl chloride[223], bromination with bromine in chlorosulphonic acid in the presence of sulphur[209]. 3,12-Dichloroisoviolanthrone has been obtained by Scholl cyclization of 3,9-dichloro-4,10-di-(4-chlorobenzoyl)perylene[222]. Nitro derivatives are obtained by direct nitration[206], and the corresponding amino derivatives by reduction of the nitro compounds either separately or during the vatting process[224]. Methyl homologues can be synthesized starting from the appropriate aroylperylenes or methylbenzanthrones[195]. 9,17-Diphenylisoviolanthrone has been prepared by alkali treatment of 3,6-diphenylbenzanthrone[225].

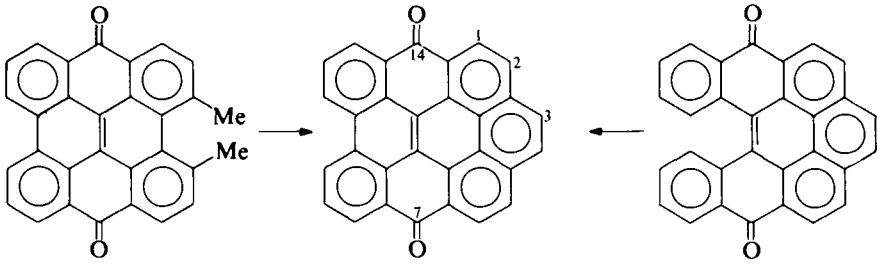
2. meso-*Anthrodianthrone*

The IUPAC notation for *ms*-anthrodianthrone (**284**) is dibenzo[*kl,no*]coronene-7,14-dione, but the first name is generally used. Syntheses of **284** had been performed already in 1926 by heating 12,13-dimethyl-*ms*-naphthodianthrone (**283**) with alcoholic alkali[226] or Scholl cyclization of tribenzoperylenequinone (**285**)[227]. The latter reaction can also be effected by exposure of **285** to light in the presence of oxygen. **284** has also been synthesized starting with a quick and quantitative Diels–Alder reaction between the blue, reactive *ms*-naphthodianthrene **286** and maleic anhydride in boiling nitrobenzene. The resulting anhydride **287** was oxidized with chromic acid and decarboxylated with soda lime to give **284**[228], which is a yellow vat dye (Indanthrenbraun).

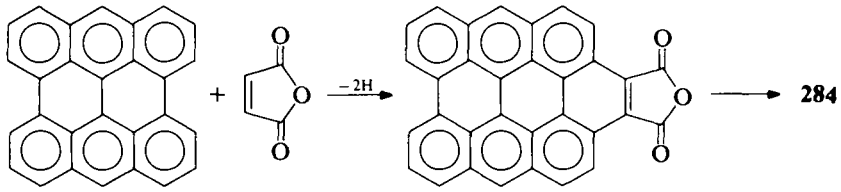
1,6,8,10,11,13-Hexahydroxy-3,4-dimethyldibenzo[*kl, no*]coronene-7,14-dione (**289**) has been obtained by sulphuric acid treatment of the naturally occurring quinone pseudo-



(282; a: R = H; b; R = Cl; c: R = Br)

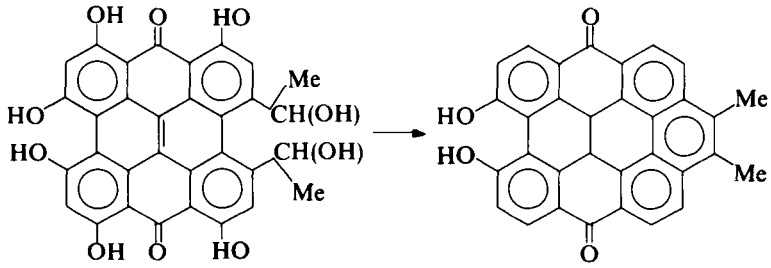


(283) (284) (285)



(286) (287)

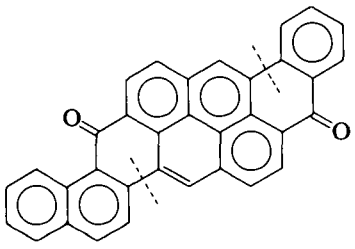
hypericine (**288**)[178]. This reaction could constitute a principal way for the anellation of a benzene ring in analogous positions.



(288) (289)

3. *Benzo*[a]*napth*o[2,1-j]*anthanthrene-5,15-dione* (**290**)

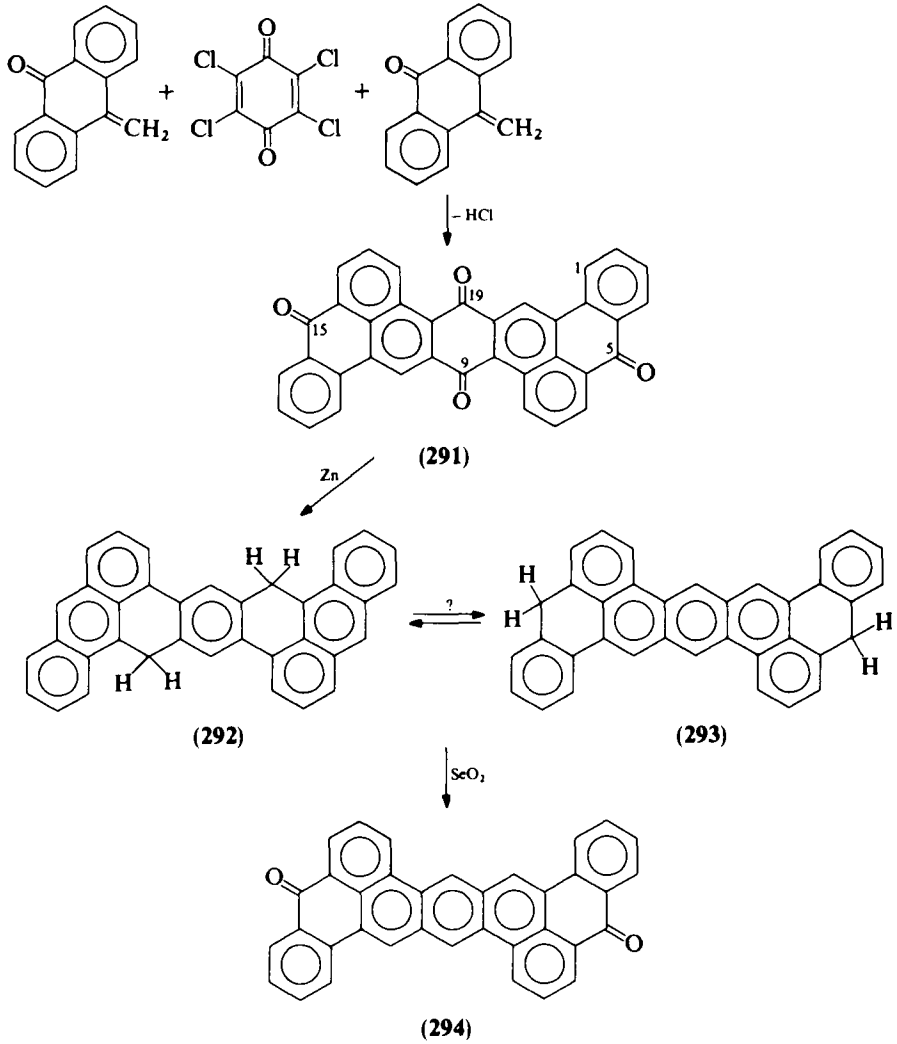
290 has been obtained by Scholl cyclization of 3,8-dibenzoylpyrene (see dotted lines), which is accessible from pyrene by successive Friedel–Crafts acylation with benzoyl chloride and 1-napthoyl chloride[161]. **290** gives a blue vat.



(290)

4. *Tetrabenzo*[a:de:l:op]*naphthacene-5,15-dione* (**294**)

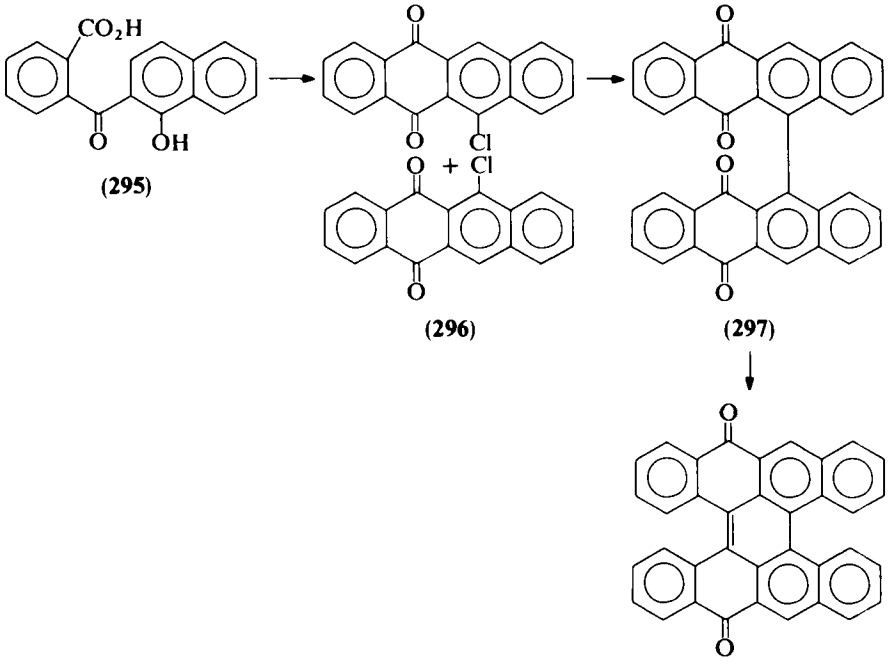
Tetrabenzo[*a*:*de*:*l*:*op*]naphthacene-5,9,15,19-tetraone (**291**) is formed by boiling methyleneanthrone with chloranil or benzoquinone in nitrobenzene or acetic acid[229]. A *cis*-biangular connection instead of the *trans*-biangular, as in **291**, cannot be excluded with certainty, but seems to be not very probable. On reduction with zinc dust in pyridine/acetic acid **291** gives the dihydro derivative of the corresponding hydrocarbon, obviously an equilibrium mixture of **292** and **293**, which on oxidation with selenium dioxide yields a dione, probably **294**. No vat dye of **294** is obtainable with alkaline dithionite.



(**291**) (**292**) (**293**) (**294**)

5. *Tetrabenzo*[a,f,j,o]*perylene-9,10-dione* (**298**)

298 has been obtained from **297** by reduction with copper powder in sulphuric acid. **297**



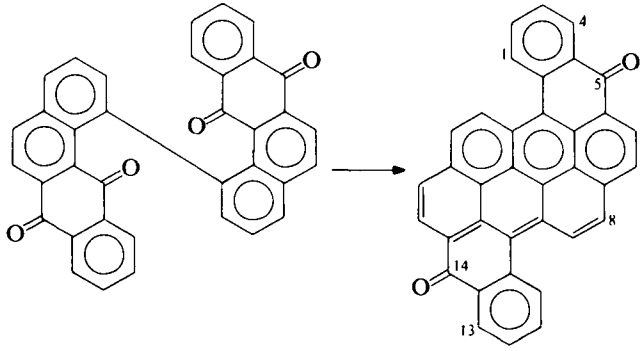
(295) (296) (297) (298)

was the product of the Ullmann reaction of 11-chloronaphthacene-5,12-dione (**296**), which is formed on treatment of **295** with phosphorous pentachloride[230].

J. Ten-ring Quinones

*1. Anthraceno[9,1,2-klm]dibenzo[a,ghi]perylene-5,14-dione (**300**)*

300 has been synthesized by copper reduction of the 1,1'-dibenzo[*a*]anthracene-7,12-dione (**299**) in sulphuric acid. **299** was obtained by Ullmann reaction of 1-chlorobenzo[*a*]anthracene-7,12-dione (**301**)[231].

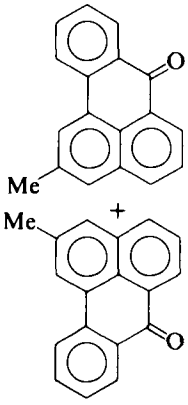


(299) (300)

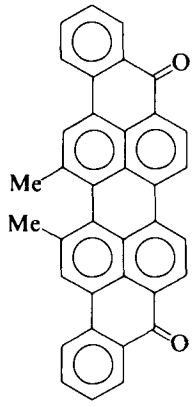
300 is a violet vat dye. Halogeno and hydroxy derivatives of **300** with other shades, some with uncertain structures, have been described in the patent literature[231,232].

2. *Dibenzopyranthrenediones*

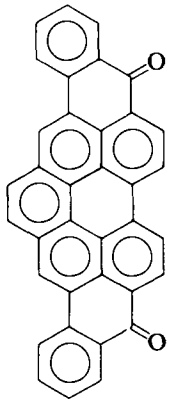
Dibenzo[*a,def*]pyranthrene-5,10-dione (**303**) has been obtained in a simple three-step synthesis. On fusion of 2-methylbenzanthrone (**301**) in potassium hydroxide with glucose or naphthalene and manganese dioxide, the dimethylviolanthrone **302** is formed. **302** is transformed to **303** by boiling in nitrobenzene, especially in the presence of barium hydroxide[233].



(**301**)

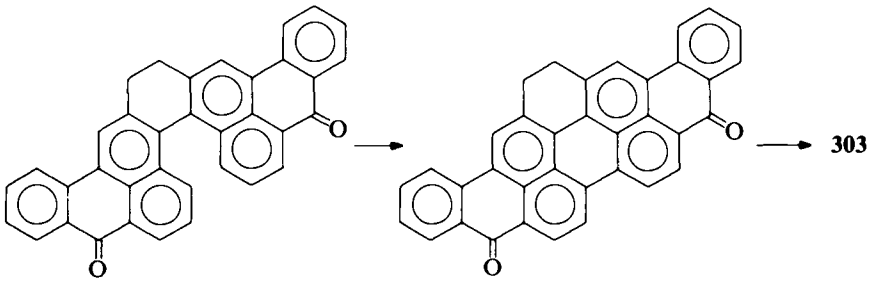


(**302**)



(**303**)

Another synthesis of **303** starts from 18,19-dihydrotetrabenzo[*c, m, pq, uv*]pentaphene-5,12-dione (**304**), which gives, on melting with alcoholic potassium hydroxide, 16,17-dihydrodibenzo[*a,def*]pyranthrene-5,10-dione (**305**). The dehydrogenation of **305** was effected with sodium nitrite[234]. **303** forms a blue vat with alkaline dithionite.

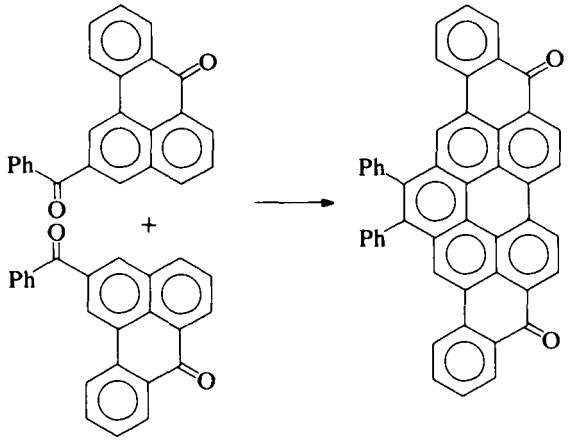


(**304**) (**305**)

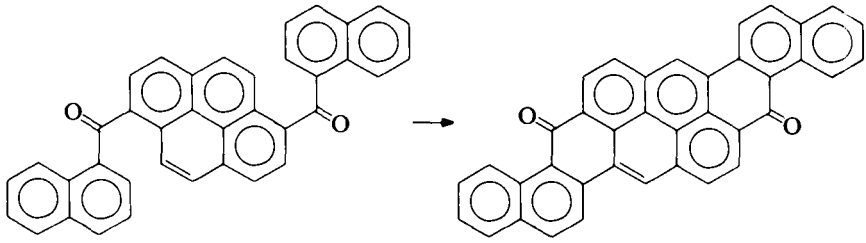
The 16,17-diphenyldibenzo[*a,def*]pyranthrene-5,10-dione (**307**) was obtained directly by fusion of 2-benzoylbenzanthrone (**306**) with alcoholic alkali[235].

Dibenzo[*a,n*]pyranthrene-10,20-dione (**309**) or dibenzo[*c,p*]pyranthrene-10,20-dione (**311**) is formed on heating 1,6-di-1-naphthoyl pyrene (**308**) and 1,6-di-2-naphthoylpyrene

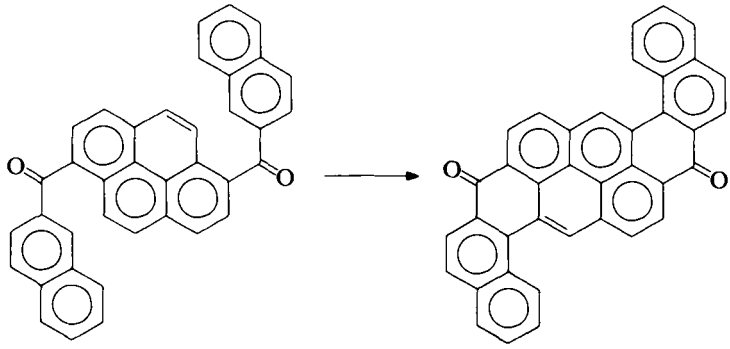
(**310**), respectively, with aluminium chloride[152]. Both quinones have properties similar to pyranthrone, but cotton is dyed from the blue vats in redder shades. **309** and **311** are not used commercially, because there is no convenient technical source for pyrene, the precursor of **308** and **310**.



(**306**) (**307**)



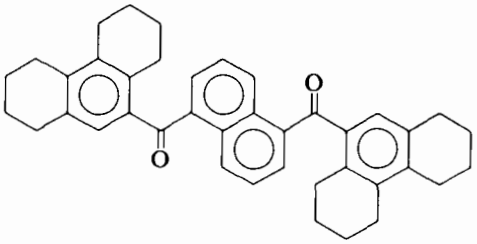
(**308**) (**309**)



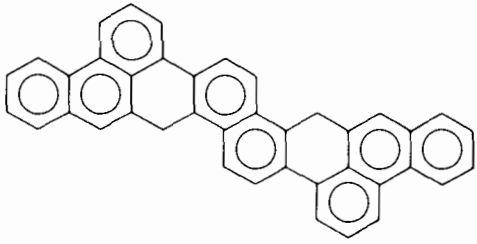
(**310**) (**311**)

3. *Dibenzo*[fgh:f'g'h']*naphthaceno*[2,1-a]*naphthacene-9,20-dione* (**314**)

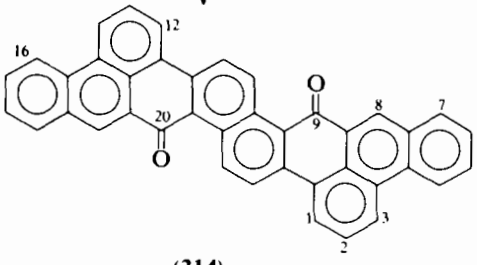
The synthesis of **314** has been accomplished by selenium dioxide oxidation of 9,20-dihydrodibenzo[*fgh*:*f'g'h'*]naphthaceno[2,1-*a*]naphthacene (**313**). **313** is readily available by heating the diketone **312** to 400°C in the presence of copper powder[236].



(**312**)



(**313**)

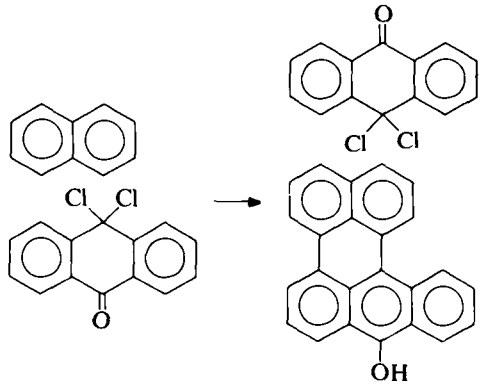


(**314**)

4. *Tetrabenzo*[a,de,kl,o]*pentaphene-5,14-dione* (**319**)

Naphthalene codenses twice with dichloroanthrone (**315**) with aluminium chloride as catalyst. **316** is formed as an intermediate. If the second dichloroanthrone attacks **316** at the 12-position, the hydroquinone of **319** is formed, while attack at the 11-position leads to the hydroquinone of tribenzo[*a,de,rst*]naphtho[4,3,2-*kl*]pentaphene-5,15-dione (**318**). The hydroquinone **317** is oxidized to **319** by boiling with nitrobenzene[237].

On reduction of **319** with zinc dust in pyridine-acetic acid the corresponding aromatic hydrocarbon is formed. With alkaline dithionite no vat is generated, probably because the (green) salt of the hydroquinone **317** is insoluble.



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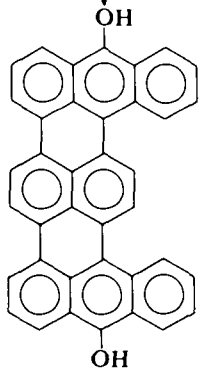
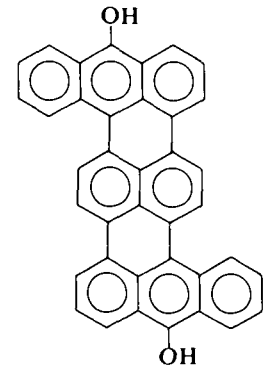
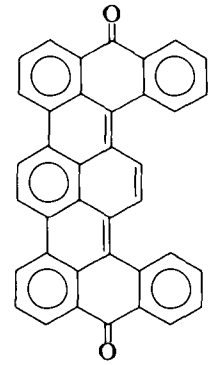


or



(317) (318)

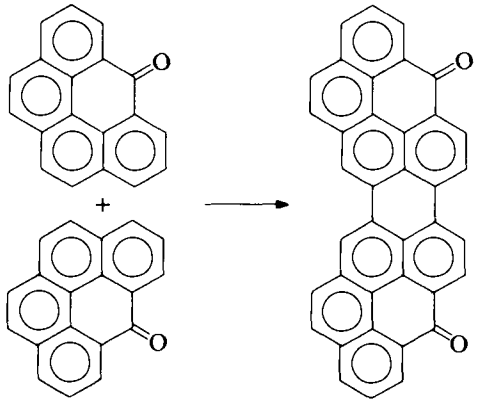


(319)

K. Eleven-ring Quinones

1. Anthraceno[2,1,9,8-klmno]naphtho(3,2,1,8,7-vwxyz)hexaphene-4,9-dione (**321**)

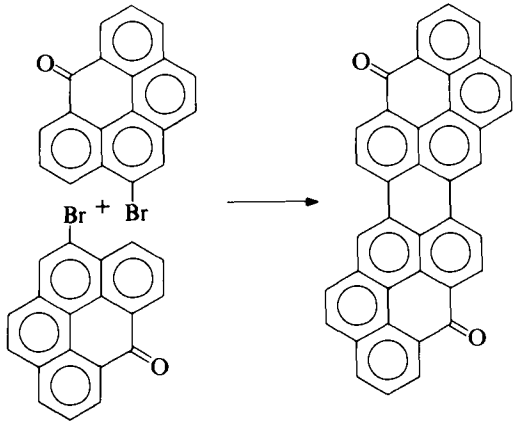
Fusion of benzo[*cd*]pyrene-6-one (**320**) resulted in the formation of a blue colouring matter, which contains 2-hydroxybenzo[*cd*]pyrene-6-one, and possibly a tetrahydroxy derivative of **321**[238]. **321** dissolves sparingly in alkaline dithionite, forming a bluish-green vat.



(**320**) (**321**)

2. Dianthraceno[2,1,9,8-stuva:2,1,9,8-hijkl]pentacene-9,18-dione (**323**)

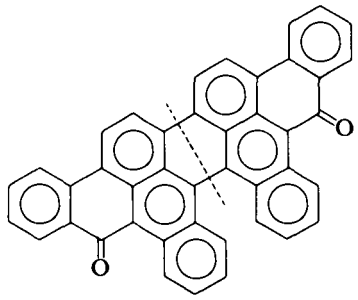
323 has been synthesized by melting 2-bromobenzo[*cd*]pyrene-6-one (**322**) with alcoholic potassium hydroxide at 120°C[238]. **323** gives, with alkaline dithionite, a blue-green vat.



(**322**) (**323**)

3. *Dibenzo*[a, o]*dinaphtho*[3,2,1-cd:1,2,3-lm]*perylene*-5,14-*dione* (**324**)

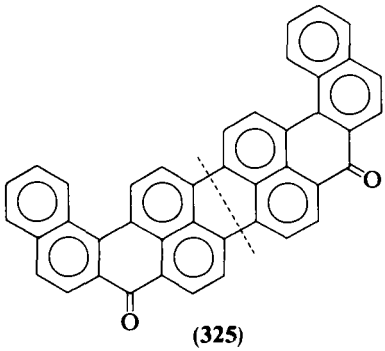
The green **324** has been synthesized from the two halves (dibenzo[*a,de*]anthracene-3-one, see dotted line) by melting with potassium hydroxide/potassium acetate at 225°C[239]. **324** may be considered to be a dibenzo derivative of violanthrone. Indeed it resembles violanthrone in its spectral properties and forms with alkaline dithionite a purple solution.



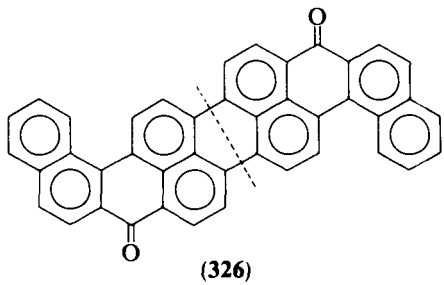
(324)

4. *Diphenanthrenoperylenediones*

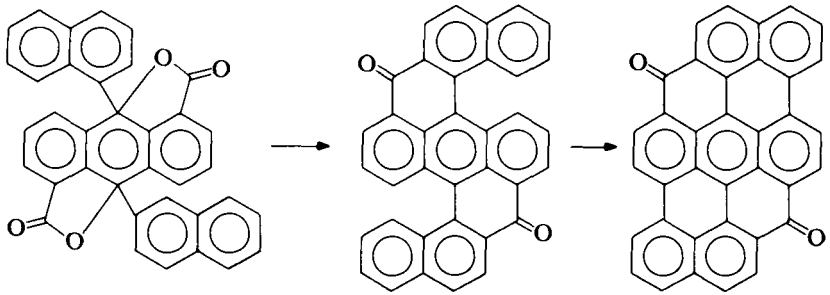
Two blue diphenanthrenoperylenediones have been described in the literature, diphenanthreno[4,3,2-*cd*:5,6,7-*lm*]perylene-5,10-dione (**325**) and diphenanthreno[4,3,2-



(325)



(326)



(327) (328) (329)

cd:4,3,2-*lm*]perylene-7,12-dione (**326**). Both quinones were obtained by alkaline treatment of the two halves of the molecule (see dotted lines), i.e., of benzo[*hi*]chrysene-7-one[240]. With sodium anilide **326** is formed, whereas potassium hydroxide, sodamide and sodium piperidide afford predominantly **325**.

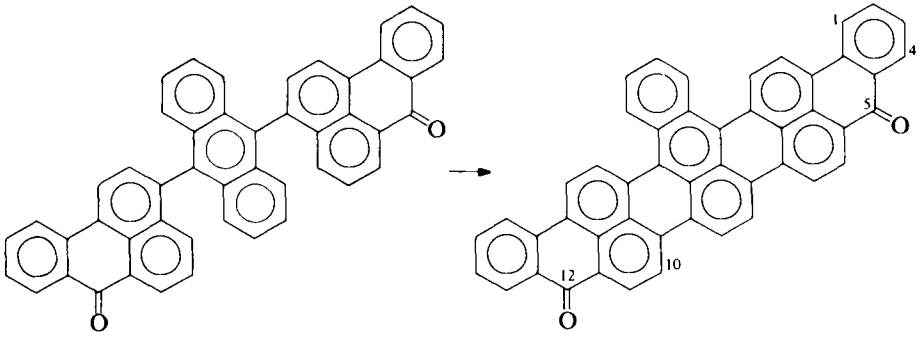
5. *Dinaphtho*[*2,1,8*-apq:*2,1,8*-ghi]*coronene-8,16-dione* (**329**)

Anthraquinone-1,5-dicarboxylic acid reacts with naphthalene and aluminium chloride in nitrobenzene to yield the dilactone **327**. Further condensation yields the dinaphthoperylenequinone **328**[124]. At elevated temperatures **329** is eventually formed[228].

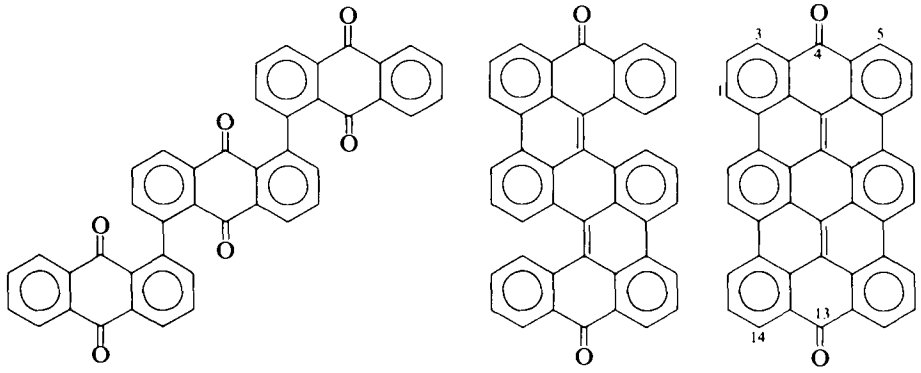
L. Thirteen-ring Quinones

1. *Benzo*[j]*dinaphtho*[3,2,1-cd:4,3,2-pq]*terrylene-5,12-dione* (**331**)

331 has been synthesized by Ullmann reaction of 3-chloro- or 3-bromo-benzanthrone with 9,10-dibromo- or 9,10-dichloro-anthracene. The resulting 9,10-bis(3-benzanthronyl)anthracene (**330**) gave **331** on heating in a potassium hydroxide/sodium acetate melt at 230°C. With alkaline dithionite it forms a dark violet vat which dyes cotton grey[241].



(330) (331)



(332) (333) (334)

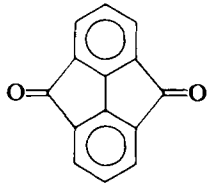
2. *Dianthraceno(1,9,8-apqr:1,9,8-ghij)-coronene-4,13-dione* (**334**)

The synthesis of the highly condensed **334** has been effected by irradiation of **333**. This quinone is easily accessible by treatment of the trianthraquinonyl **332** with powdered copper in sulphuric acid[135]. In contrast to simple helianthrones, **333** is unstable and reverts to **332**, even in the solid state.

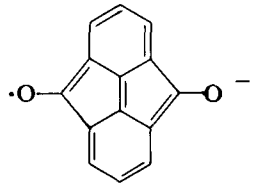
The synthesis of the 5,14-dichloro derivative of **334** has also been described[135].

IV. ANNULENEDIONES

One of the most important properties of quinones is the reversible formation of dihydroxy aromatics or their dianions, on two-electron reduction. Therefore, non-benzenoid diones, which yield on reduction compounds containing cyclic conjugated double bonds with $4n\,\pi$ electrons, i.e., non-aromatic systems, cannot be regarded as quinones[242]. In contrast, dibenzo[*cd,gh*]pentalene-4,8-dione (**335**) produces on electrolytic reduction the radical anion (**336**). In **336**, 14 π electrons are contained in cyclic conjugated double bonds, hence it may be considered a Hückel aromatic and **335** a quinone.

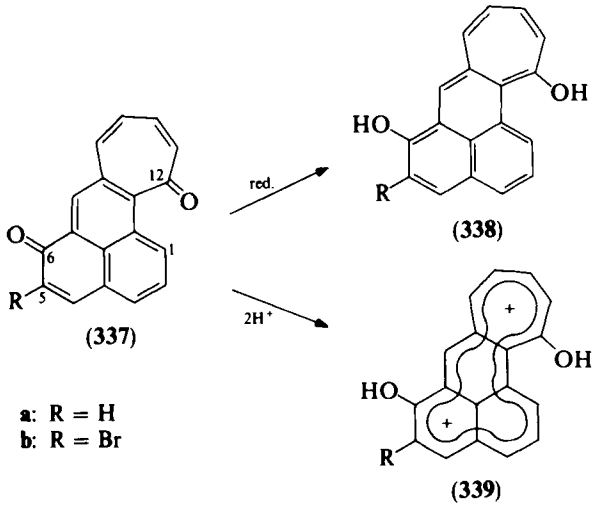


(**335**)



(**336**)

Another example has recently been described by Kuroda and coworkers[243]. They synthesized cyclohepta[*a*]phenalene-6,12-dione (**337a**) and the 5-bromo derivate (**337b**).



(**337**)

a: R = H
b: R = Br

(**338**)

(**339**)

The conjugate hydroquinones **338** with 18 conjugated π electrons represent non-benzenoid Hückel aromatics and indeed **337** behaves as a true quinone. It shows reversible

redox properties, with reduction potentials at $E(\frac{1}{2})_1 = -1.05$, $E(\frac{1}{2})_2 = -1.44$ and $E(\frac{1}{2})_1 = -0.90$, $E(\frac{1}{2})_2 = -1.37$ V, respectively. These potentials resemble those of anthraquinone.

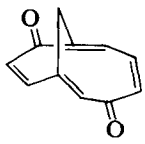
The dications (**339**) are formed in concentrated sulphuric acid. The shift of the proton signals in the ^{1}H-NMR spectrum suggests that the dications are surprisingly diatropic. Also quinones of azulene are known. They are reviewed in Chapter 27.

The first syntheses of annulenes constitute a milestone in the search for non-classical ($4n + 2$) Hückel aromatics. Soon after the question arose as to whether the annulenes parallel the classical aromatics also in their ability to form quinones. Indeed several annulenoquinones have meanwhile been described. The first was synthesized in 1967 by Boekelheide and Phillips[244]. In most cases the quinonoid character of the annulenediones was established carefully by means of their chemical and electrochemical properties.

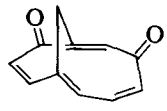
A. [10]Annulenediones

1. Homoazulenequinones

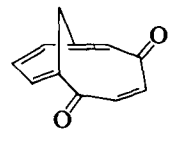
Outstanding syntheses of the 1,5-, 1,7- and 4,7-homoazulenequinones (**340–342**) have recently been described by Scott and Oda[245]. The synthesis of the 1,5- and 1,7-quinones



(**340**)



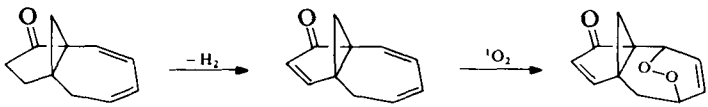
(**341**)



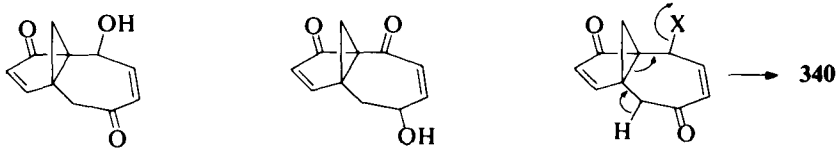
(**342**)

starts with the propellane **343**. Dehydrogenation via the alpha-phenyl selenide gave **344**, which was photo-oxidized to the endoperoxide **345**. A mixture of **346** and **347** was obtained by isomerization of **345** with Hünig's base. **346** yielded in a Grob fragmentation reaction (trifluoroacetic anhydride/triethylamine) the 1,5-quinone **340–348**. This last amazing step has been performed with 77% yield. A closely related synthesis was performed for the preparation of the 1,7-quinone **341**, starting from **349**, which could be obtained by isomerization of **344**.

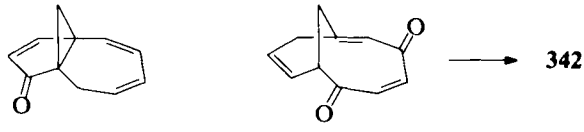
The 4,7-quinone **342** could be obtained by NBS bromination of the known dione **350** followed by triethylamine treatment. Though prepared in pure form in solution, the 4,7-quinone could not be isolated. The stabilities of the homoazulenequinones **340–342**



(**343**) (**344**) (**345**)



(**346**) (**347**) (**348**) **340**

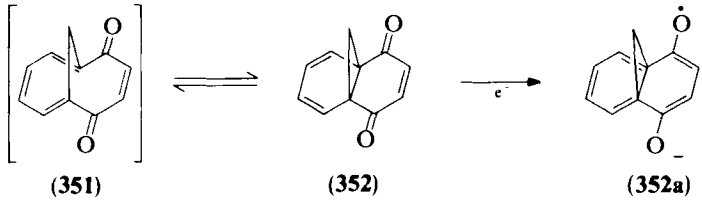


(349) (350)

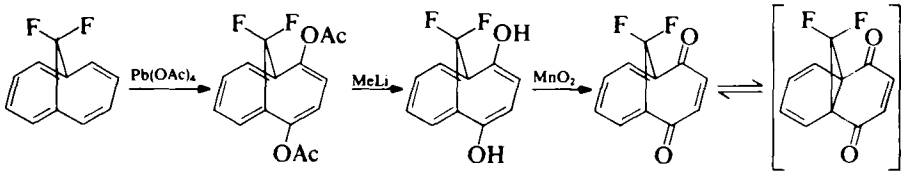
parallel those predicted for the corresponding azulenequinones[246]. Up to now only the 1,5- and 1,7-azulenequinones could be isolated in substance[247] (see also Chapter 24).

2. *Homonaphthoquinones*

Attempts have been made to synthesize bicyclo[4.4.1]undeca-3,6,8,10-tetraene-2,5-dione or 2,5-homonaphthoquinone (**351**). Surprisingly, the dynamic isomer with the norcaradiene structure **352** proved to possess the lower energy[248]. Treatment of **352** with a mild reducing agent, such as the enolate ion of propiophenone, yields a free radical anion wherein, judging from the ESR spectrum, the unpaired electron is extensively delocalized into the entire π system. Hence the semiquinone structure **352a** has been proposed for the radical anion[249].



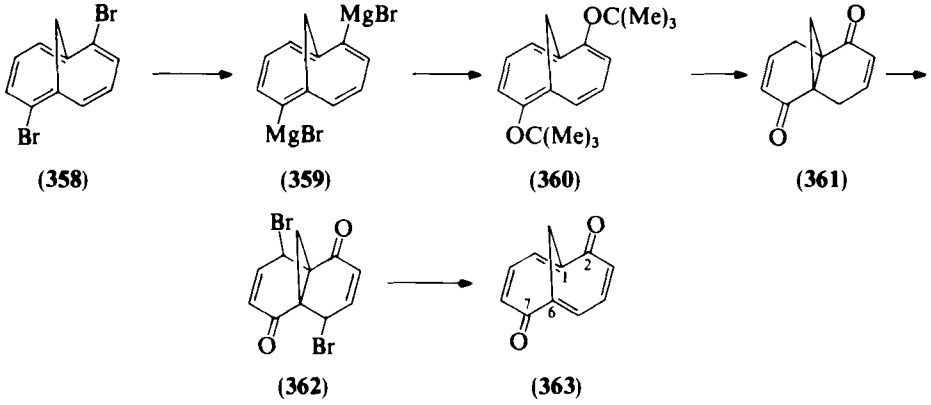
(351) (352) (352a)



(353) (354) (355) (356) (357)

As is well known, cyclopropane ring strain is increased by geminal fluorine substituents. Therefore replacement of the methylene protons in **351** should favour the structure **356** over the norcaradiene structure **357**. Indeed oxidation of **353** with lead tetraacetate gave the diacetate **354**, which yielded the diol **355** on treatment with methyllithium. Manganese dioxide oxidation of **355** gave a dione, which from its NMR spectra has the annulenedione structure **356**.

Bicyclo[4.4.1]undeca-3,5,8,10-tetraene-2,7-dione or 2,7-homonaphthoquinone (**363**) is the annulene pendant of the unstable 1,5-naphthoquinone. **363** has been synthesized[250] starting with the 2,7-dibromo-1,6-methano-[10]annulene (**358**). Its Grignard compound reacted with perbenzoic acid *t*-butyl ester to give the ether (**360**). Cleavage of **360** with catalytic amounts of *p*-toluenesulphonic acid in benzene at 80° C (10 min) yielded the diketone **361**. It was not possible to dehydrogenate **361** directly with 2,3-dichloro-5,6-dicyanobenzoquinone, but with *N*-bromosuccinimide the dibromide **362** was formed and gave the quinone **363** on treatment with potassium iodide. **363** possesses at least one



(358) (359) (360) (361)

(362) (363)

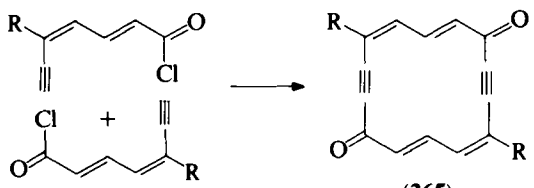
important property of quinones: it is transformed by reductive acetylation into the 2,7-diacetoxy-1,6-methano[10]annulene, the diacetate of the conjugate (quasi-)aromatic hydroquinone. **363** is a stable compound, which crystallizes from acetone in orange-yellow crystals. The stability of **363** is surprising because it was not possible to isolate the analogous 1,5-naphthoquinone[27]. However, the very low tendency of **363** to undergo Michael additions or Diels–Alder condensations and, on the other hand, the high reactivity of 1,5-napthoquinone are in accord with the results of PMO calculations on both compounds[27, 30].

B. [14]Annulenediones

Several [14]annulenediones with and without inner alkano bridges have been described. They are treated in alphabetical order.

1. Bisdehydro[14]annulenediones

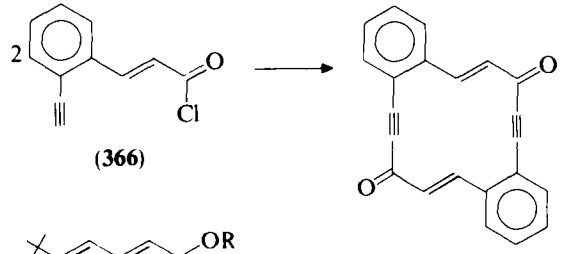
The synthesis of bisdehydro[14]annulenediones seemed of interest considering the high aromatic nature of the bisdehydro[14]annulenes[251]. A very elegant synthesis of the di-*t*-butyl- and diphenyl-bisdehydro[14]annulenediones **365a** and **365b**, respectively, was possible by cyclodimerization of the acid chlorides **364a** and **b**, respectively, in the presence of a palladium/copper catalyst[252].



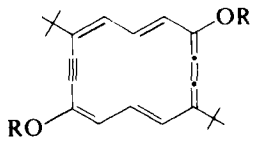
(364) (365)

a: R = *t*-Bu
b: R = Ph

The dibenzo derivative **367** has been obtained by the catalytic dimerization of the acid chloride **366**[252], or from the copper salt of *o*-iodocinnamoylacetylene[253].



(366) (367)



(368)

a: R = Ac
b: R = Me

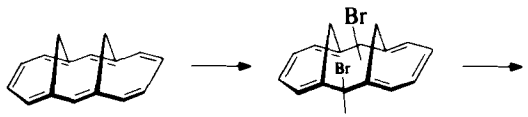
The diones **365a, b** and **367** are stable compounds. They crystallize in the form of yellow to orange needles. The chemical and electrochemical reduction of **365a** has been investigated in order to obtain evidence for its quinonoid nature[254].

Reductive acetylation with zinc powder/acetic anhydride in the presence of pyridine yielded the diacetoxy-bisdehydro[14]annulene **368a** and reductive methylation with dimethyl sulphate/sulphuric acid and zinc powder the dimethyl ether **368b**.

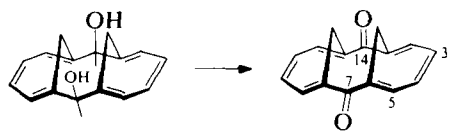
On cyclic voltammetry **365a** exhibits electrochemical reversibility at both the first and second waves even at low scan rates (16 mV s^{-1}). The well-defined two-wave pattern corresponds to the two discrete one-electron transfer processes forming radical anions initially and then dianions. This behaviour is consistent with that observed for quinones. The reduction potential of **365a** ($E(\frac{1}{2})_1$: −0.63, $E(\frac{1}{2})_2$: −1.02 V) is similar to that of 1,4-naphthoquinone ($E(\frac{1}{2})_1$: −0.59, $E(\frac{1}{2})_2$: −1.40 V).

2. *1,6;8,13-Bismethano-[14]annulene-7,14-diones (bishomoanthraquinones)*

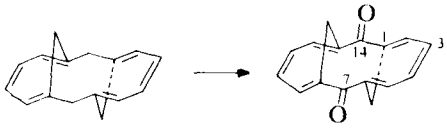
Two stereoisomers of bishomoanthraquinones are possible, the *syn* and *anti* form (**372** and **374**, respectively). Both have been synthesized. *syn*-Bishomoanthraquinone (**372**) was accessible from the *syn*-bishomoanthranthracene (**369**)[255]. Bromination yielded the 7,14-addition product **370**, which could be transformed to the diol **371** by reaction with silver nitrate in wet acetone. **371** yielded **372** on oxidation. The best results were obtained by oxidation with dimethyl sulphoxide/trifluoroacetic anhydride/triethylamine, a reagent especially suited for the oxidation of sterically hindered alcohols.



(369) (370)



(371) (372)



(373) (374)

374 has been obtained by successive oxidation of the hydrocarbon **373** with selenium dioxide in dioxane/water and chromium(III) oxide in pyridine[256]. For steric reasons and in contrast to the *syn*- isomer (**369**) the *anti*-1,6;8,13-bismethano-[14]annulene (**373**) exhibits no aromatic character but behaves as a readily polymerizable olefin. Nevertheless, with zinc/acetic anhydride in pyridine both the *syn* and *anti* diones (**372** and **374**) undergo facile reductive acetylation to the corresponding 7,14-diacetoxy-1,6;8,13-bismethano-[14]annulenes.

At cyclic voltammetry both isomers exhibit typical behaviour of quinones in that they show two reversible one-electron transitions to the corresponding radical anions and dianions[255]. The reduction potential of **374** (−2.29 V) is lower than that of **372** (−1.79 V), reflecting the differences in the aromaticity of the conjugate hydrocarbons.

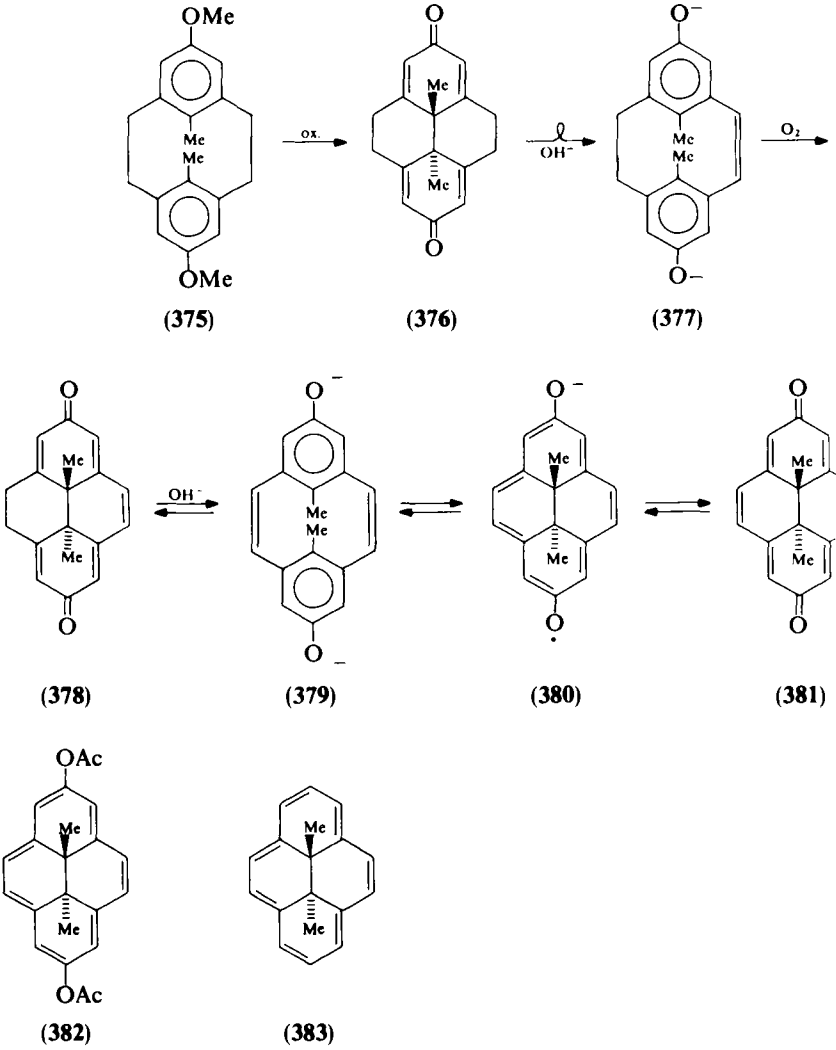
3. trans-*15,16-Dimethyldihydropyrene-2,7-dione* (**381**)

An elegant synthesis of a fascinating quinonoid system (**381**) has been described by Boekelheide and Phillips[244]. The 5,13-dimethoxy-8,16-dimethyl[2.2]metacyclophane (**375**) undergoes a smooth reaction with chromic acid in acetone or with iron(III) chloride in dry chloroform to give the bisdienone **376** in nearly quantitative yield. The fact that a coupling of two phenol ethers was accomplished under the conditions of the oxidative-radicalic phenolic coupling is quite surprising.

The bisdienone **376** might be expected to undergo a dienone–phenol rearrangement, but it is recovered unchanged from boiling hydrochloric acid. In contrast, it is readily soluble in aqueous alkali. This surprising property can be readily explained by a double enolization followed by valence tautomerism to give the dianion of the metacyclophane **377**. This in turn should undergo readily phenolic oxidation. In fact further oxidation by bubbling air through a basic solution of **376** or with *N*-bromosuccinimide occcurs smoothly to give **381**, again in nearly quantitative yields. The transient green-violet colour that appears during this oxidation suggests a pathway involving the semiquinone anion **380**, which is formed by enolization/valence tautomerism of **378** to **379** and further radicalic coupling.

The oxidation steps leading from **376** to **381** are reversible. This has been shown in a detailed study of the ESR spectrum of the violet semiquinone **380**[257], which is obtained by treatment of the yellow **381** with glucose in the presence of alkali. Further addition of glucose leads to the formation of the colourless hydroquinone-dianion **379**. This sequence of colour changes is exactly reversed by introduction of oxygen. Undoubtedly the hydroquinone dianion **379** is in equilibrium with the corresponding dihydropyrene valence tautomer, the proper hydroquinone dianion of **381**, but, in this case, relief of charge repulsion shifts the equilibrium in favour of **379**. As by-product of the alkaline oxidation, minor amounts of 4-hydroxy-*trans*-15,16-dimethyldihydropyrene-2,7-dione could be isolated. When the quinone **381** was subjected to reductive acetylation with zinc/acetic anhydride it was converted in 90% yield to the hydroquinone diacetate **382**, a further proof of the quinonoid character of **381**.

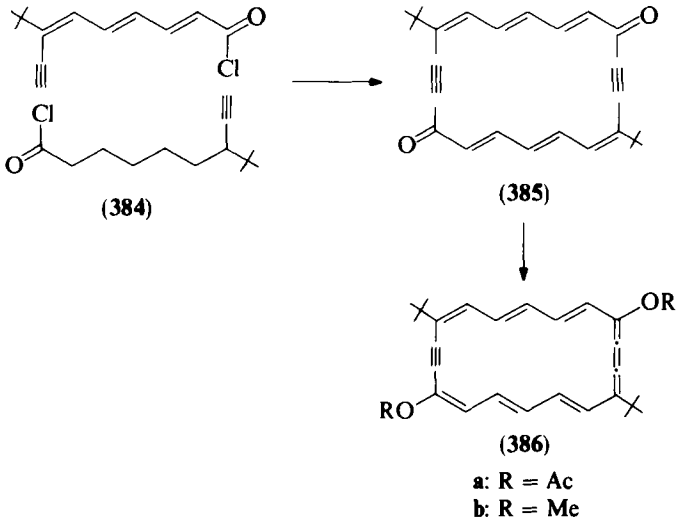
The conversion of **381** to the parent hydrocarbon, the *trans*-15,16-dimethyldihydropyrene (**383**), was effected by treatment with a lithium aluminium hydride/aluminium chloride mixture at room temperature.



C. [18]Annulenediones

1. Cyclooctadecahexaenediynedione (bisdehydro[18]annulenedione)

The 4,13-di-*t*-butylcyclooctadeca-4,6,8,13,14,15-hexaene-2,11-diyne-1,10-dione (**385**) has been prepared in the same way as the bisdehydro[14]annulene homologue (see Section IV.B.1) by cyclodimerization of the acid chloride **384** under the influence of a palladium/copper(I) catalyst[252]. Reductive acetylation of **385** with zinc/acetic anhydride in the presence of pyridine gave the diacetoxybisdehydro[18]annulene **386a** as a dark red solution. **386a** was found to be unstable even at $-10°C$, but the structure is obvious from the spectrum of the solution. The product of reductive methylation of **385** with dimethyl



(384) (385) (386)

a: R = Ac
b: R = Me

sulphate/sulphuric acid and zinc, the dimethoxybisdehydro[18]annulene **386b**, could be isolated in the form of dark reddish violet crystals.

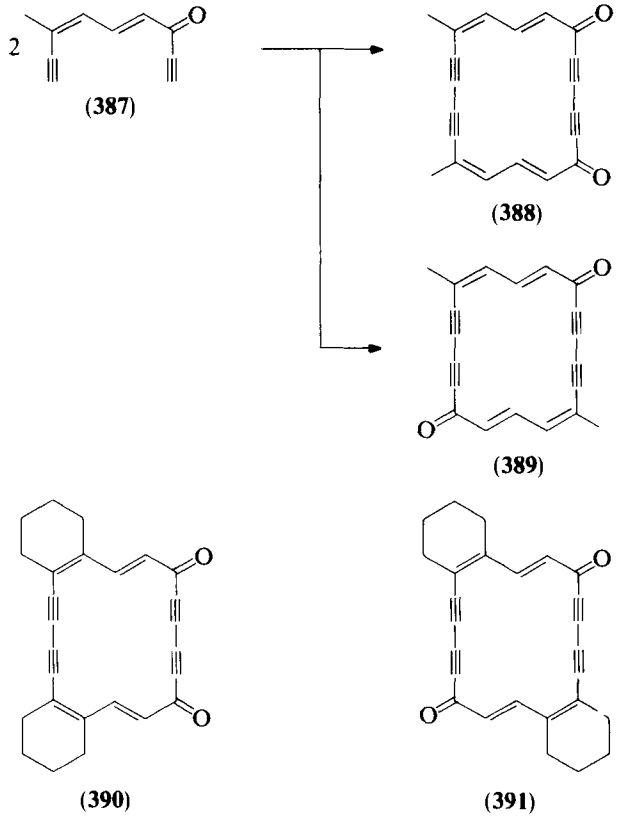
Further proof for the quinonoid character of **385** is given on electrochemical reduction by cyclic voltammetry[254], which showed electrochemical reversibility at both the first and second waves, corresponding to the formation of the anion radical and hydroquinone dianion. The redox potential of **385** (− 0.92 V) is more positive than that of benzoquinone (− 1.18 V) and by 0.1 V even more positive than that of the [14]annulenequinone homologue. This is by no means a measure for the growing aromaticity of the corresponding hydrocarbons, but may be connected with the increasing charge separation in the larger ring systems. Indeed the first half-wave potentials become more *negative* going from benzoquinone, over [14]annulenedione to **385** ($E(\frac{1}{2})_1$ = − 0.42, − 0.63 and − 0.72 V, respectively).

2. *Cyclooctadecatetraenetetraynediones (tetradehydro[18]annulenediones)*

A mixture of 10,15-dimethylcyclooctadeca-7,9,15,17-tetraene-2,4,11,13-tetrayne-1,6-dione (**388**) and 6,15-dimethylcyclooctadeca-6,8,15,17-tetraene-2,4,11,13-tetrayne-1,6-dione (**389**) has been obtained by oxidative coupling of **387** with oxygen, copper(I) chloride, ammonium chloride and concentrated hydrochloric acid in aqueous ethanol and benzene[258]. **388** is bright red and relatively soluble, while **389** is bright yellow and very insoluble.

The dicyclohexenotetradehydro[18]annulenediones **390** and **391** have been synthesized in a similar way[258]. **390** has also been obtained by another unambiguous route[259].

The electrochemical reduction of the diones **388–390** was examined by cyclic voltammetry[260]. All compounds exhibited chemical and electrochemical reversibility at both the first and second waves. The first wave corresponds to the addition of one electron to produce the radical anion and the second wave corresponds to the addition of a second electron to produce the dianion. The reduction potentials of **388–390** lie at more positive values (− 1.60 to − 1.74 V) than that of benzoquinone (− 1.92 V). This is by no means a measure for an increased aromatic character of the conjugate hydroquinone anions of **388–390** but may be partially due to the greater charge separation in the larger rings.



(387) (388) (389) (390) (391)

Indeed the potentials of the first wave ($E(\frac{1}{2})_1$: −0.66 to −0.70 V) are more negative than that of benzoquinone ($E(\frac{1}{2})_1$: −0.52 V). At any rate **388–390** are very easily and reversibly reduced at both waves and by this experimental criterion it is reasonable to regard these annulenediones as quinones of an aromatic system.

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CHAPTER **26**

Non-benzenoid quinones

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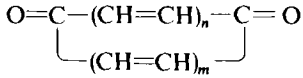
I. INTRODUCTION

The format of this report on non-benzenoid quinones follows the one so neatly set by our predecessor[1]. Although the present authors seek to cover material published from 1974 to 1985, a few developments in this area which were omitted previously have also been included. As no encyclopaedic coverage is intended, the progress on the chemistry of non-benzenoid quinones is presented here mainly in conformity with the interests of the authors. Nevertheless, we hope there is sufficient material in this chapter to give the reader a bird-eye's view of the subject matter.

II. EVEN-MEMBERED RINGS

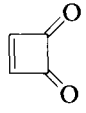
A. General Formula

In accord to the previous review[1], non-benzenoid quinones under the titled classification may be regarded as being generated from the following general formula:



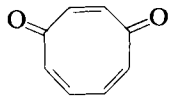
in which either m or n, but not both, may be zero, and m and n are positive integers.

Cyclobutenequinone (**1**) is the case where $m = 1$, $n = 0$. The cases $m = 0$, $n = 2$ (*o*-benzoquinone) and $m = 1$, $n = 1$ (*p*-benzoquinone) are of course outside the scope of this chapter.

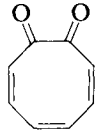


(**1**)

When $m = 2$, $n = 1$ or $m = 3$, $n = 0$, cycloocta-2,5,7-triene-1,4-dione (**2**) and cycloocta-3,5,7-triene-1,2-dione (**3**) are generated respectively.



(**2**)

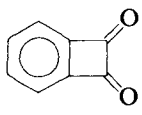


(**3**)

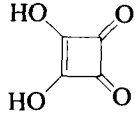
Annulenequinones, which can be generated by the general formula where $m + n \geqslant 6$ (where some of the double bonds may be replaced by triple bonds) will also be discussed here.

B. Four-membered Ring Systems

The chemistry of cyclobutenequinone[2] and derivatives[3-5], benzocyclobutenequinone (**4**) and derivatives[6,7], squaric acid (**5**) and derivatives[6,8-17] has been extensively



(**4**)

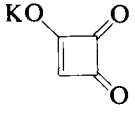


(**5**)

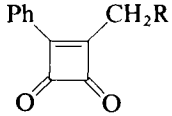
reviewed[2-17]. Hence we will restrict ourselves in this chapter to the discussion of the latest progress in this field.

1. Cyclobutenequinone, squaric acid and their derivatives

The chemistry of four-membered ring quinones was highlighted by the isolation of a new microbial toxin moniliformin (**6**)[18], the structure of which was confirmed by X-ray crystallography[19].

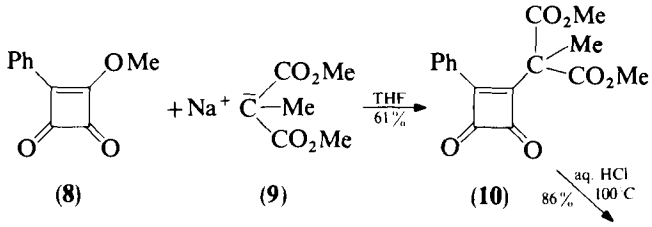


(**6**)

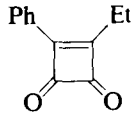


(**7**)

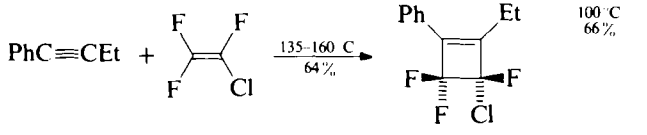
New synthetic routes to 3-alkyl-4-phenylcyclobutene-1,2-dione (**7**) have been reported[20]. In one of them, quinone **8** reacts with the sodium salt **9** to produce diester **10**,



(**8**) (**9**) (**10**)



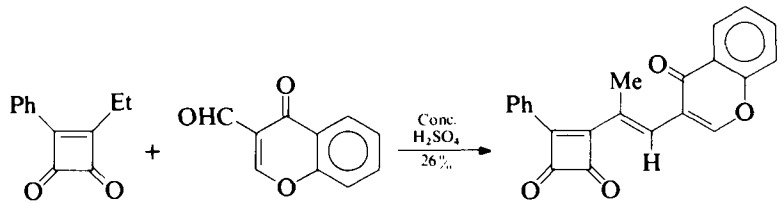
(**7a**)

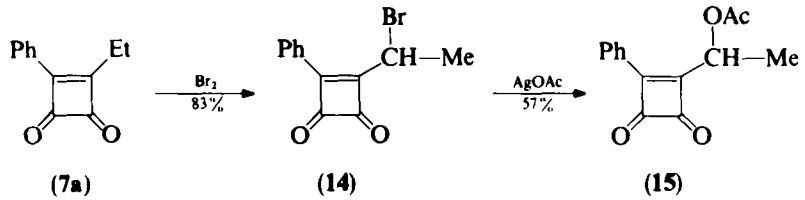


(**11**)

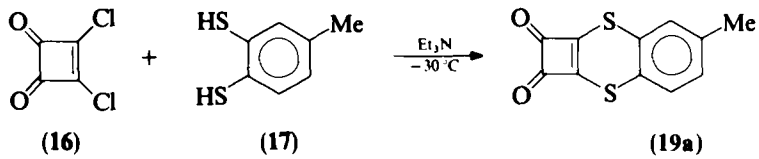
which can be hydrolysed to **7a**[20]. Alternatively, **7a** can also be prepared by the thermal [2 + 2] cycloaddition of ethyl phenyl acetylene and chlorotrifluoroethylene which yields cyclobutene **11**. Hydrolysis of **11** furnishes **7a**[20].

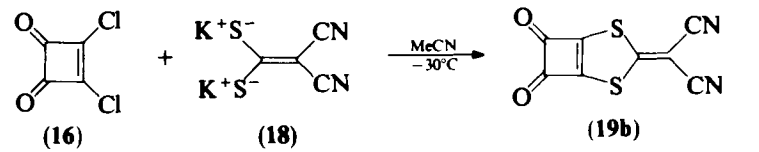
The methylene group of **7** is sufficiently activated to undergo condensation with various aldehydes[21]. For example, **7a** reacts with aldehyde **12** to provide the dehydration product **13**[21]. Furthermore, the methylene group of **7** can also be brominated[22] to **14**, which upon treatment with silver acetate gives **15**[22].

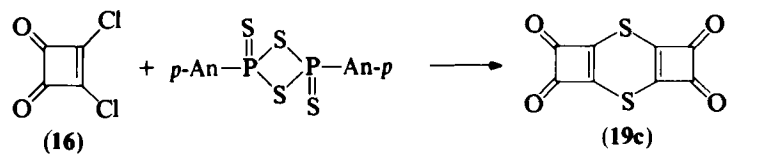




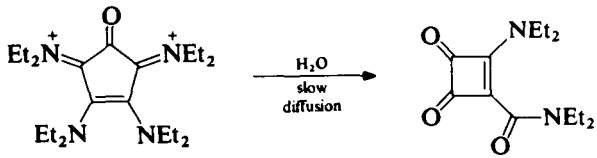
It has been reported that 3,4-dichloro-3-cyclobutene-1,2-dione (**16**) readily reacts with dithiol or dithiolate to give 1,4-dithiin- as well as 1,3-dithio-derivatives[23]. At −30°C, **16** reacts with **17** and **18**, to give **19a** and **19b** in 50% and 30% yields, respectively[23]. Moreover, Lawesson reagent has been used to convert **16** to dicyclobuta[1,4]dithiin-1,2,4,5-tetraone (**19c**) in quantitative yields[23].







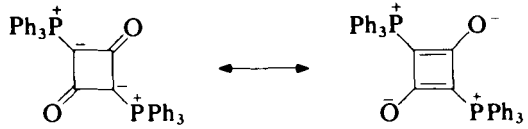
Slow diffusion of atmospheric moisture to an acetonitrile solution of **20** affords the colourless, water-soluble 4-diethylaminocyclobutenedione-3-*N*, *N*-diethylcarboxamide (**21**)[24], whose structure has been confirmed by X-ray diffraction study[24].



(20) **(21)**

2. *Betaines of squaric acid derivatives*

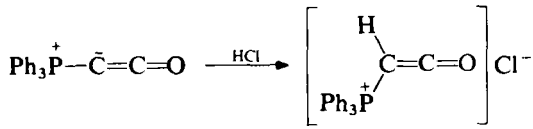
Compounds **22** and **23** are of interest because their resonance forms **22b** and **23b** are examples of 'push–pull' cyclobutadienes. The synthesis of **22** has been realized by addition



(22a) **(22b)**

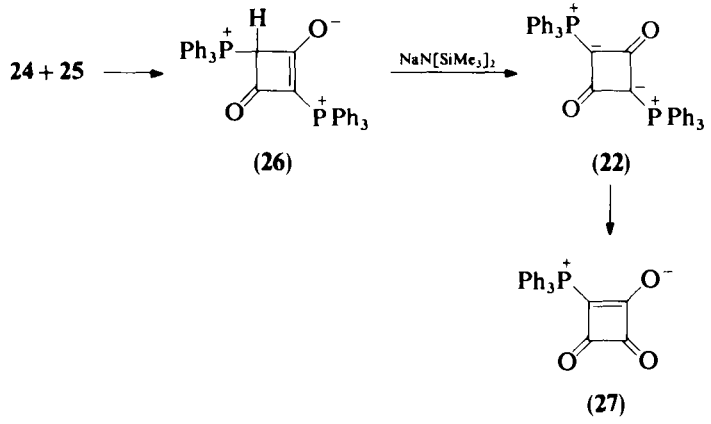
(23a) **(23b)**

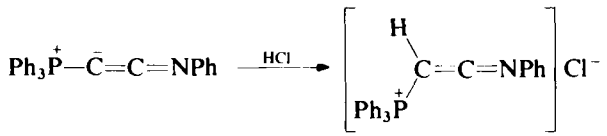
of HCl to a solution of the heterocumulene ylide **24**. Presumably the ketenic phosphonium salt **25** is generated first, which undergoes [2 + 2]cycloaddition with excess **24** to give **26**.



(24) **(25)**

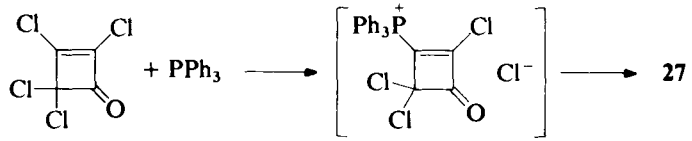
Subsequent treatment of **26** with sodium bis-(trimethylsilyl)amide affords the bis-ylide **22**[25]. It is interesting to note that, oxidation of **22** with ozone–triphenylphosphite adduct affords the cyclobutanetrione derivative **27**[25]. Similarly, **28** gives the ketenimine **29** which leads to **23**. The CO stretching frequencies which have been located at 1650 and 1610 cm^{-1} and at 1563 and 1527 cm^{-1} respectively for **22** and **23** lend support to the notion that **22b** and **23b** contribute significantly to the overall structures[25].





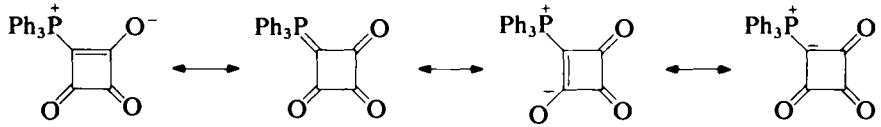
(28) (29)

Compound **27** has also been prepared by addition of triphenylphosphine to perchlorocyclobutenone (**30**), which leads to **31**. Upon hydrolysis, **31** provides **27**[26].



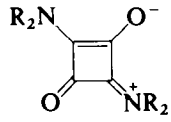
(30) (31)

In principle, the cyclobutanetrione **27** can possess four resonance structures **27a**, **27b**, **27c** and **27d**[26]. However, their relative importance has not been settled.

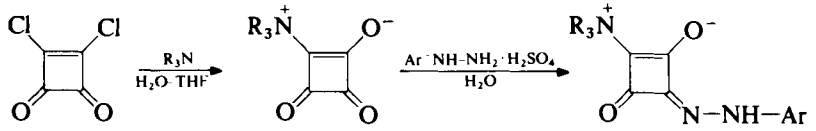


(27a) (27b) (27c) (27d)

The chemistry of the *N*-betaines, namely, squaraines (**32**) has been comprehensively reviewed[27]. A new class of *N*-betaines of squaric acid (**5**), namely **33**, have been prepared by reaction between an amine and 3,4-dichloro-3-cyclobutene-1,2-dione (**16**) in aqueous THF[28]. In the IR spectra of betaines **33**, the existence of strong bands at 1650–1570 cm^{-1} indicates that they should have the cyclobutenequinone structure[28].

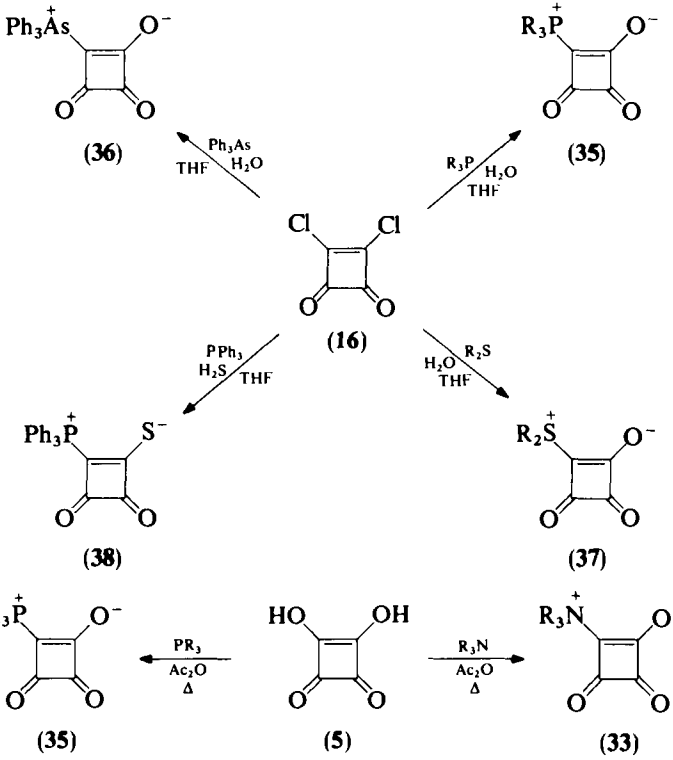


(32)



(16) (33) (34)

Condensation of **33** with arylhydrazines yields arylhydrazones **34**[28]. By the same strategy, **16** can be converted to **35**, **36**, **37** and **38**[29].



(36) (35) (16) (38) (37)

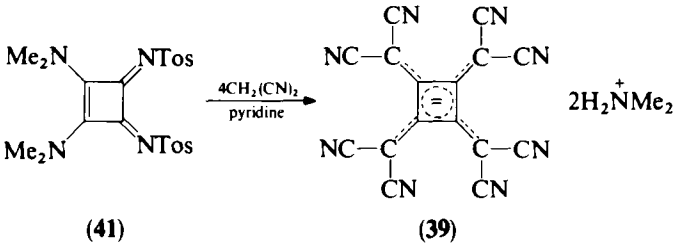
(35) (5) (33)

Alternatively, **33** and **35** can also be obtained from squaric acid (**5**)[30].

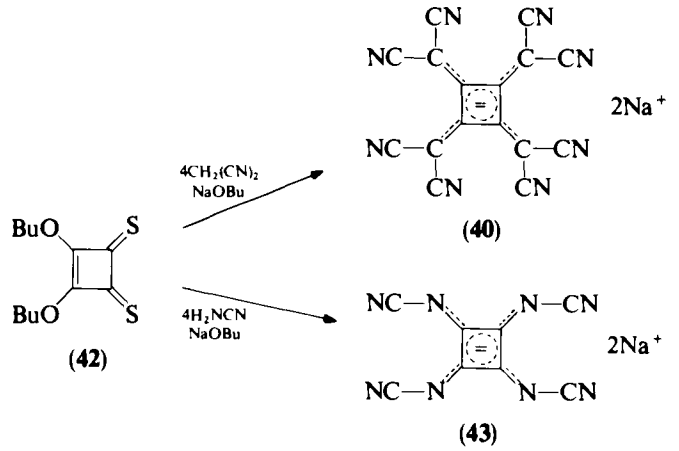
3. Pseudooxocarbon dianions

The chemistry of thioxocarbon dianions and their derivatives has been reviewed[31]. Novel pseudooxocarbon dianions of the C_4 series such as **39** and **40** can be prepared from

41 and **42** respectively[32, 33]. Similarly, **42** can also be converted to dianion **43**[32, 33]. The highly symmetrical structures of **39**, **40** and **43** have been revealed by ^{13}C-NMR spectroscopy[32, 33]. The X-ray structural analysis of **39**, however, indicates that the dianion is twisted and the central four-membered ring is non-planar[32, 33].



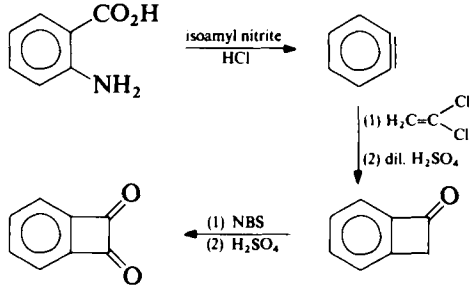
(41) (39)



(42) (40) (43)

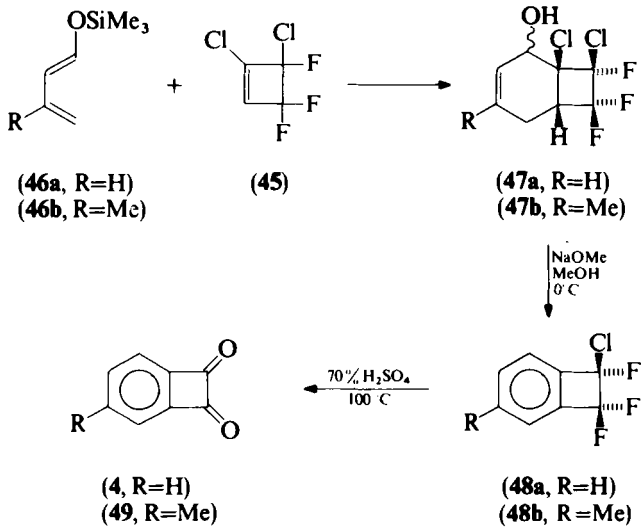
4. Benzocyclobutenequinone and derivatives

Making use of two known procedures, a large scale synthesis of benzocyclobutenequinone (**4**) has recently been described[34-36]. Thus, conversion of anthranilic acid to benzyne and the subsequent [2 + 2]cycloaddition with vinylidene chloride yields benzocyclobutenone (**44**)[34, 35]. Bromination and hydrolysis finally transform **44** to **4**[34, 36].



(4) (44)

Alternatively, reaction of cyclobutene **45** with 1-trimethylsiloxydiene **46a** gives **47a** after desilylation[34]. Aromatization and hydrolysis affords **4** in 63% overall yield[34].



(**46a**, R=H)
(**46b**, R=Me)

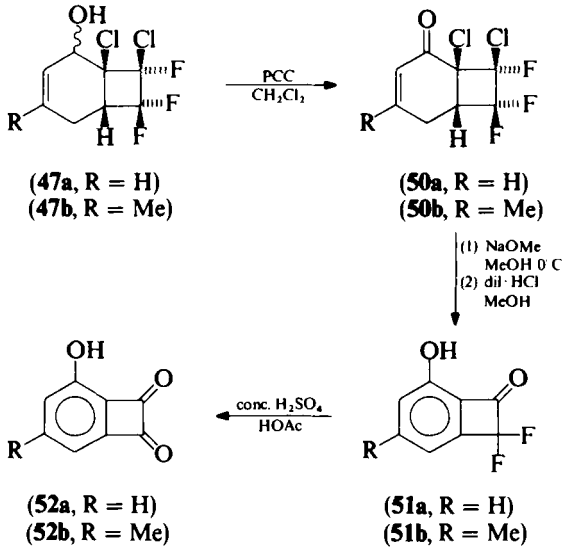
(**45**)

(**47a**, R=H)
(**47b**, R=Me)

(**4**, R=H)
(**49**, R=Me)

(**48a**, R=H)
(**48b**, R=Me)

Similarly, 4-methylbenzocyclobutenequinone (**49**) can also be obtained in 72% overall yield from **46b**[34]. Furthermore, **47a** can be oxidized to **50a**, which is aromatized and



(**47a**, R = H)
(**47b**, R = Me)

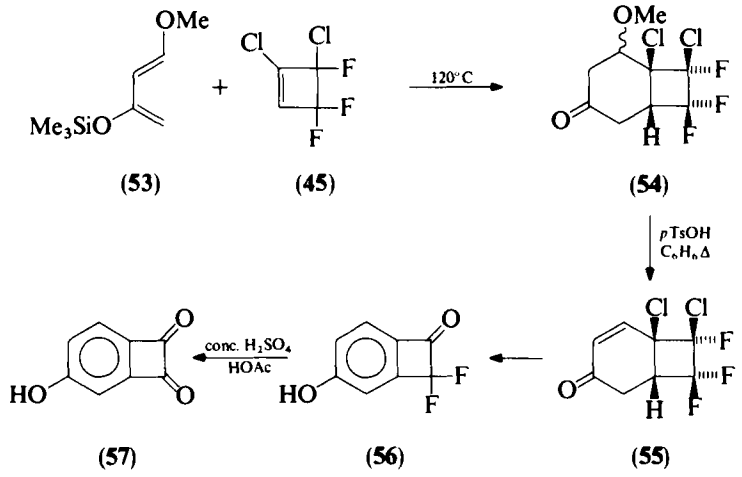
(**50a**, R = H)
(**50b**, R = Me)

(**52a**, R = H)
(**52b**, R = Me)

(**51a**, R = H)
(**51b**, R = Me)

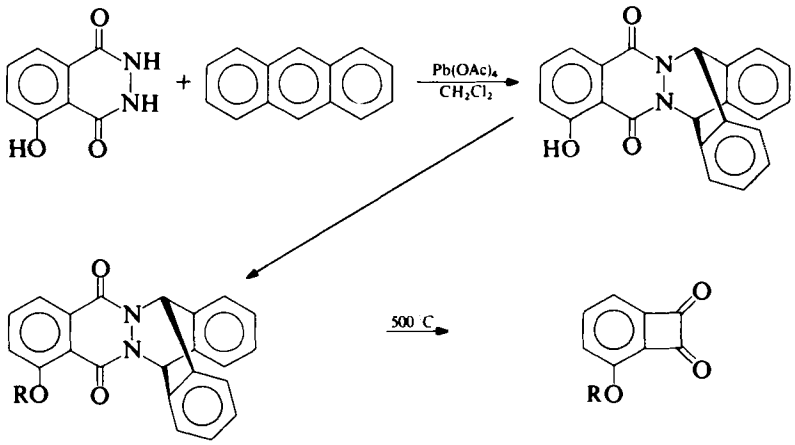
hydrolysed to **51a**. More vigorous hydrolysis converts **51a** to 3-hydroxybenzocyclobutenequinone (**52a**) in 36% overall yield[34]. Similarly, 3-hydroxy-5-methylbenzocyclobutenequinone (**52b**) can be prepared in 63% overall yield[34].

The Danishefsky's diene **53** reacts smoothly with **45** to give cycloadduct **54** after hydrolysis. Adduct **54** can be converted to enone **55**, which undergoes aromatization as well as mild acid hydrolysis to afford the gem-difluoride **56**. More vigorous acid hydrolysis of **56** yields 4-hydroxybenzocyclobutenequinone (**57**) in 43% overall yield[34].



(**53**) (**45**) (**54**) (**55**) (**56**) (**57**)

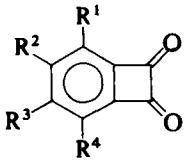
The McOmie–Rees procedure[37, 38] has been applied extensively to prepare substituted benzocyclobutenequinones[39]. As an example, the protected Diels–Alder adduct **58** can be pyrolysed in the vapour phase to afford 3-alkoxybenzocyclobutenequinones (**59**)[39], which



(**58a**, R = Me)
(**58b**, R = CH_2OMe)

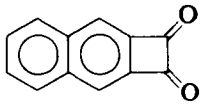
(**59a**, R = Me)
(**59b**, R = CH_2OMe)

serve as starting material for the total synthesis of islandicin and digitopurpone[39]. Similarly, 4-chlorobenzocyclobutenequinone (**60**)[40], 3,6-dichlorobenzocyclobutenequinone (**61**)[40], 4,5-dichlorobenzocyclobutenequinone (**62**)[40], 4,5-dibromobenzocyclobutenequinone (**63**)[40], 4,5-dimethylbenzocyclobutenequinone (**64**)[40],

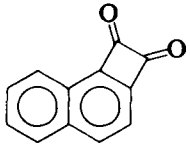


(60–64, 69, 70)

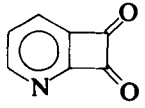
(60, R^3 = Cl; R^1 = R^2 = R^4 = H)
(61, R^1 = R^4 = Cl; R^2 = R^3 = H)
(62, R^2 = R^3 = Cl; R^1 = R^4 = H)
(63, R^2 = R^3 = Br; R^1 = R^4 = H)
(64, R^2 = R^3 = Me; R^1 = R^4 = H)
(69, R^3 = OMe; R^1 = R^2 = R^4 = H)
(70, R^2 = R^3 = OMe; R^1 = R^4 = H)



(65)



(66)



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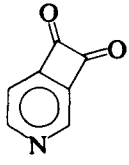
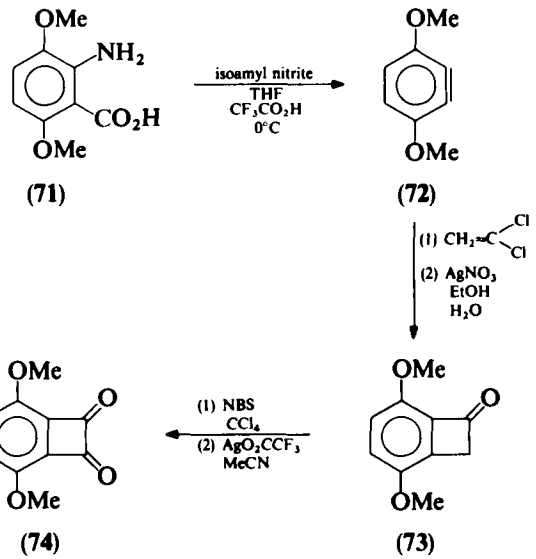


(68)

cyclobuta[*b*]naphthalene-1,2-dione (**65**)[40], cyclobuta[*a*]naphthalene-1,2-dione (**66**)[40], cyclobuta[*a*]pyridine-1,2-dione (**67**)[40], cyclobuta[*b*]pyridine-1,2-dione (**68**)[40], 4-methoxybenzocyclobutenequinone (**69**)[41] and 4,5-dimethoxybenzocyclobutenequinone (**70**)[41] have been prepared by applying the same methodology[37,38]. Compounds **66**, **67** and **68** are reported to be very unstable[40].

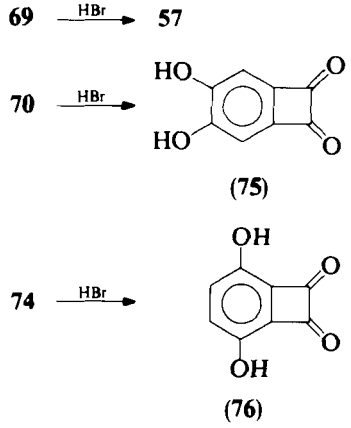
The amino acid **71** can be converted to the benzyne **72**, which is trapped with vinylidene chloride. Subsequent hydrolysis of the resulting dichloride intermediate affords the ketone



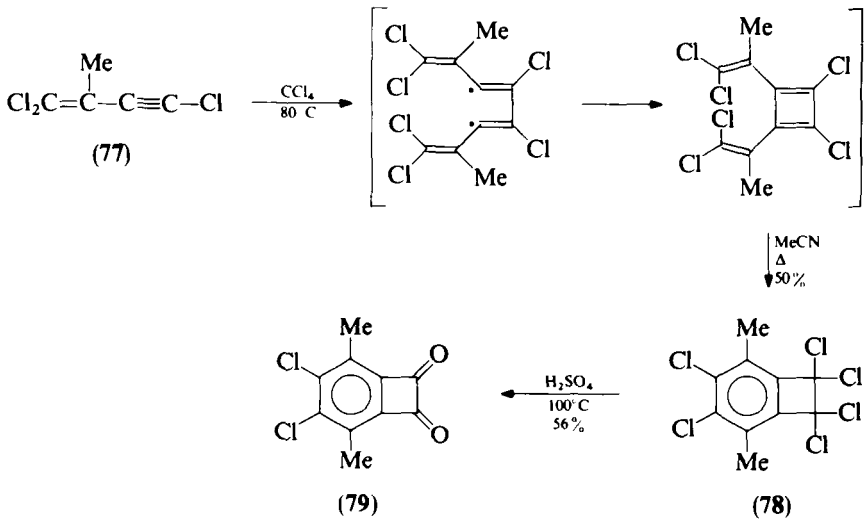
73[42], which is brominated and hydrolysed to furnish 3,6-dimethoxybenzocyclobutenequinone (**74**) in 15% overall yield[41].

The methoxy compounds **69**, **70** and **74** can be demethylated by heating with hydrobromic acid to give the hydroxy compounds **57**, **75**, and **76** respectively[41]. It is

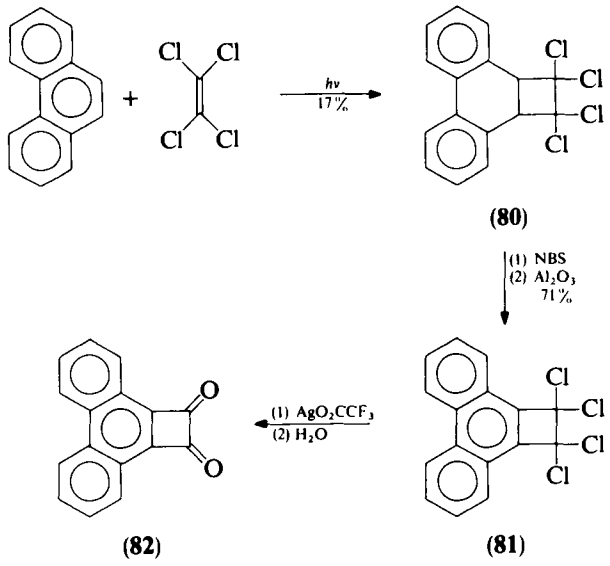
interesting to point out that these products are all relatively strong acids, and the acidities of **57** and **75** are stronger than those of **52a** and **76** respectively[41]. Furthermore, the acidities of **75** and **76** are weaker than that of squaric acid (**5**)[41].



Thermal dimerization of **77** leads to a radical intermediate which rearranges to benzocyclobutene **78**[43]. Acid hydrolysis converts **78** to the benzocyclobutenequinone **79**[43].

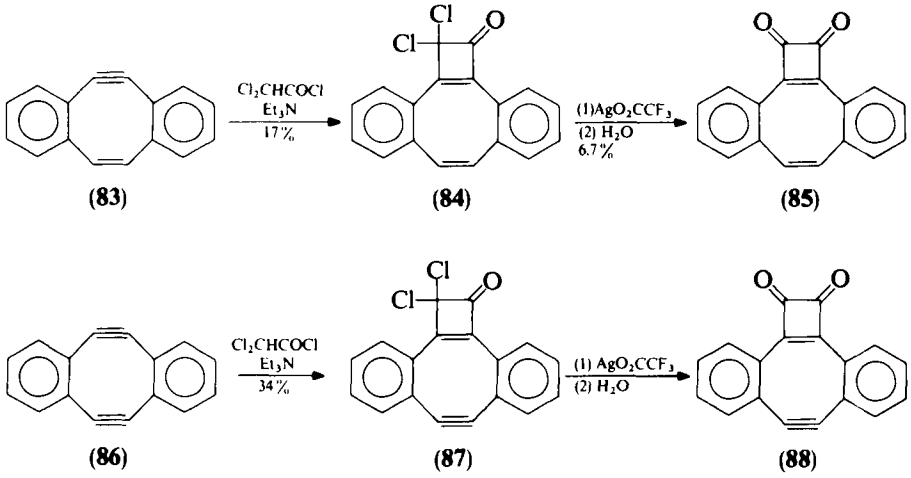


Photo[2 + 2]cycloaddition of tetrachloroethene to phenanthrene gives the adduct **80**, which can be aromatized to **81** by consecutive treatment of NBS and alumina. Treatment of **81** with silver trifluoroacetate, followed by hydrolysis of the resulting tetrakis (trifluoroacetate) with water finally leads to cyclobuta[1]phenanthrene-1,2-dione (**82**)[44]. The molecular structure of **82** has been determined by X-ray crystallography[44].



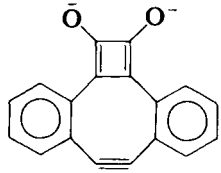
5. *Eight-membered ring-fused cyclobutenequinones*

The monoacetylene **83** undergoes smooth [2 + 2]cycloaddition with dichloroketene, whereby the dichloroketone **84** is obtained[45,46]. Subsequent treatment of **84** with excess silver trifluoroacetate and hydrolysis leads to the eight-membered ring-fused cyclobutenequinone **85**[45,46], which is a relatively stable crystalline compound. Similar treatment of



the diacetylene **86** leads to the presumably coplanar cyclobutenequinone **88** which is obtained as an unstable red crystalline solid[45,46]. The electrochemical reduction of **88** to its radical anion and then to the dianion **89** has been studied[46] and was found to be a facile process[46]. This observation lends some support to the general idea that the fusion of two

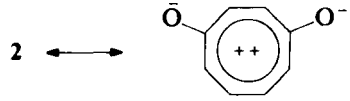
planar antiaromatic $4n\pi$ systems as is the case in **89** would constitute an overall $(4n + 2)\pi$ aromatic periphery, and hence would give rise to certain degree of aromatic stabilization[46].



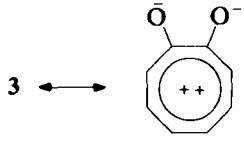
(89)

C. Eight-membered Ring Systems

Cycloocta-2,5,7-triene-1,4-dione (**2**) and cycloocta-3,5,7-triene-1,2-dione (**3**) have attracted wide interest due primarily to the possible existence of their corresponding eight-



(2a)

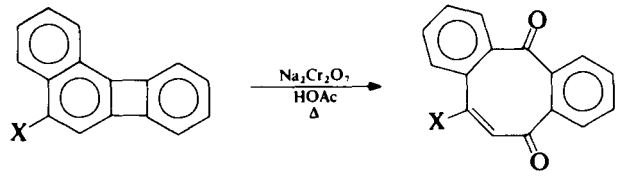


(3a)

carbon 6π canonical forms **2a** and **3a**. If **2a** and **3a** indeed make appreciable contribution, **2** and **3** should be planar and exhibit diatropic properties.

1. Cycloocta-2,5,7-triene-1,4-dione and derivatives

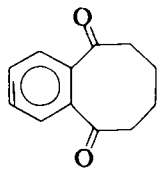
The first known derivatives of **2** were reported by Cava in 1962[47]. Compounds **91** were obtained in good yields by oxidation of the corresponding bromide **90a** and iodide **90b**[47].



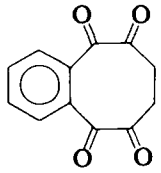
(90a, X = Br)
(90b, X = I)

(91a, X = Br, 76.6%)
(91b, X = I, 81.3%)

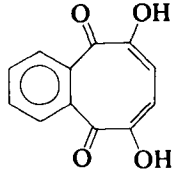
Attempts to convert the diketone **92** to the tetraketone **93**, were in vain[48]. Compound **93** is of interest because its enol form **93a** may yet be another derivative of **2**[48]. An attempt to



(92)

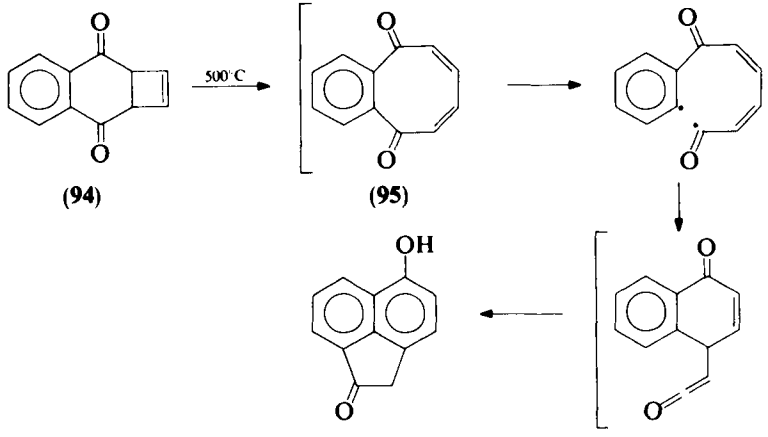


(93)



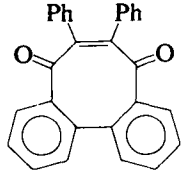
(93a)

generate **95** from **94** by thermolysis resulted in the formation of **96**. However, compound **95** has been proposed as an intermediate in association with the rearrangement[49].



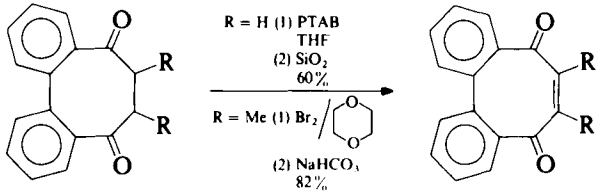
(94) (95) (96)

In the presence of air, 2,2′-bis(phenylacetyl)biphenyl reacts with sodium methoxide in methanol to give **97**, which is a dibenzo derivative of **2**[50].



(97)

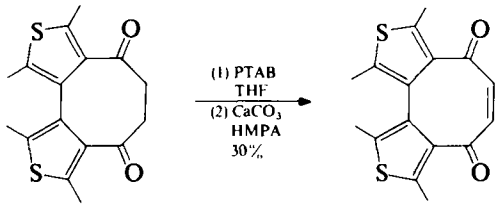
The conversion of diketone **98** to **99** has been achieved by bromination and dehydrobromination. Similarly, **100** has been converted to **101**[51]. However, no extended conjugation is observed for **99a**, **99b** and **101** in their corresponding UV spectra[51]. Moreover, the fact that the vinylic protons of **99a** and **101** do not exhibit detectable diamagnetic shift leads to the conclusion that these compounds do not behave as eight-carbon 6π electron aromatic species[51]. Nevertheless, downfield shift is observed when the



(**98a**, R = H)
(**98b**, R = Me)

(**99a**, R = H)
(**99b**, R = Me)

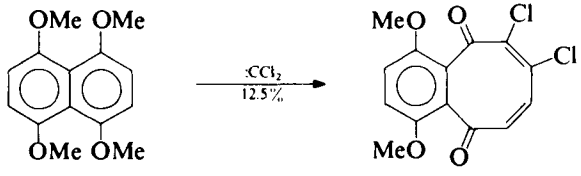
PTAB: phenyltrimethylammonium perbromide



(**100**) (**101**)

NMR spectra are recorded in deuteriotrifluoroacetic acid, suggesting that some mono- or diprotonated diatropic species might have been formed[51].

Addition of large excess of dichlorocarbene to **102** results in the isolation of **103**, whose eight-membered moiety does not indicate any aromatic property[52, 53].

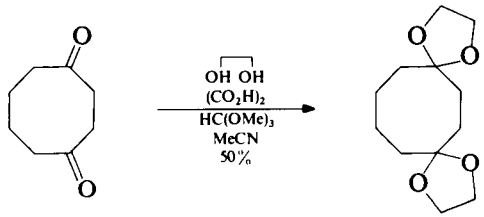


(**102**) (**103**)

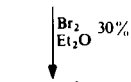
In view of the lack of evidence for possible contribution of their charged distropic canonical forms in **91**, **97**, **99**, **101** and **103**, (viz. **2a**), the attention of the organic chemists was then drawn to the realization of their parent compound **2**. Starting from cyclooctane-1,4-dione (**104**), cyclooctatriene-1,4-dione bisethylene ketal (**105**) was prepared, but all attempts have been unsuccessful in the hydrolysis of **105** to **2**[54, 55].

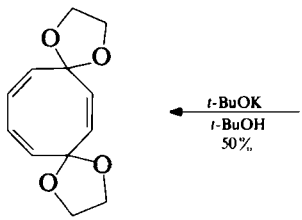
The synthesis of some valence tautomers of **2** have been recorded. Thus, photolysis of a mixture of methoxyl-*p*-benzoquinone and various acetylenes leads to isolation of **106**[56].

The direct synthesis of the parent valence tautomer **107** of **2**, however, poses considerable difficulty because *p*-benzoquinone would react photochemically with acetylenes at the carbonyl bond. To avoid this problem, Yates has converted *p*-benzoquinone to **108** by reaction with anthracene. Photoaddition of the adduct **108** to acetylenes gives compounds **109** which undergo retro Diels–Alder reaction to yield **110**[57].

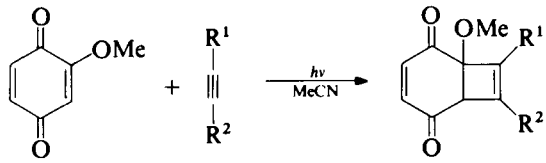


(104)

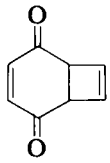




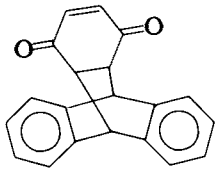
(105)



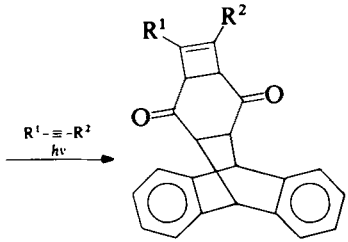
(**106a**, $R^1 = R^2 = Ph$)
(**106b**, $R^1 = R^2 = Me$)
(**106c**, $R^1 = Ph$, $R^2 = H$)
(**106d**, $R^1 = H$, $R^2 = Ph$)



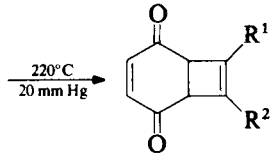
(107)



(108)

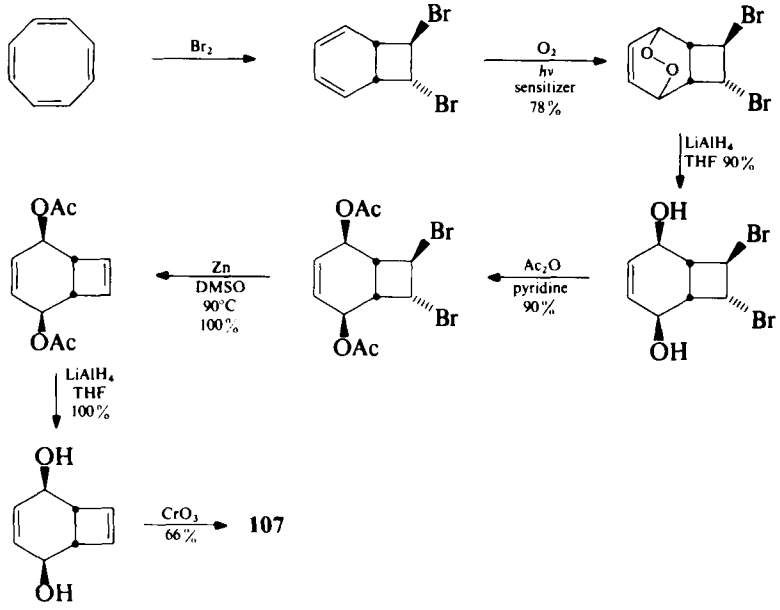


(**109a**, $R^1 = R^2 = Me$)
(**109b**, $R^1 = H$, $R^2 = Ph$)

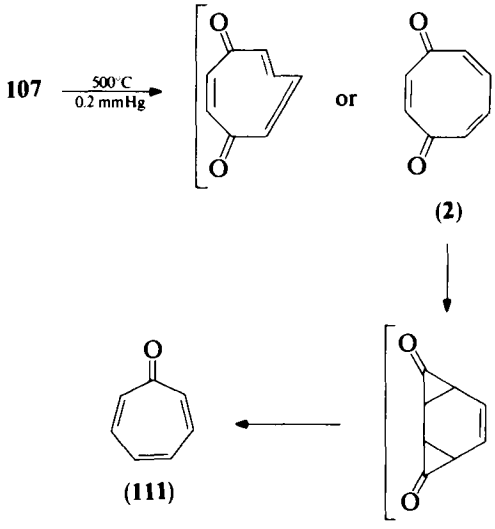


(**110a**, $R^1 = R^2 = Me$)
(**110b**, $R^1 = H$, $R^2 = Ph$)

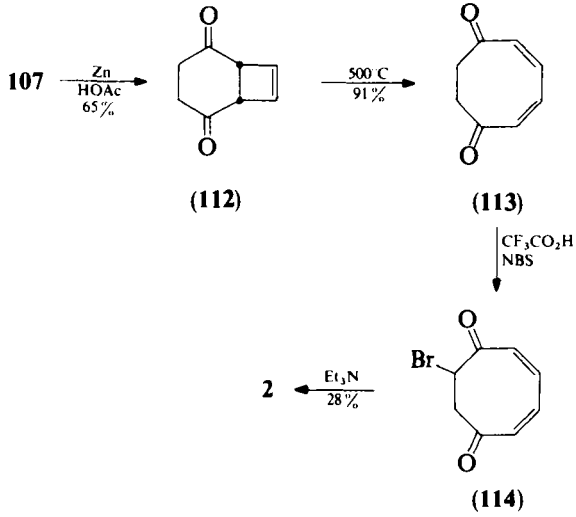
The synthesis of the parent compound **107** was finally realized by Kitahara using the scheme shown below[58].



All attempts to convert **107** into its tautomer **2** have failed. Thermolysis of **107** at 500°C affords tropone (**111**) in 49% yield together with trace amounts of an unstable and unidentified compound[59]. It has been assumed that either **2** or its *trans* isomer may be the possible intermediate in the thermal reaction[59].



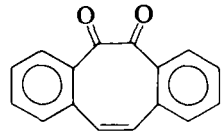
The parent compound **2** was eventually isolated in 1975[60]. Prior reduction of **107** to **112**, followed by thermolysis of the latter gives **113** in excellent yield. Bromination of **113** can be achieved by using NBS in CF_3CO_2H–CH_2Cl_2 at room temperature.



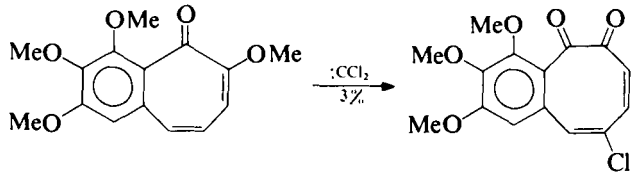
Dehydrobromination of the unstable bromide **114** furnishes **2** as a yellow liquid. The UV and NMR spectra unequivocally show that **2** is an ordinary olefinic ketone. Therefore the contribution of **2a** can be neglected. Compound **2** is stable in aprotic solvents, but decomposes readily in acidic solvents.

2. Cycloocta-3,5,7-triene-1,2-dione and derivatives

The synthesis and structure of dibenzo[*a*, *e*]cyclooctene-5,6-dione (**115**) has been recorded[61,62] and reviewed[1]. It is not surprising that, like other benzannelated derivatives of **2**, **115** is non-planar and non-aromatic. This situation is also true for compound **117**



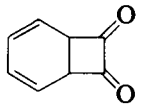
(**115**)



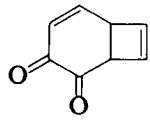
(**116**) (**117**)

which can be conveniently synthesized by subjecting **116** to a large excess of dichlorocarbene[52, 53].

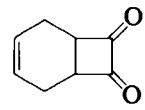
The parent compound **3** itself and its valence tautomers **118** as well as **119** have become target molecules of various research groups. Carpino has reported the synthesis of **120**, which resisted transformation into **118**[63]. The synthesis of the other valence tautomer **119**



(118)

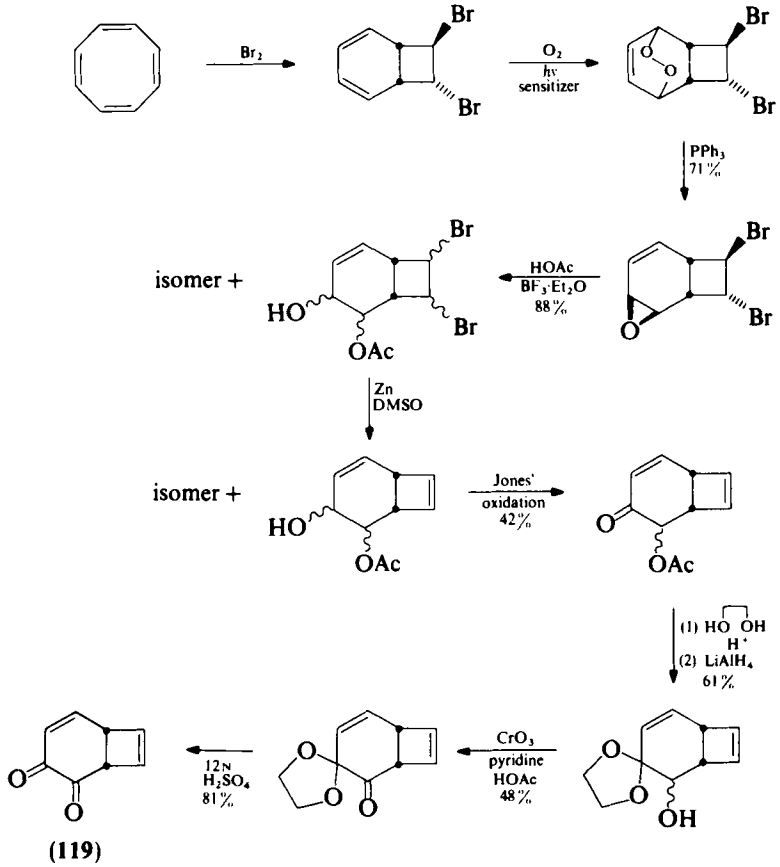


(119)



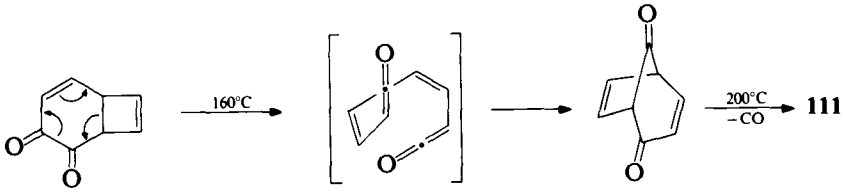
(120)

has however been successful[64]. Starting from cyclooctatetraene, **119** can be obtained from the series of reactions[64] outlined below.



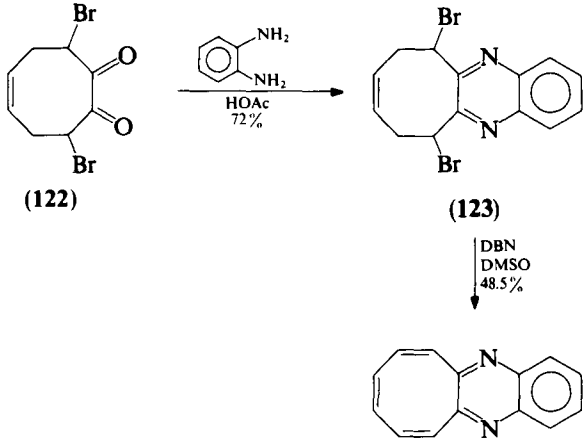
The thermolysis of **119** has been examined with the aim to effect its valence tautomerization into **3**. However, **119** undergoes an intriguing rearrangement to give

bicyclo[3.2.1]octa-3,6-diene-2,8-dione (**121**), which is decarbonylated rapidly at 200°C to tropone (**111**)[65].



(**119**) (**121**)

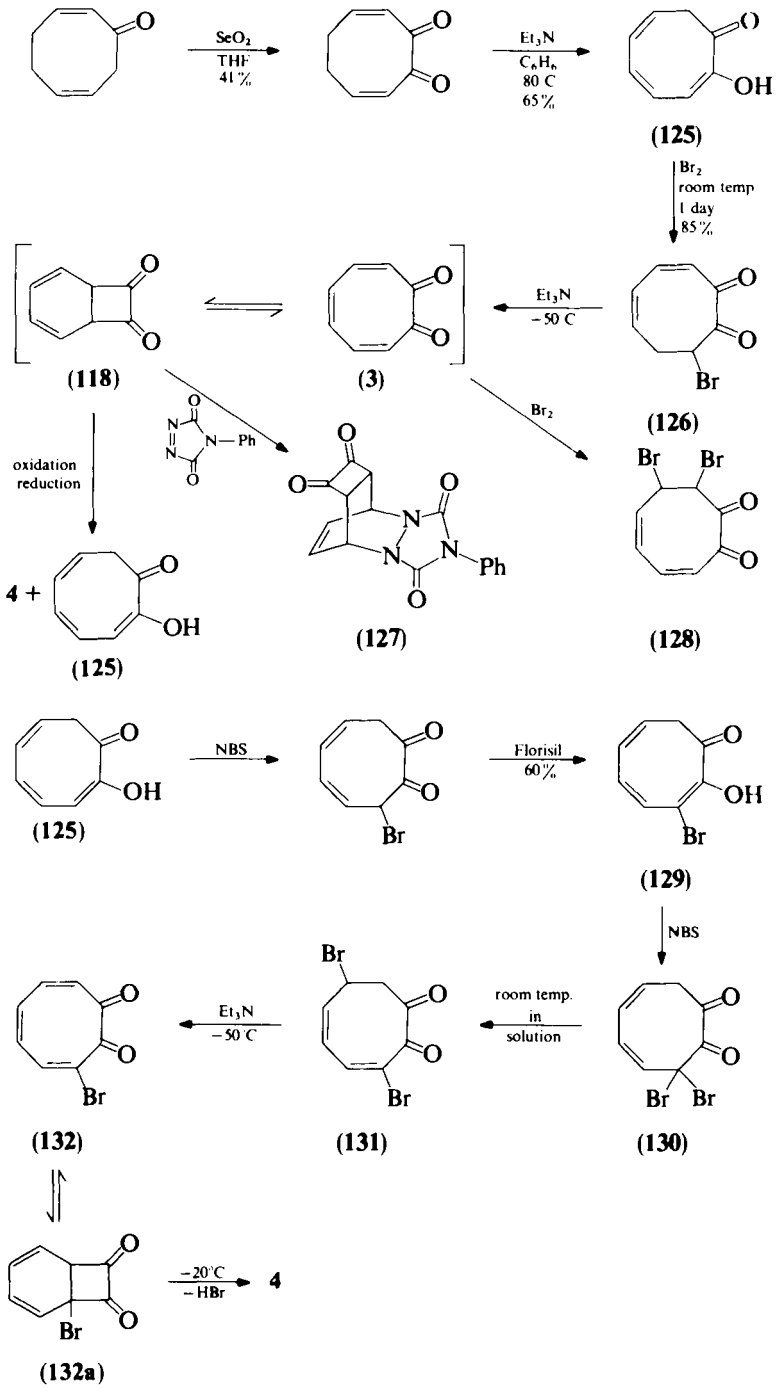
Dehydrobromination of **122** fails to give **3**[66]. On the other hand, reaction of **122** with *o*-phenylenediamine furnishes the quinoxaline **123**, which is dehydrobrominated to **124**, a quinoxaline derivative of **3**[66].



(**122**) (**123**) (**124**)

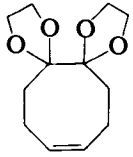
Dehydrobromination of the dibromide **126**[67,68] with triethylamine at −50°C leads successfully to **3** which can be detected by NMR spectroscopy[69]. However, if the NMR solution of **3** in $CDCl_3$ is brought up to room temperature, the relevant NMR signals vanish and from this solution, compounds **4** and **125** can be isolated. This result indicates that at room temperature, **3** equilibrates with its valence tautomer **118**, and the mixture undergoes oxidation–reduction reaction to afford **4** and **125**[69]. Furthermore, a crude yellow solution of **3** can be obtained by low temperature chromatography at −78°C. When this yellow solution is allowed to react with *N*-phenyltriazolinedione at room temperature, the Diels–Alder adduct **127** can be isolated. The existence of **3** is further confirmed by action of bromine at −30°C which results in the formation of the dibromide **128**[69].

3-Bromo-cycloocta-3,5,7-triene-1,2-dione (**132**) was first reported to be a transient intermediate in the dehydrobromination of **122**[66]. Its existence has subsequently been established spectroscopically at low temperature[69]. Thus, treatment of **129**[68] with NBS leads to the dibromide **130** which rearranges smoothly to **131**. Dehydrobromination of

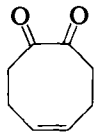

SeO2
THF
41%
Et3N
C6H6
80 C
65%
(125)
Br2
room temp
1 day
85%
Et3N
-50 C
(118)
(3)
(126)
oxidation
reduction
N-Ph
Br2
4 +
(125)
(127)
(128)
NBS
Florisil
60%
(125)
(129)
NBS
Et3N
-50 C
room temp.
in
solution
(132)
(131)
(130)
-20°C
-HBr
4
(132a)

131 at $-50°C$ with Et_3N gives **132**, whose structure is shown to be non-planar and non-aromatic by NMR spectroscopy at $-50°C$. When the $CDCl_3$ solution of **132** is allowed to warm up to $-20°C$, the signals of **132** vanish and benzocyclobutenequinone (**4**) and an unidentified compound can be isolated. This observation indicates that **132** is even more unstable than **3**[69].

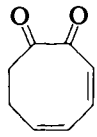
In several related studies, the preparations of a number of potential precursors of **3** such as **133**[70], **134**[71], **135**[72] and **136**[73] have also been described.



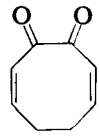
(133)



(134)



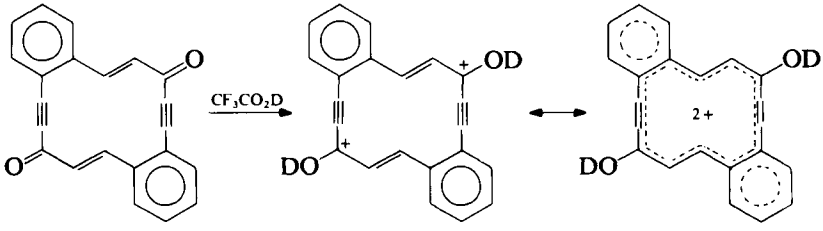
(135)



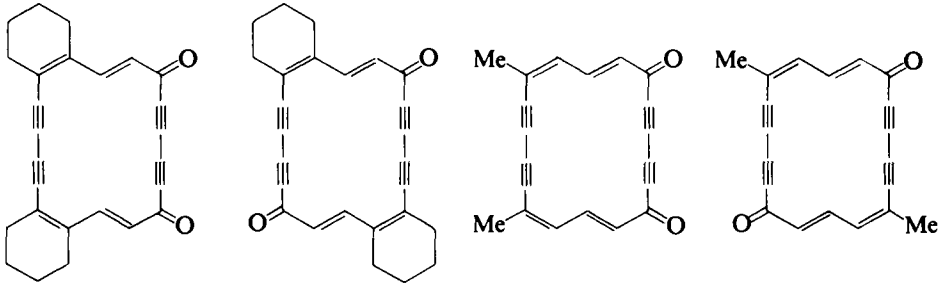
(136)

D. Annulenequinones

The synthesis of [14]annulenequinone **137** has been reported[74]. Protonation of **137** leads to the 12π paratropic dication **138**, whose inner protons exhibit low field shift[74]. The [18]annulenequinones **139**[75], **140**[76], **141**[76] and **142**[76] have been synthesized. The proton NMR spectra of these compounds in $CDCl_3$ with added CF_3CO_2D are consistent with the ketonic structures and as expected no detectable ring current can be observed[76].



(137) (138a) (138b)

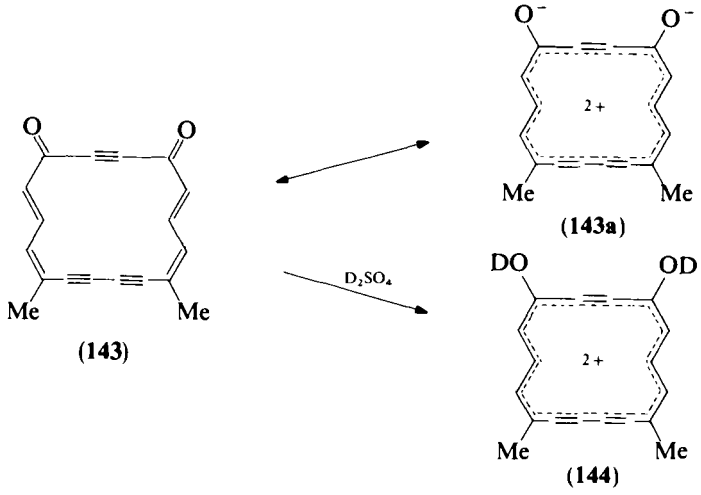


(139) (140) (141) (142)

However, results obtained from the electrochemical reduction of **139**, **141** and **142** to their respective 18π aromatic dianions[77] are in accord with the reduction behaviour of

quinones. It has been found that **139**, **141** and **142** are more easily reduced than is *p*-benzoquinone, possibly because the resulting negatively charged oxygen atoms are further apart than in a six-membered ring, so that electrostatic repulsion is greatly diminished.

The [16]annulenequinone **143** has also been prepared[78]. Surprisingly, the proton NMR spectrum shows that **143** is rather diatropic, probably arising from a significant contribution from its 14π aromatic canonical form **143a**[78].

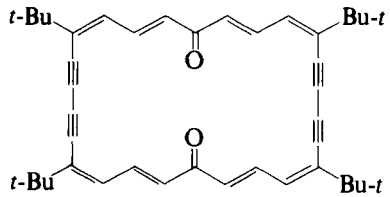


(143) **(143a)** **(144)**

Treatment of **143** with deuteriated sulphuric acid gives **144** which is strongly diatropic[78]. Moreover, electrochemical reduction of **143** to its corresponding dianion has been found to be more difficult than is **141**. This observation can be explained in terms of an antiaromatic 16π dianion[78].

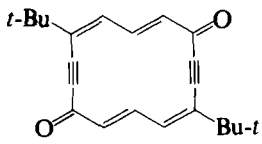
Radical anions of **141**, **142** and **143** have been investigated by ESR spectroscopy[79]. The results demonstrate that $\mathbf{141}^{\cdot-}$ and $\mathbf{142}^{\cdot-}$ are aromatic whereas $\mathbf{143}^{\cdot-}$ is antiaromatic[79].

The [26]annulenequinone **145** has been isolated and used as a precursor towards the synthesis of an [18]annuleno[18]annulene. The quinonoid properties of **145** have not, however, been examined[80].

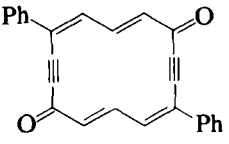


(145)

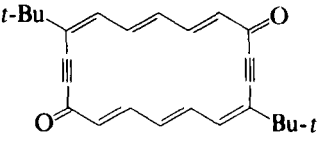
The synthesis of [14]annulenequinones **146**, **147** and [18]annulenequinone **148** together with a modified method for the preparation of **137** have been described[81]. The proton NMR spectra of these annulenequinones, exhibit no sign of any appreciable ring current[81]. The electrochemical reduction of **146** and **148** to their 14π and 18π aromatic dianions respectively is relatively easy and reversible, which indicates that **146** and **148** indeed possess characteristic quinonoid properties[82].



(146)



(147)

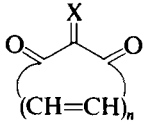


(148)

III. ODD-MEMBERED RINGS

A. General Formula

In agreement with the previous review[1], these compounds may be regarded as being generated from the formula in which *n* can be 0, 1, 2, 3, etc., and X must not produce an

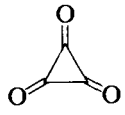


immobile electron system on the carbon attached to the two carbonyls. Hence, X can be oxygen, methylene or an imine moiety, etc.

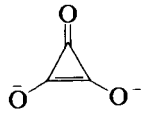
B. Three-membered Ring Systems

1. Cyclopropanetrione derivatives

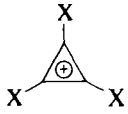
The simplest member of this class is cyclopropanetriquinone (**149**) which remains an unknown compound. However, the deltate dianion (**150**) is well known and its chemistry has been reviewed[12, 13, 16, 83]. The application of the graph theory of aromaticity has shown that **149** has a very small resonance energy[84]. On the other hand, the deltate dianion (**150**) has been predicted to be both highly aromatic and highly diatropic[84].



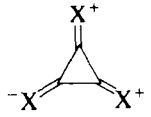
(149)



(150)



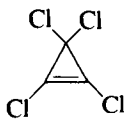
(151)



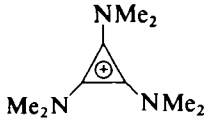
(152)

The heteroatom-substituted cyclopropenyl cation system **151** has received widespread attention[85]. One of its resonance forms may have the quinonoid or hetero-[3]-radialene structure **152**. Treatment of tetrachlorocyclopropene (**153**) with dimethylamine yields trisdimethylaminocyclopropenyl cation (**154**) which has been isolated as the perchlorate

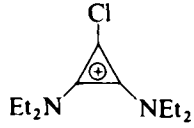
salt[86]. Interestingly, diethylamine affords not the tris, but only the 1,2-bisdiethylaminocyclopropenyl perchlorate (**155**)[86].



(**153**)

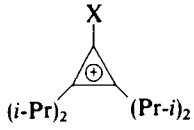


(**154**)

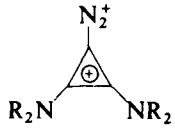


(**155**)

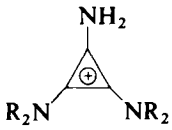
It has been noted that the C–N bond in **155** has partial double bond character. As a result, the rotational barrier about the C–N bond is increased[86]. The chlorine atom in the related diisopropyl derivative **156** is readily substituted by redox hydrolysis with Ph_3P/H_2O to give **157**[87]. The synthesis of cyclopropeniumyldiazonium salts **158** has recently been achieved in excellent yields from diazotization of **159** with $NO^+BF_4^-$, or from the oxidation of **160** with SO_2Cl_2 and ICl[88]. MNDO calculations on the parent



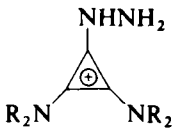
(**156**, X = Cl)
(**157**, X = H)



(**158a**, R = Me)
(**158b**, R = *i*-Pr)
(**158c**, R = H)

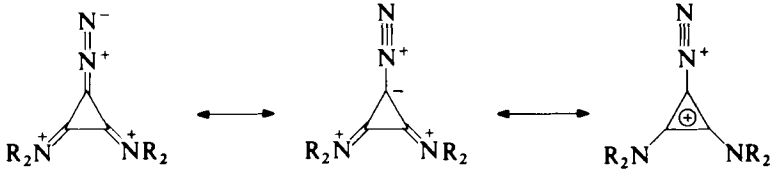


(**159a**, R = Me)
(**159b**, R = *i*-Pr)



(**160a**, R = Me)
(**160b**, R = *i*-Pr)

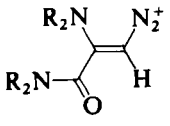
system suggests that **158c** can be conceived of as a resonance hybrid made up from an acceptor-stabilized/cycloaliphatic diazo system **161**, **162** and a donor-stabilized aromatic diazonium system **163**[88]. The cations **158** undergo hydrolysis to give, after ring-opening,



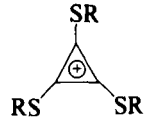
(**161**) (**162**) (**163**)

vinyldiazonium salts **164**[88]. Trialkylthio- and triphenylthiocyclopropenyl cations **165** have also been prepared[89]. However, contribution of the hetero-[3]radialene structure

152 (X = SR) might be neglected based on the NMR data in comparison with those of related compounds[89].

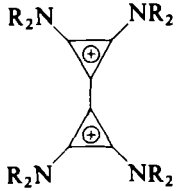


(**164a**, R = Me)
(**164b**, R = *i*-Pr)

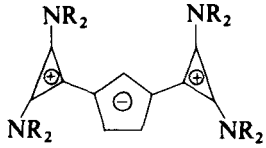


(**165a**, R = alkyl)
(**165b**, R = Ph)

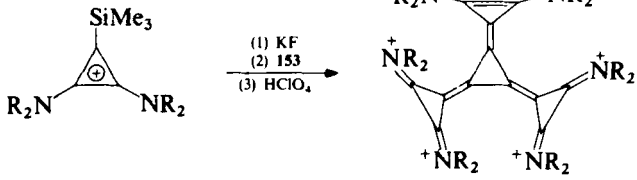
Tetraaminotrifulvalene dications **166**[90,91] and the 1,3-bis(diamino-cyclopropenylio)cyclopenta-dienide system **167**[92] have been prepared. Tris(cyclopropenylio)cyclopropenylium salt (**168**) can be prepared from the reaction of **169** with KF followed by addition of **153** and perchloric acid[93]. Compound **168** is the first isolated tetravalent cation[93]. Radialenoid, fulvenoid and aromatic resonance structures can be formulated for each of the four rings of **168**[93].



(**166**, R = Me or *i*-Pr)



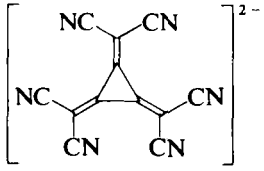
(**167**, R = *i*-Pr)



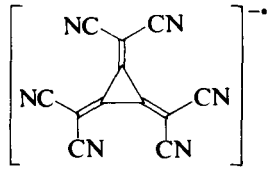
(**169**, R = *i*-Pr)

(**168**, R = *i*-Pr)

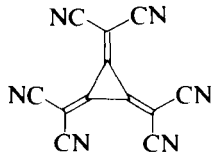
Treatment of tetrachlorocyclopropene (**153**) with malononitrile and sodium hydride affords the dianion **170**[94]. The tetrabutylammonium salt of **170** has been isolated as crystalline solid[94]. Upon oxidation with potassium persulphate, the dianion **170** gives an



(**170**)



(**171**)

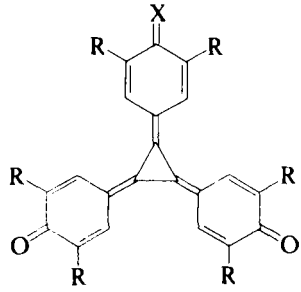


(172)

equilibrium mixture containing **170**, **171** and **172**[94]. The ESR spectrum of **171** exhibits thirteen lines due to the C≡N groups[94].

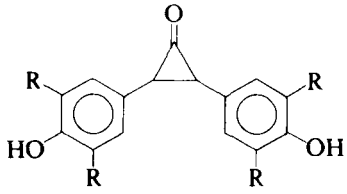
2. Quinocyclopropane derivatives

The chemistry of triquinocyclopropanes **173**[95] has been discussed in the previous review[1]. Syntheses and properties of quinocyclopropanes **174**[96] and quinoiminocyclopropanes **175**[97] have been reported.

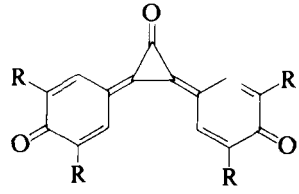


(**173**, X = O)
(**174**, X = O; R = *t*-Bu)
(**175**, X = NH; R = *t*-Bu)

Bis(*p*-hydroxyaryl)cyclopropenones (**176**) can be oxidized to the bright purple bis-quinonoid derivatives **177**[98]. Compounds **177** are highly unstable and readily

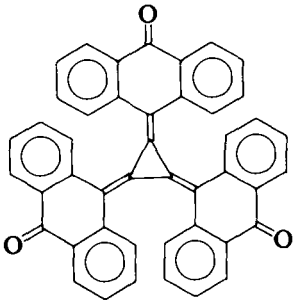


(**176**)

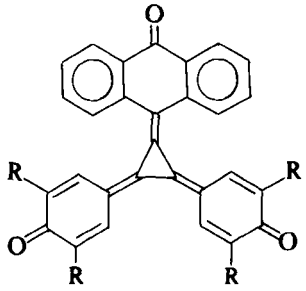


(**177**)

extrude carbon monoxide. However, immediate reduction of **177** with hydroquinone reverts them back to **176**[98]. Upon treatment with sodium–potassium alloy, compounds **177** are converted into the corresponding anion radicals[98]. Tris(9-anthron--10-ylidene)cyclopropane (**178**) has been prepared by oxidation with ferricyanide or PbO_2[99]. The related compounds **179**, **180** and **181** can also be prepared by similar

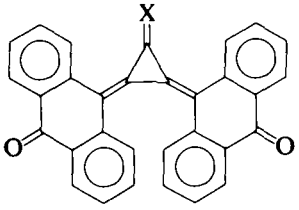


(178)



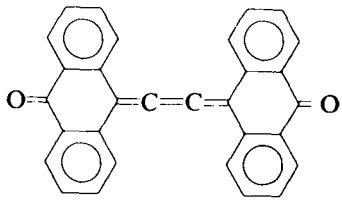
(180)

procedures[99]. It is noteworthy that the electronic absorptions for these intensely coloured materials appear in the near infrared region[99]. Furthermore, the anthraquinone derivatives **178–181**, in general, are more stable than the corresponding benzoquinone analogues **177**. For example, **180** is stable indefinitely in benzene, although it is photolytically decomposed to dianthraquinoethylene (**182**)[99]. The redox properties of anthraquinocyclopropanes **178–181** have been studied in detail[100]. Compounds **183** have been synthesized from **176** by condensation with appropriate substrates followed by oxidation[101]. These compounds are luminously coloured dichroic solids which are potentially useful dyes and photographic agents[102]. Furthermore, they are powerful oxidants[101].

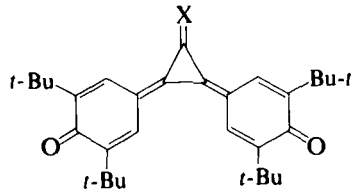


(**181**, X = O)

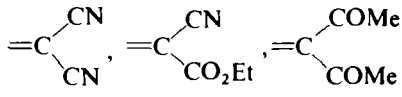
(**179**, X = )

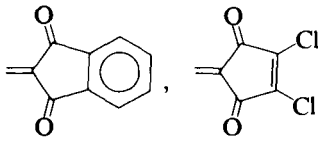


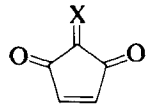
(**182**)



(**183**)

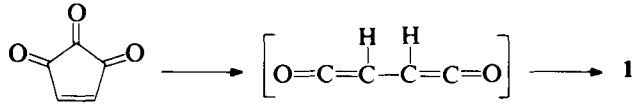
=X= 



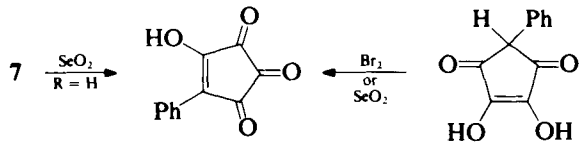


(184)

this family is **184a**[103, 104] whose structure has been determined by X-ray crystallography[105]. Pyrolysis of **184a** affords the decarbonylated intermediate **185** which cyclizes to **1** or can be trapped with methanol to yield dimethyl succinate[104]. Oxidation of **7** (R = H) with selenium dioxide furnishes the cyclopentenetrione **186** which can also be obtained from the reaction of **187** with bromine or selenium dioxide[106]. The He(I) photoelectron spectra of **184a** have been measured[103]. The results show that the lone pair electrons on the oxygen atoms interact strongly with the σ framework[103].

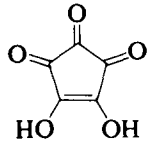


(184a) (185)



(186) (187)

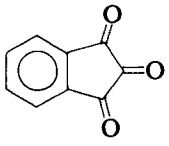
The chemistry of croconic acid (**188**) is well documented[12, 13, 16, 107]. A mass spectral study of **188** has been carried out[108]. The ^{13}C-NMR spectra of **188** are solvent dependent[109]. In DMSO solution, **188** exhibits signal averaging. On the other hand, **188** can be observed as an non-dynamic species in anhydrous THF[109]. Compound **188** readily forms hydrate or hemiketal with water or methanol[109].



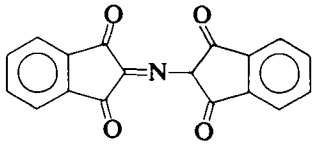
(188)

The chemistry of indane-1,2,3-trione (**189**) has been extensively reviewed[110]. The mass spectral and pyrolytic fragmentation of **189** has been studied in detail[111]. The structure of **189** has been determined by X-ray crystallography[112]. The reaction of its 'monohydrate' (ninhydrin) with α-amino acids gives the well-known purple coloured product **190**[113].

The synthesis of 5,8-dithiafulvalene-1,4-diquinone (**191**) has been described[114]. Alkylidene-1,3-indanedione (**192**) can easily be prepared by the condensation of 1,3-indanedione and the corresponding aldehyde or ketone[115, 116]. A complete kinetic analysis of the four-step hydrolysis of **192** (R = Ph) to benzaldehyde and 1,3-indanedione

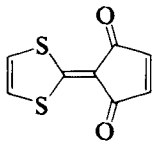


(189)

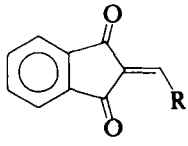


(190)

in aqueous DMSO has recently been recorded[117]. The rate and equilibrium constants of the reversible addition of 1,3-indanedione anion to **192** (R = Ph) in 50% aqueous DMSO at 20 °C have been determined[118].

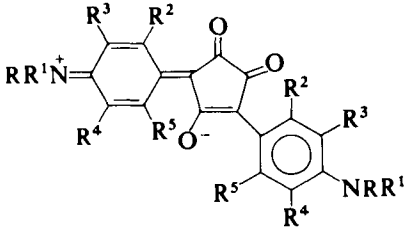


(191)



(192)

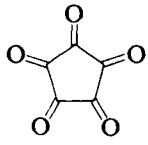
Compound **193** has been shown to be an electrophotographic photoconductive material, sensitive to an (AlGa)As semiconductor laser[119].



(193)

2. *Cyclopentanepentaone*

The parent compound **194** exists as its hydrate, or leuconic acid. It can be synthesized by nitric acid oxidation of croconic acid (**188**)[109, 120]. The mass spectral[108] and ^{13}C-NMR data[109] of **194** have been recorded.



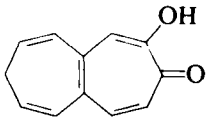
(194)

D. Seven Membered Ring Systems

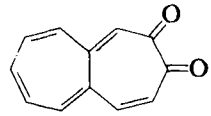
1. *Diketones*

No monocyclic seven-membered diones can be formulated according to the general formula described earlier in this section. When tropolone **195** is treated with 2,3-dichloro-

5,6-dicyano-1,4-benzoquinone (DDQ) in methylene chloride, a bright red coloration appears which may be caused by the formation of heptalene-2,3-dione (**196**)[121]. However, the solution turns quickly to brown and no clear product can be isolated[121].



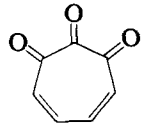
(**195**)



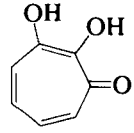
(**196**)

2. *Triketones*

a. o-Tropoquinone and related compounds The title compound **197** was first synthesized in solution in 1975 by the oxidation of the 3-hydroxytropolone (**198**) with DDQ[122]. It was subsequently isolated in crystal form in 1978 and an X-ray analysis was also reported[123]. Compound **197** instantaneously reacts with water or methanol to give

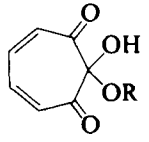


(**197**)

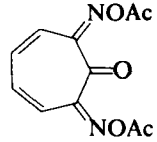


(**198**)

the hydrate **199** or hemiacetal **200**, respectively[122]. The hydrate **199** can be converted to the corresponding oxime **201** as reddish purple crystals which are stable in anhydrous form[122]. The half-wave potential of **197** is more positive than that of *o*-benzoquinone, and its electronic spectrum exhibits maxima, at 334.5 and 574 nm[123]. The latter absorption maximum coincides with that of *o*-benzoquinone[123]. The He(I) photoelectron spectra of **197** and *o*-benzoquinone also reveal such a resemblance[103, 124]. Most of the reactions of **197** are similar to those of *o*-benzoquinone and other cyclic vicinal triketones[125]. In line with expectation, compound **197** can readily be reduced to **198**[125].



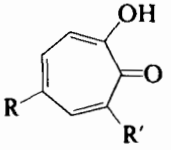
(**199**, R = H)
(**200**, R = Me)



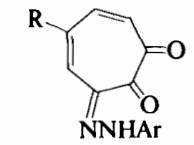
(**201**)

5-Substituted tropolones **202** couple at the 3-position with aryldiazonium ion containing *para*-electron-withdrawing groups. Mixtures of azo compounds **203** and hydrazones **204** are formed[126, 127]. The preparations of benzo-*o*-tropoquinone (**205**)[128] and diazo compound **206**[129] have been described.

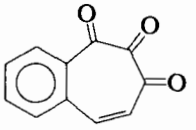
3,5-Dibromo-7,8-diphenylheptatriafulvalene-1,2-quinone (**207**) has been prepared by reaction of 3,5-dibromotropolone (**208**) and 1,2-diphenyl-3-ethoxycyclopropenium ion (**209**) in the presence of Et_3N in MeCN[130]. The product **207** recrystallizes as reddish



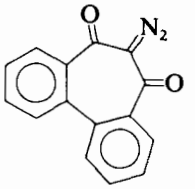
(202, R′ = H)
(203, R′ = N=NAr)



(204)

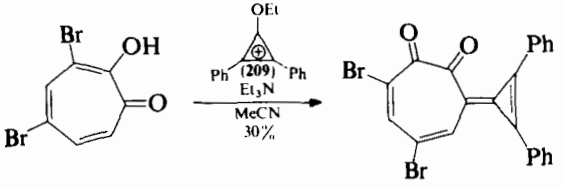


(205)

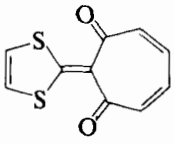


(206)

violet needles[130]. The electronic spectrum of **207** indicates extended conjugation and semiempirical calculations likewise predict a nearly coplanar structure with strong interaction between the three- and seven-membered rings[130]. 7,10-Dithiasesquifulvalene-1,6-quinone (**210**) has also been synthesized[131].

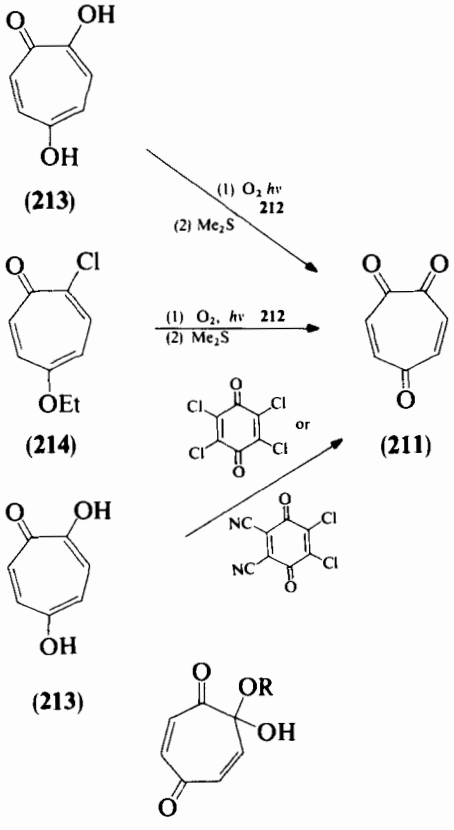


(208) (207)

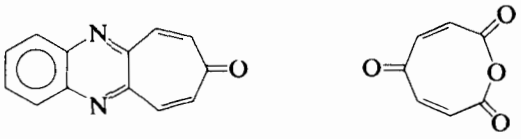


(210)

b. p-*Tropoquinone and related compounds* The parent quinone **211** has been obtained as pale yellow needles from the haematoporphyrin (**212**)-sensitized photooxidation of tropolone or 5-hydroxytropolone (**213**) followed by treatment in each case with dimethyl sulphide[132]. A similar result has been observed for 2-chloro-5-ethoxytropone (**214**). Alternatively, **211** can also be prepared from the oxidation of **213** with chloranil or DDQ[132]. Compound **211** is stable in non-polar solvents, but gradually decomposes in acids and in DMSO. In contrast to **197**, the quinone **211** forms hydrate **215** and hemiacetal **216** reversibly at room temperature[132]. In other words, **216** easily reverts to **211** by evaporation of methanol or on addition of non-polar solvents[132].

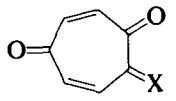


Reaction of **211** with *o*-phenylenediamine gives quinoxalotropone (**217**) quantitatively[132,133]. Oxidation of **217** with *m*-chloroperbenzoic acid or with anhydrous acetaldehyde and aerial oxygen affords the eight-membered acid anhydride **218**[133].

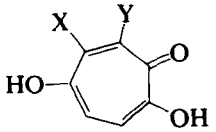


(**217**) (**218**)

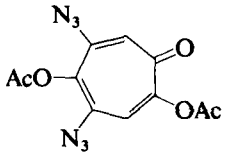
The *p*-tosylhydrazone **219** is converted into the diazoketone **220** which upon photolysis or thermolysis in methanol gives methyl 4-hydroxybenzoate in quantitative yield[133]. In agreement with theoretical prediction, most of the nucleophiles are found to attack at the C(4) position of **211** under standard conditions. As an example, hydrogen chloride reacts with **211** to yield 4-chloro-5-hydroxytropolone (**221**). Sodium benzenesulphinate in acetic



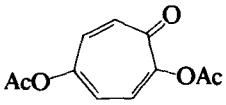
(**219**, =X = =NNHTs)
(**220**, =X = $=N_2$)



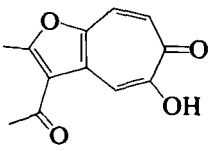
(**221**, X = Cl; Y = H)
(**222**, X = SO_2Ph; Y = H)
(**223**, X = H; Y = SO_2Ph)



(**224**)

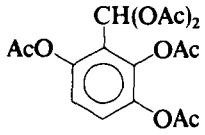


(**225**)

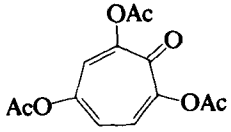


(**226**)

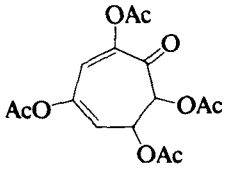
acid solution has been found to add in the same manner to give **222**[133]. Interestingly, when the reaction is carried out in aqueous solution, the isomeric product **223** can also be obtained[133]. Sodium azide in acetic acid also adds to **211**, and after acetylation, the 4,6-diazido compound **224** along with 5-hydroxytropolone diacetate (**225**) are produced[133]. Reaction of acetylacetonate with **211** in the presence of sodium acetate gives the adduct **226**[133]. Thiele type acetylation of **211** in the presence of sulphuric acid yields **227** and



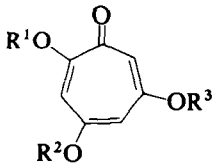
(**227**)



(**228**)



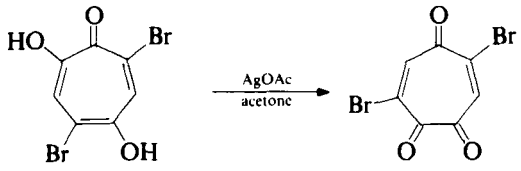
(**229**)



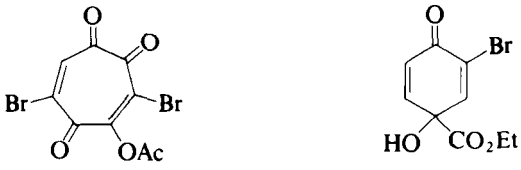
(**230a**, $R^1 = R^2 = OAc$; $R^3 = BF_2$)
(**230b**, $R^1 = BF_2$; $R^2 = R^3 = OAc$)

228[134]. The acetoxy group attacks the C(3) position exclusively and as a result C(3) becomes the aldehydic carbon in **227**[134]. When BF_3 is employed, the regioselectivity of the nucleophilic attack diminishes and a mixture of **229** and **230** is thus obtained[134]. Based on He(I) photoelectron spectral data, the HOMO of *p*-tropoquinone (**211**) resembles that of *p*-benzoquinone[103, 124].

Treatment of dibromo-5-hydroxytropolone (**231**) with silver acetate in acetone affords the corresponding *p*-tropoquinone **232** in good yield[135]. When **231** is oxidized in acetic acid, the Michael-type adduct **233** is formed, while oxidation in ethanol gives rise to the ring contraction product **234**[135]. It is worthwhile to point out that, in the course of the oxidative rearrangment of 5-hydroxytropolone to hydroquinone with cerium(IV) salts in a faintly alkaline solution, **211** has been proposed as an intermediate[136].

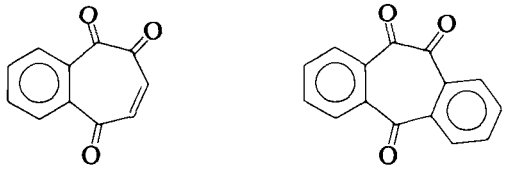


(**231**) (**232**)

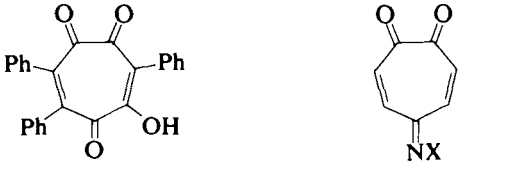


(**233**) (**234**)

Benzo-*p*-tropoquinone (**235**)[137] and dibenzo-*p*-tropoquinone (**236**)[138] have been synthesized. 4-Hydroxy-3,6,7-triphenyl-*p*-tropoquinone (**237**)[139] and some of the 5-



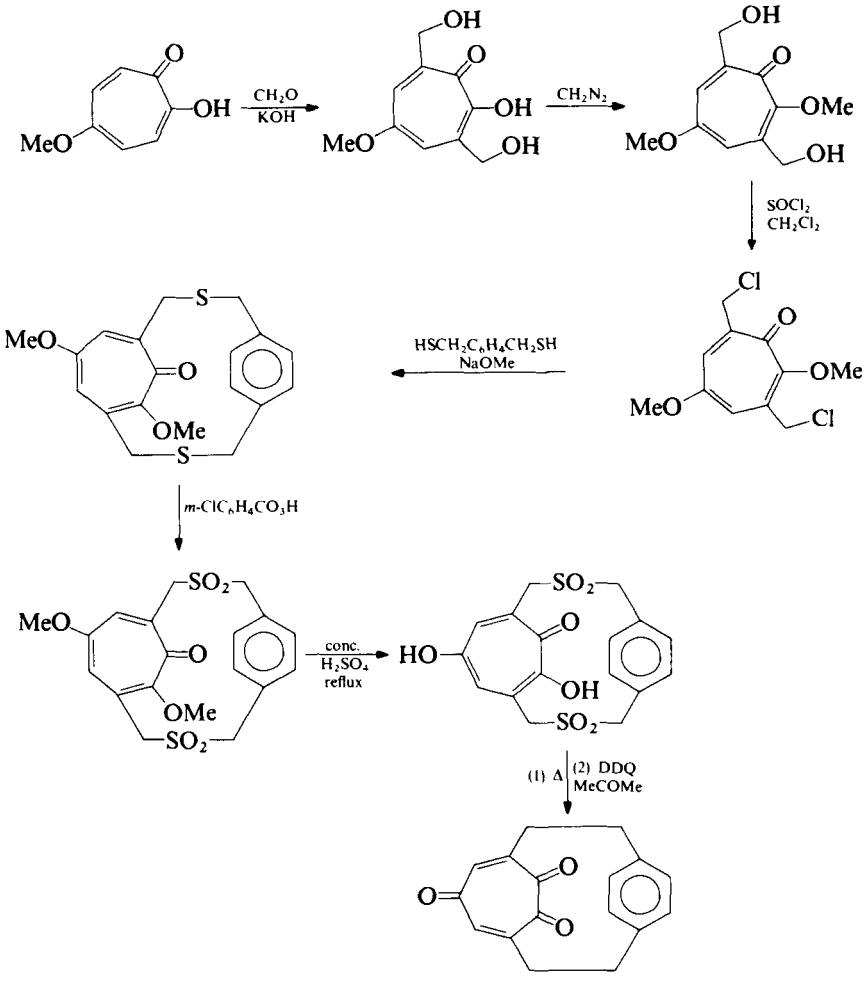
(**235**) (**236**)



(**237**) (**238**, X = OH)
(**239**, X = NHAr)

substituted tropolones such as **238**[140] and **239**[141] are also known to behave as quinonoid derivatives.

More recently, a novel cyclophane which contains a *p*-tropoquinone **240** has been synthesized[142] by the scheme outlined below. Preliminary X-ray crystallographic analysis

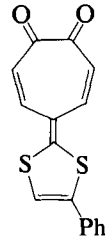


(240)

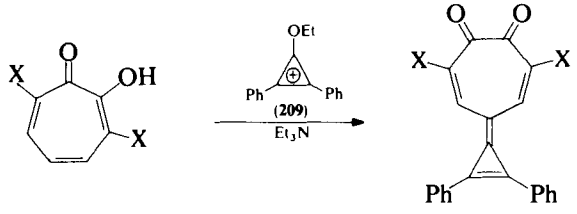
has shown that the four carbons and the two oxygens in the α-diketone moiety form a plane parallel to the mean plane of the benzene ring, and the remaining three carbons and oxygen in the dienone part are away from the mean plane[142]. Electronic spectral data and polarographic measurements further disclose the presence of sizeable intramolecular charge transfer interaction and the deformation of tropoquinone ring in **240**[142].

The 7,10-dithiasesquifulvalene-3,4-quinone **241** has been prepared. A noticeable dipolar character has been observed in this compound[143]. Cyclopropenylation of dibromo- or diiodo-tropolones (**242**) with **209** in the presence of triethylamine affords the

diphenylheptatriafulvalene-3,4-diones **243** as orange needles[144]. These compounds are stable to light at room temperature and to heat up to about 150°C in solid states. However, they slowly decompose in solution[144].

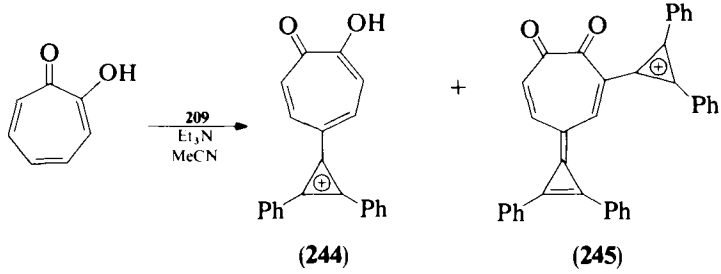


(241)

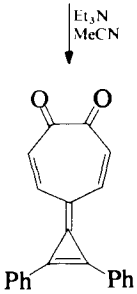


(242, X = Br or I) **(243, X = Br or I)**

In a similar manner, **244** and **245** are obtained when tropolone is treated with an equimolar amount of **209** in acetonitrile in the presence of triethylamine. It is interesting to note that the addition of excess triethylamine to **244** in acetonitrile promotes its immediate



(244) **(245)**



(246)

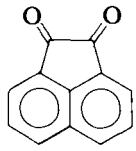
and complete conversion to the corresponding dione **246** as orange needles[145] Compound **244** can be regenerated upon treatment with acid[145].

IV. OTHER DICARBONYL SYSTEMS

A. 1,2-Dicarbonyl Systems

1. 1,2-Acenaphthylenedione

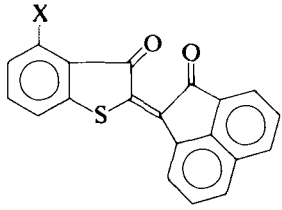
1,2-Acenaphthylenedione (**247**) is a well-known compound and a standard procedure for its preparation has been described[146]. Much of the chemistry investigated on this dione



(**247**)

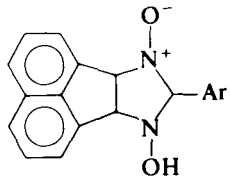
in recent years has centred on its application as a starting material for the synthesis of new heterocyclic and carbocyclic systems, and we believe it is instructive and worthwhile to discuss several of these syntheses.

A majority of the heterocyclic compounds prepared from **247** have been intended as potential dyes or pharmacological agents. In a large number of cases, the reactions



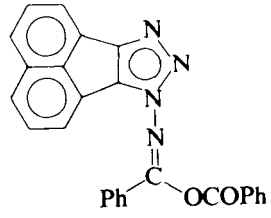
(**248**, X = Br, I)

involved are rather standard. Among the recent examples are the indigoid dyes **248**[147, 148] which can be prepared by condensing **247** with 4-halo-3-hydroxythionaphthenes. The



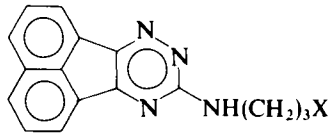
Ar = 2-furyl, phenyl, *p*-chlorophenyl, *p*-*N*,*N*-dimethylaminophenyl.

(**249**)

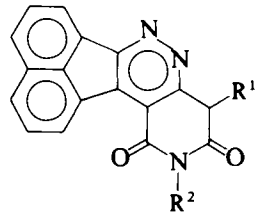


(**250**)

acenaphthylene-fused 1-hydroxy-2-arylimidazole-3-oxides **249** and related compounds[149] have been prepared by reacting **247** with hydroxylamine hydrochloride in the presence of an aromatic aldehyde. Oxidative cyclization of the bisbenzoylhydrazone of **247** has been found to give the acenaphtho[1,2-*d*]triazole **250**[150]. The 9-(3-substituted

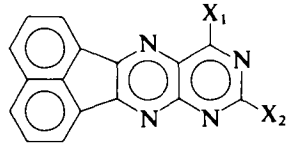


(**251**, X = OH, NMe_2, NEt_2, NBu_2)



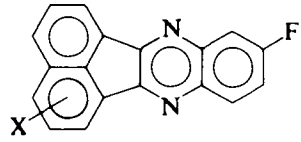
(**252**)

propylamino)-acenaphtho[1,2-*e*]-*as*-triazines **251**[151], of which some are active against vesicular stomatitis virus, can be synthesized by condensation of **247** with thiosemicarbazide followed by treatment of the resulting acenaphtho[1,2-*e*]-*as*-triazine-9(8*H*)-thione with 3-substituted propylamines. The 3,4-acenaphtho-5,7-dioxotetrahydropyrimido[4,5-*c*]pyridazine systems **252**[152] are conveniently constructed by reacting **247** with 6-hydrazinouracils. Along the same line, the synthesis of a series of 2,4-substituted 6,7-acenaphthopteridines **253**[153] is effected by condensing **247** with various 5,6-diaminopyrimidines. The list of the phenazine group of dyes has been expanded to include the



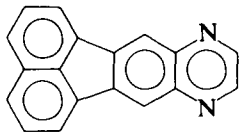
(**253**)

fluoroacenaphthoquinoxalines **254**[154], which are obtainable by treatment of substituted **247** with 4-fluoro-*o*-phenylenediamine. It has also been found that the methyl groups of

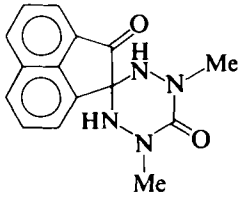


(**254**)

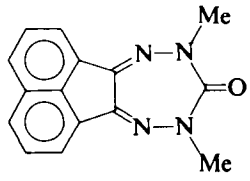
2,3-dimethylquinoxaline-1,4-dioxide are sufficiently activated to undergo facile cyclocondensation with **247** to give acenaphtho[1,2-*b*]phenazine (**255**)[155]. The hexahydro-1,2,4,5-tetrazine derivative **256** is obtained when equimolar quantities of **247** and 2,4-dimethylcarbonohydrazide are heated in boiling methanol. Upon heating in glacial acetic acid, **256** is converted to the cyclic dihydrazone **257**[156].



(**255**)

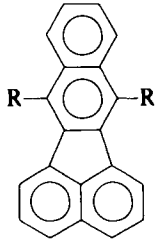


(**256**)

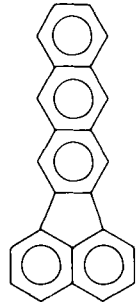


(**257**)

In the past decade, a number of interesting carbocyclic systems have been prepared from (**247**). An improved procedure for the preparation of benzo[*k*]fluoranthene (**259**) has been described in which **247** is first condensed with *o*-phenylenediacetonitrile to 7,12-dicyanobenzo[*k*]fluoranthene (**258**). Heating of **258** in phosphoric acid affords **259**[157] in 60% overall yield. The related naphthofluoranthene **260** has been synthesized by a bis-Wittig reaction of the bis(triphenylphosphonium) salt of 2,3-bis(bromomethyl)naphthalene and **247**[158]. It is noteworthy that the reaction can be carried out in a



(**258**, R = CN)
(**259**, R = H)

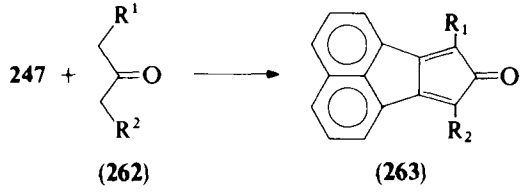


(**260**)

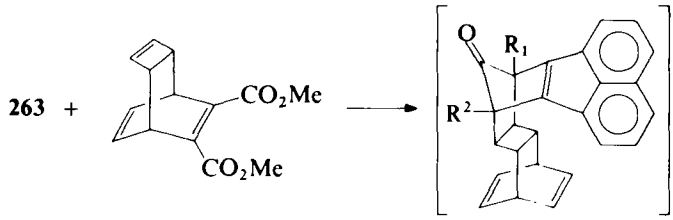
heterogeneous mixture of dichloromethane and an alkaline aqueous solution, in which the phosphonium salt serves dually as a phase-transfer catalyst.

The synthesis of 1,2-acenaphtho-3,8-disubstituted derivatives of cyclooctatetraene **261**[159] from **247** has been accomplished in several steps. Base-catalysed condensation of

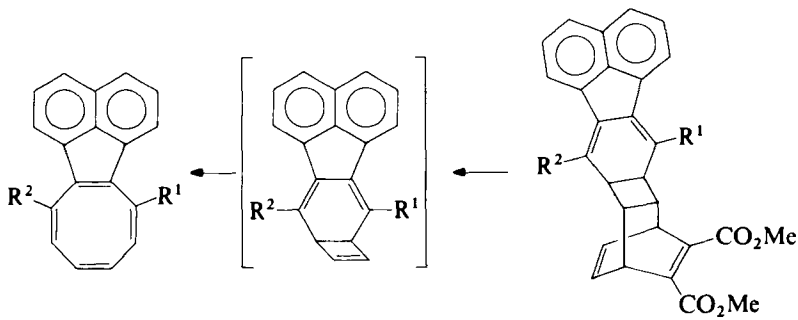
247 with ketones **262** readily gives cyclopentadienones **263** which upon heating with the cyclooctatetraene dimethyl acetylenedicarboxylate adduct **264** affords **266**, presumably via



(262) (263)

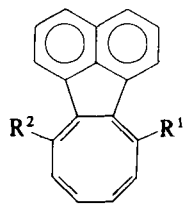


(264) (265)



(261) (267) (266)

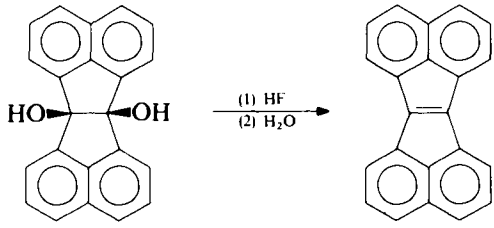
cheletropic loss of carbon monoxide from the initial [4 + 2] adduct **265**. Further heating of **265** in boiling xylenes leads to extrusion of dimethyl phthalate by thermal [4 + 2] cycloreversion to give **261** by way of its valence tautomer **267**. NMR evidence[159] indicates



(268)

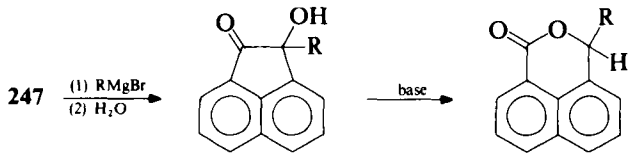
that compounds **261** contain conformationally rigid, bond-fixed, non-planar cyclooctatetraene rings, and rules out the possibility of the bond-shift isomers **268**.

Three reports[160-162] of the synthesis of acenaphth[1,2-*a*]acenaphthylene (**269**) from **247** have appeared in the literature. The best yield[162] can be obtained by treatment with anhydrous HF of diol **270** which is derived from reaction of 1,8-dilithionaphthalene with **247**.



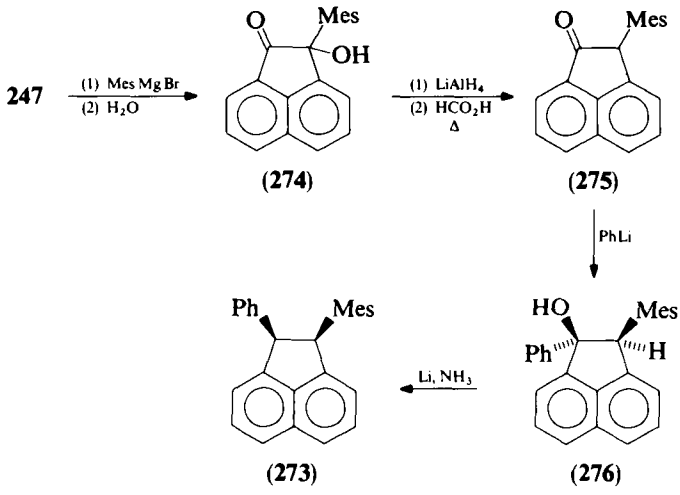
(270) **(269)**

As expected, **247** reacts readily with Grignard reagents to give 2-hydroxyacenaphthenones **271** which undergo a facile base-catalysed carbon-to-oxygen acyl rearrangment[163]



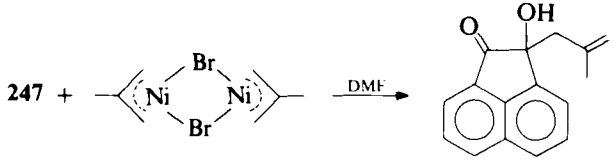
(271) **(272)**

to peri ring-expanded naphthalides **272**. The synthesis of the torsionally rigid *cis*-1-phenyl-2-mesitylacenaphthylene **273** involves a first step of addition of mesitylmagnesium bromide to **247**. Reduction of the hydroxy ketone **274** to the corresponding diol followed by a pinacol rearrangment yields ketone **275**. Addition of phenyllithium to **275** gives



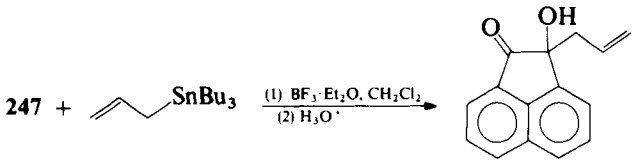
(274) **(275)** **(273)** **(276)**

benzyl alcohol **276** which is converted to **273** via a Li/Na alloy variation of the Birch reduction. Hydrocarbon **273** together with *cis*-1-phenyl-2-(2,4,6-triisopropyl)acenaphthylene has been used for the investigation of internal rotation of the face-to-face aromatic rings[164]. The carbonyl functions in **247** are also susceptible to attack by other organometallic reagents. It has been found that π-2-methylallylnickel bromide selectively attacks one of the carbonyl groups to give the homoallylic alcohol **277**[165], even



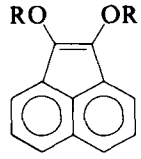
(277)

if an excess of reagent is used. In addition, BF_3-catalysed allylation of **247** with allyltributyltin gives high yield of 2-allyl-2-hydroxyacenaphthenone (**278**)[166].



(278)

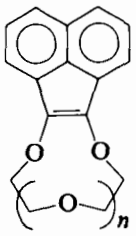
Several enediol derivatives of 1,2-acenaphthylenedione (**247**) have been reported. Electroreductive methylation of **247** gives 1,2-dimethoxyacenaphthylene (**279**) among other products, the formation of which are accountable by the coupling of a radical anion derived from **247** with a methyl radical[167]. As expected, similar cathodic reduction of **247**



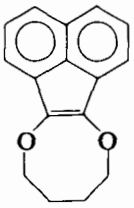
(279, R = Me)
(280, R = COR')

in the presence of acylating reagents yields the corresponding enediol diesters **280**[168]. Extension of the electroreductive alkylation methodology has led to the synthesis of acenaphtho crown ethers **281**[169]. More recently, it has been found that reductive cyclization of **247** can also be effected by treatment with sodium followed by addition of 1,4-dichlorobutane, as demonstrated by the preparation of the 1,4-dioxacine **282**[170]. In a related study, the synthesis of the bisacenaphtho-[18]crown-6, **283**, has been described[171].

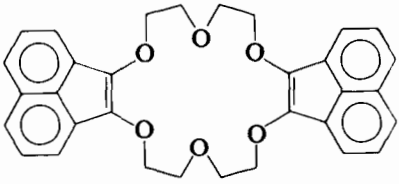
The photochemistry of **247** has been investigated by several groups[172-176]. In the presence of oxygen photolysis of **247** leads to naphthalene-1,8-dioic acid anhydride (**284**) in good yield[172,173]. On the other hand, irradiation of **247** in degassed tetrahydrofuran



(**281**, $n = 1, 2$)

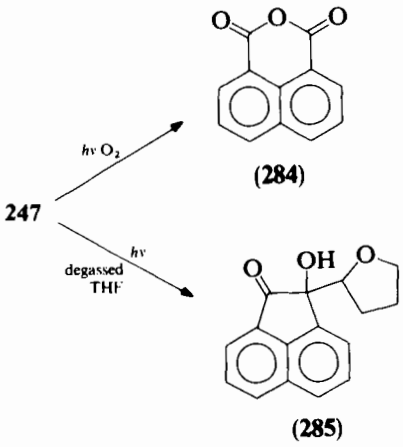


(**282**)



(**283**)

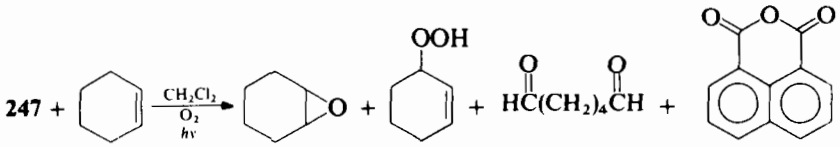
gives mainly the hydroxyacenaphthenone **285**[172]. Interestingly, when an olefin, e.g. cyclohexene is photoxidized with **247** as the sensitizer, the formation of cyclohexene oxide,



(**284**)

(**285**)

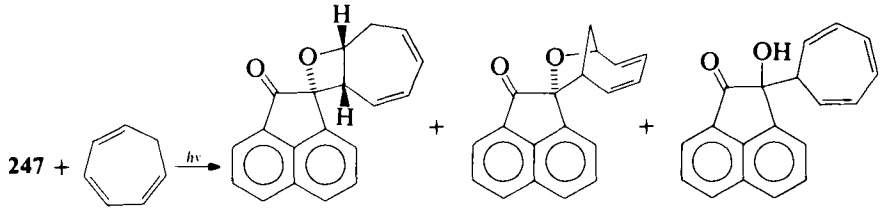
3-hydroperoxycyclohexene and adipaldehyde is accompanied by the oxidation of **247** to **284**[173].



33% 44% trace

(**284**)
65% with
respect to **247**

The photochemical cycloadditions of **247** to several olefinic systems have been reported. With cycloheptatriene[174], both the [2+2] and [2+6] cycloadducts, **286** and **287**, respectively, are obtained together with the ene product **288**. With norbornadiene the sole product is the [2+2] keto oxetane **289**, but with quadricyclane, the photorearrangement product **290** is also formed[175]. In the photochemical addition of **247** to ketene acetals, 1,1-dimethoxypropene gives mainly the [2+2] cycloadducts oxetane and bisoxetane.

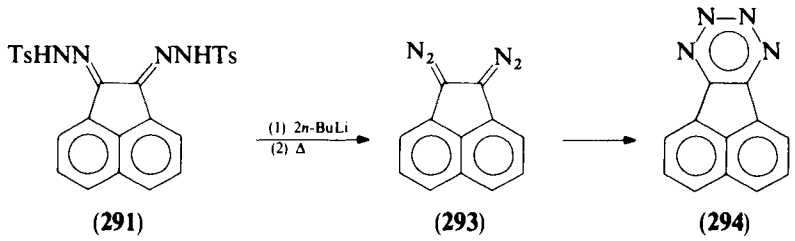


(286) (287) (288)

(289) (290)

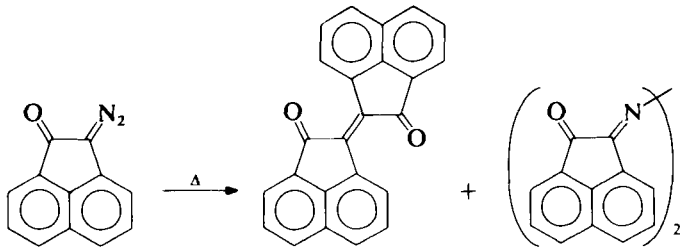
However, in a similar reaction with tetramethoxyethene, the [4+2] product dihydrodioxin is obtained[176].

The chemistry of the diazo compounds derived from **247** has attracted some attention recently. It has been found that the thermolysis of the dilithium salt of 1,2-acenaphthylenedione bistosylhydrazone (**291**) gives 1,8-dicyanonaphthalene (**292**)[177]. The reaction occurs presumably by way of the intermediacy of the bisdiazo derivative **293** which cyclizes to 1,2,3,4-tetrazine **294** and loses a molecule of nitrogen to produce **292**.



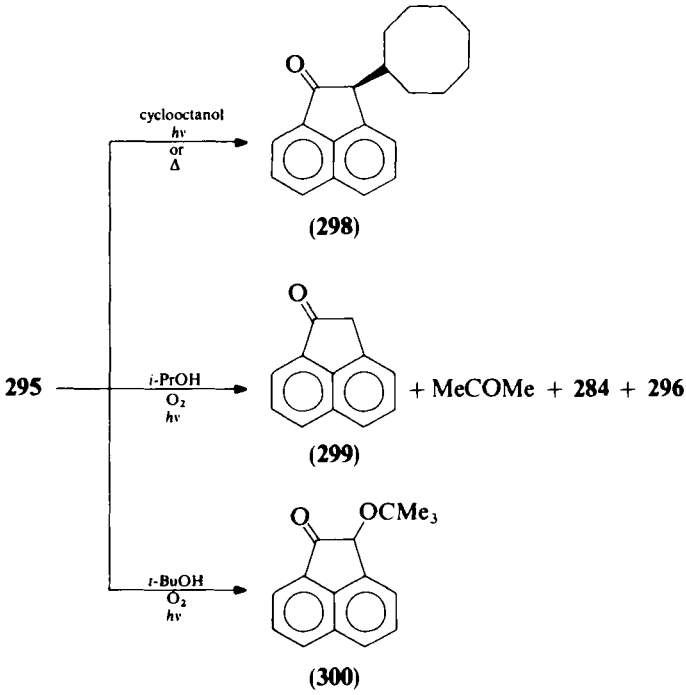
(291) (293) (294) (292)

The thermolysis of 2-diazo-1(2*H*)-acenaphthylenone (**295**)[178] has been reported[179,180] to yield biacenedione (**296**) together with a small amount of the azine **297**. On the other hand, the photosensitized (by *meso*-tetraphenylporphine or methylene blue) oxidation of **295** has been found to give **247** and the anhydride **284**[181].

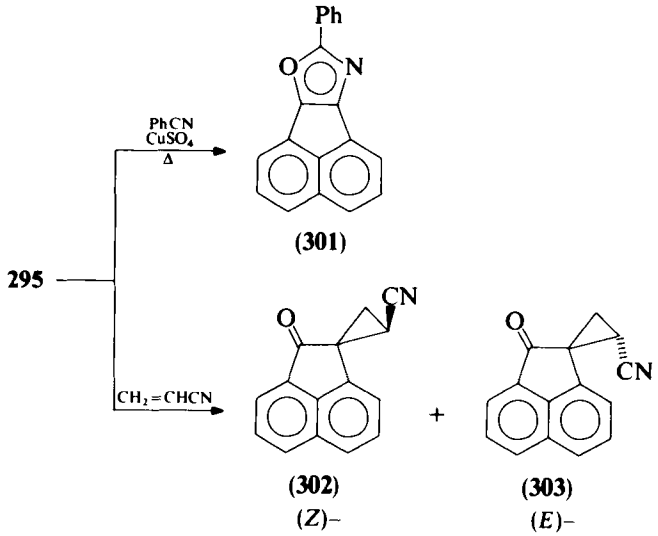


(295) (296) (297)

The thermolysis and photolysis of **295** in various environments have been investigated again recently [182–186] in relation to the mechanism of the Wolff rearrangement. Under standard conditions, neither thermolysis nor photolysis of **295** gives rise to any product attributable to the Wolff rearrangement[184]. Thus, thermal and photochemical decompositions of **295** in cyclooctane result in loss of nitrogen and formation of 2-cyclooctylacenaphthenone (**298**). In 2-propanol solution containing oxygen, photolysis



leads to a mixture of acenaphthenone (**299**), acetone, the anhydride **284** and **296**. Irradiation of **295** in oxygen-saturated *t*-butanol gives rise to the solvent-captured product **300**. Furthermore, thermolysis of **295** in benzonitrile with added cupric sulphate results in the formation of 8-phenylacenaphth[1,2-*d*]oxazole (**301**), and heating **295** in acrylonitrile containing palladium acetate leads to a mixture of the isomeric spirocyclopropanes **302**

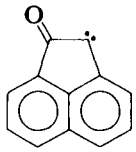


(301)

(302) (*Z*)-

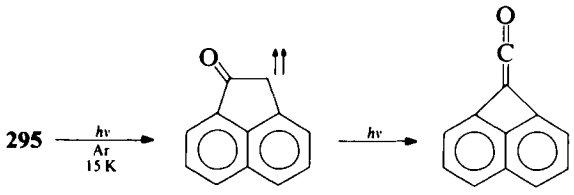
(303) (*E*)-

and **303**. These and other related results can be accounted for by the intermediacy of 2-oxoacenaphthylidene (**304**) either in its singlet or triplet state[184]. Photolysis of **295** in an



(304)

argon matrix at 10–15 K produces the triplet ground state ketocarbene **305** as the primary photoproduct. The identity of ketocarbene **305** has been established by UV–VIS, IR and

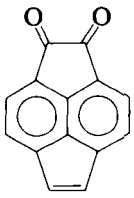


(305) (306)

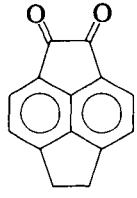
ESR spectroscopy[182, 183, 185, 186]. Subsequent excitation (T_0–T_1) of **305** results in ring contraction to the strained ketene **306**. It has been suggested that the overall non-concerted Wolff rearrangement proceeds via the S‴ state of ketocarbene **304** which is reached from T_1 by internal conversion[186].

2. *Cyclopent[fg]acenaphthylene-1,2-dione (pyracycloquinone) and 5,6-dihydrocyclopent[fg]acenaphthylene-1,2-dione (pyracenequinone)*

The work of Trost in the late 1960s on the preparation[187,188], ESR studies[189–191] and some aspects of the chemistry[188] of cyclopent[*fg*]acenaphthylene-1,2-dione (pyracycloquinone, **307**) and the related 5,6-dihydro derivative (pyracenequinone, **308**) has been presented in the previous review[1].

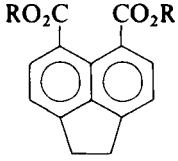


(307)



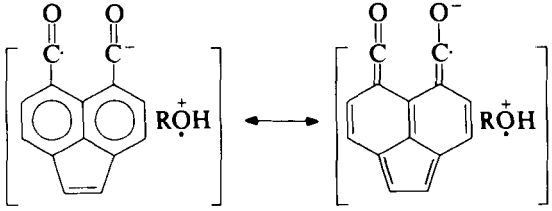
(308)

The photochemical behaviour of **307** was subsequently reported by Castellano and coworkers[192,193]. Irradiation of **307** under argon in protic solvents such as methanol, ethanol and 2-propanol gives the corresponding 5,6-acenaphthenedicarboxylic acid diester **309**, while under identical conditions **308** fails to give a product. A detailed



(309)

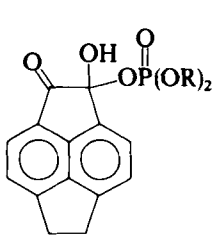
investigation of the luminescence spectra of **307** coupled with kinetic data have led to the conclusion that the photolysis of **307** in protic solvents proceeds through a singlet encounter complex represented as structure **310**[193].



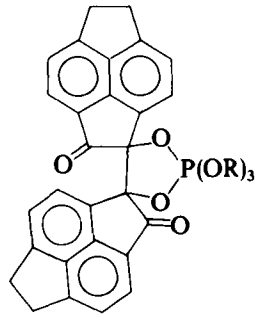
(310)

Reaction of **308** with dialkyl phosphites yields the adducts **311**[194]. With trialkyl phosphites, the products are the cyclic phosphates **312** which can be hydrolysed to **313**[194].

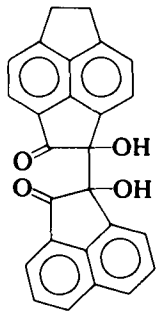
In conjunction with the study of the strain in acenaphth[1,2-*a*]acenaphthylene (**269**), the structurally similar alkene **314** has been synthesized from **308**[162]. Reaction of **308** with 5,6-dilithioacenaphthene (**315**) gives the diol **316** which on treatment with



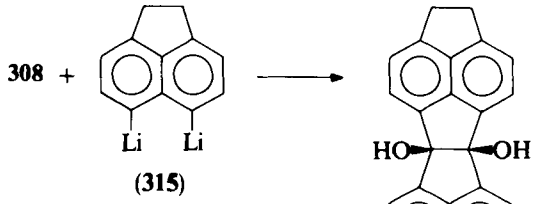
(311)



(312)



(313)



(315)

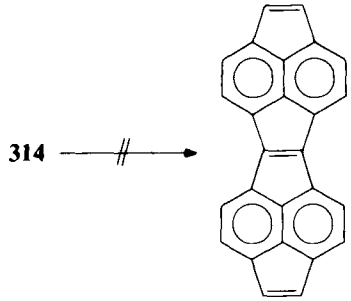
(316)

(1) HF
(2) H_2O

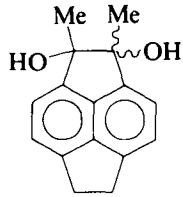
(314)

HF followed by H_2O yields **314**. Alternatively, **314** may also be prepared from **316** by the Corey–Winter procedure[162, 195]. Attempts to convert **314** into the [4n + 4n] fused system **317** were unsuccessful.

The additions of organomagnesium and organolithium reagents to pyracenequinone (**308**) have been examined by Tanaka[196]. The reaction of **308** with methylmagnesium bromide gives a mixture of *cis* and *trans* diols **318**, whereas the reaction of **308** with 5,6-dilithioacenaphthene-*N*,*N*,*N'*,*N'*-tetramethylethylenediamine complex yields the *cis* diol **316**, as previously noted by Mitchell and coworkers[162].

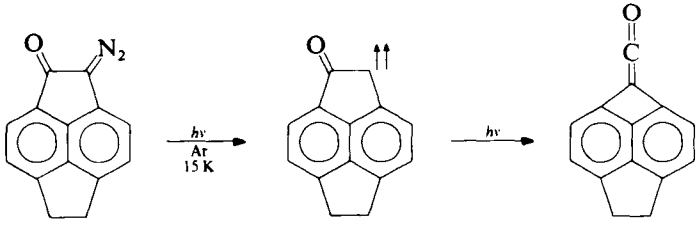


(317)

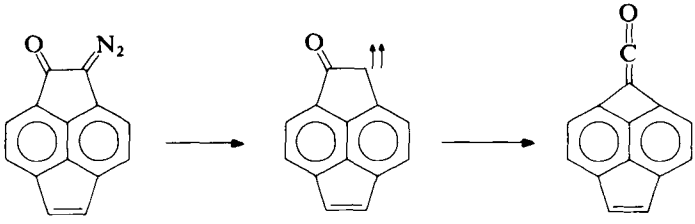


(318)

The photolysis of diazoketones **319** and **320** have also been included in the recent studies by Chapman and coworkers[182, 183, 185, 186] on the mechanism of the Wolff rearrangment. As with the results observed for 2-diazo-1(2*H*)-acenaphthylenone (**295**) described above, photochemical extrusion of nitrogen from **319** in an argon matrix at 15 K produces the triplet ground state (T_0) ketocarbene **321**, which is characterized by ESR and IR spectroscopy. Subsequent excitation (T_0–T_1) of **321** leads to slow ring contraction to **322**.



(319) (321) (322)

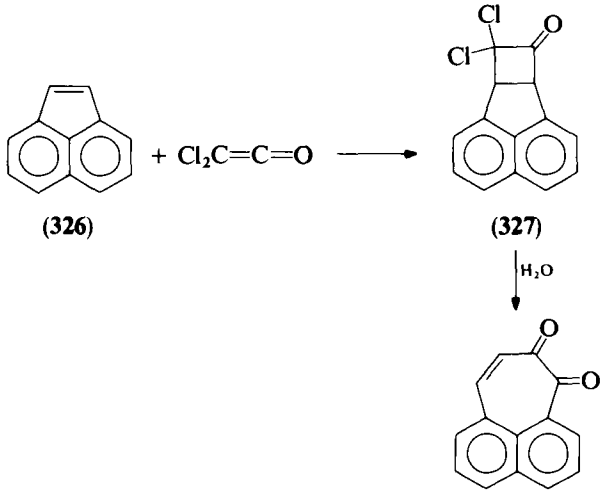


(320) (323) (324)

However, due to experimental complications the transformation sequence **320** → **323** → **324** has not been rigorously established[186].

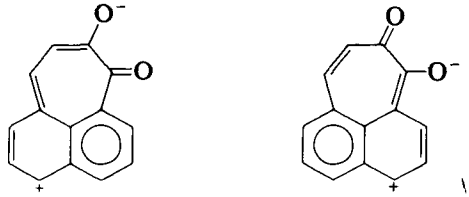
3. *Cyclohepta*[de]*naphthalene-7,8-dione (o-pleiadienequinone) and acepleiadylene-5,6-dione*

o-Pleiadienequinone (**325**), which may be regarded as a higher analogue of 1,2-acenaphthylenedione (**247**), has been synthesized by Tsunetsugu and coworkers[197,198] by cycloaddition of acenaphthylene **326** with dichloroketene followed by hydrolysis of the



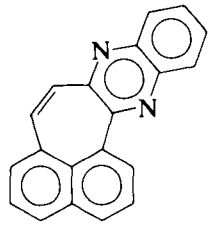
(**326**) (**327**) (**325**)

resulting adduct **327**. NMR data suggest that **325** has some contribution from such canonical forms as 2,3-(**325a**) and/or 4,5-benzotropolonate (**325b**) ions. The half-wave reduction potentials for **325** in aqueous ethanol have been determined[198].

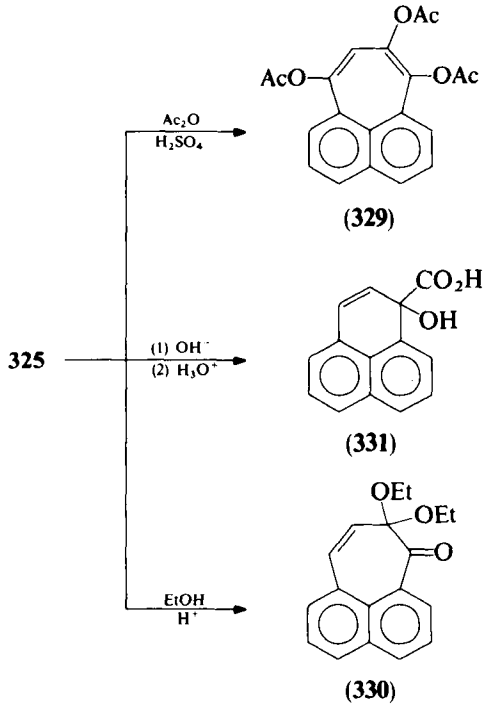


(**325a**) (**325b**)

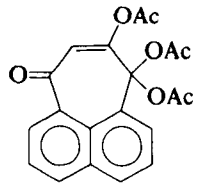
As expected, dione **325** reacts with *o*-phenylenediamine to give the quinoxaline **328**. Reaction of **325** with acetic anhydride in the presence of a catalytic amount of sulphuric acid yields the triacetate **329**. Treatment of **325** with ethanol and acid gives the diethyl acetal **330**, and with 1 M sodium hydroxide, a rearranged product, 1-hydroxyphenalene-1-carboxylic acid (**331**) is formed. Attempts to effect the Diels–Alder reaction of **325** with cyclopentadiene, cycloheptatriene, furan or anthracene have not been successful[198].



(328)



It has been found subsequently[199] that the reaction of **325** with acetic anhydride in the presence of perchloric acid yields keto triacetate **332** instead of **329**. The conversion of **325** into the corresponding epoxide **333** has also been described[199].



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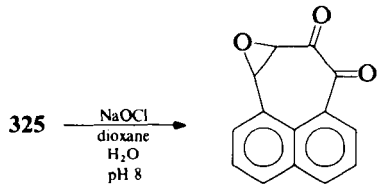
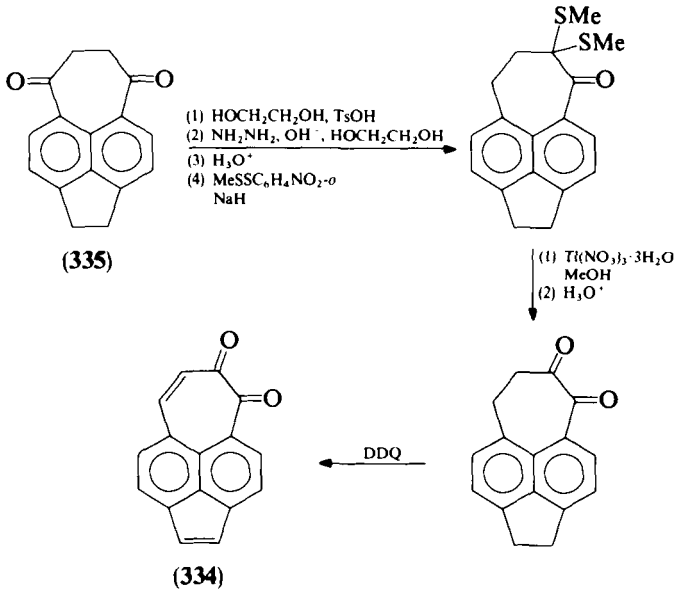


(333)

Acepleiadylene-5,6-dione (**334**), a higher analogue of pyracycloquinone (**307**), has been synthesized by Tsunetsugu and coworkers[200] from the diketone **335** in seven steps. The



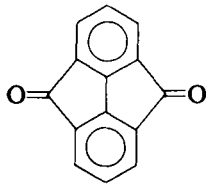
(334)

values of E_1, E_2 and $(E_1 + E_2)$ for **334** are appreciably higher than those of pyracycloquinone (**307**). These data, as well as the low-field carbonyl carbon resonances (190.6 and 192.3 ppm for C(5) and C(6), respectively) in **334** are taken as evidence for the high quinonoid character of this compound[200].

B. Other Dicarbonyl Systems

1. *Cyclopenta*[def]*fluorene-4,8-dione (dibenzo*[cd,gh]*pentaleno-4,8-quinone)*

The synthesis of cyclopenta[*def*]fluorene-4,8-dione (**336**) was first reported by Kinson and Trost[201] in 1971. Since this compound was last reviewed[1], a full paper[202] detailing its preparation as well as its spectroscopic properties has appeared. Both UV and IR data reflect decreased conjugation between the carbonyl groups and the benzene rings, which has been ascribed to the unusually long bonds α to the carbonyl functions. This notion is further supported by the NMR spectrum of the bisprotonated quinone **337**, which indicates poor delocalization of excess positive charge into the benzene rings. The



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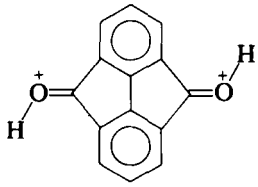

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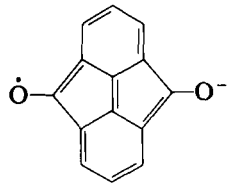
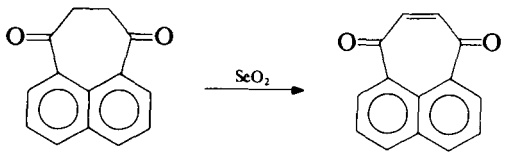


(338)

polarographic characteristics of **336** and the ESR spectral properties of the semiquinone radical anion **338** strongly support the view that electron delocalization in **338**, which possesses a 4n-π periphery, leads to destabilization[202].

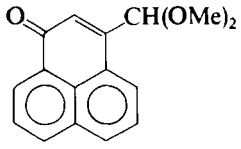
2. *Cyclohepta*[de]*naphthalene-7,10-dione (1,4-pleiadienequinone) and cyclohept*[fg]*acenaphthylene-5,8-dione (acepleiadylene-5,8-dione)*

Cyclohepta[*de*]naphthalene-7,10-dione (**339**) has been prepared by dehydrogenation of dione **340** with selenium dioxide[203]. On treatment with sulphuric acid in methanol, **339**

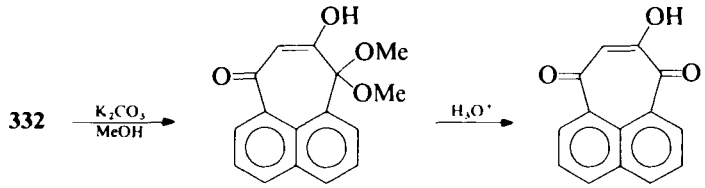


(340) (339)

undergoes ring contraction to give 3-(dimethoxymethyl)phenalenone (**341**). The hydroxy derivative **343**[199] has been prepared subsequently by treatment of **332** above with methanolic potassium carbonate followed by acid hydrolysis of the acetal **342**.

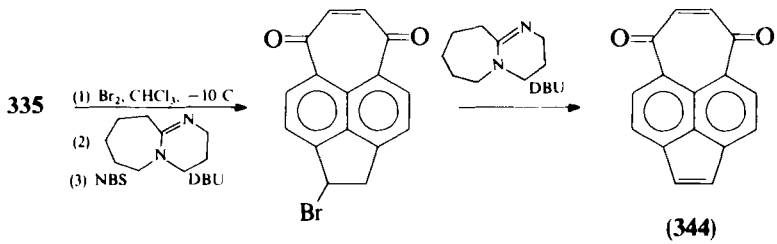


(341)



(342) (343)

Cyclohept[*f g*]acenaphthylene-5,8-dione(acepleiadylene-5,8-dione, **344**) has been synthesized from diketone **335** in four steps[200]. Comparison of the reduction potentials E_1

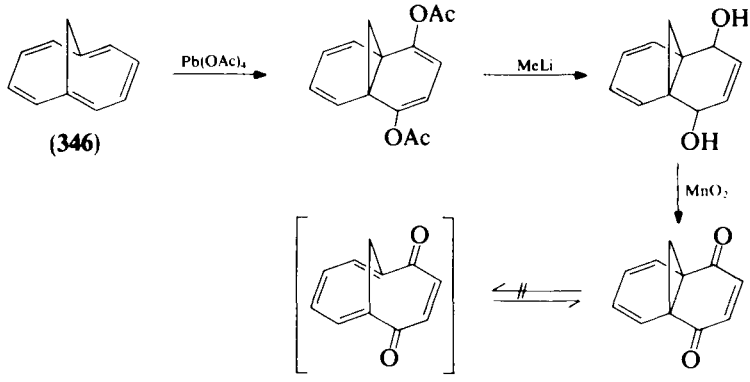


(344)

and E_2 of **344** with those of pyracycloquinone (**307**) lends support to the notion that the former may be regarded as [14]annulenequinone with a vinyl cross-link[200].

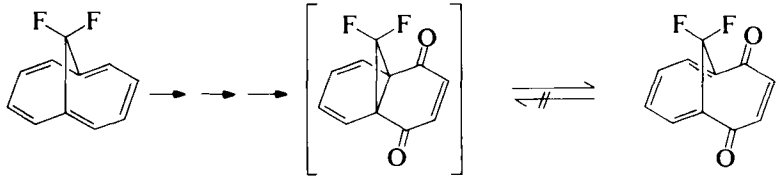
3. *Bridged Annulenediones*

An initial attempt to synthesize bicyclo[4.4.1]undeca-3,6,8,10-tetraene-2,5-dione (**345**) from 1,6-methano[10]annulene (**346**) by the steps outlined below failed to materialize because the anticipated valence tautomerization rests on the side of the norcaradiene-enedione structure **347**[204]. However, an analogous reaction sequence starting from 11,11-fluoro-1,6-methano[10]annulene (**348**) yields the bridged annulenedione **349**[204]. The ESR spectrum[205] of the radical anion of **347** can be interpreted in terms of a structure intermediate to **347** and **345**, but is probably closer to the ketonic structure **347**. On the



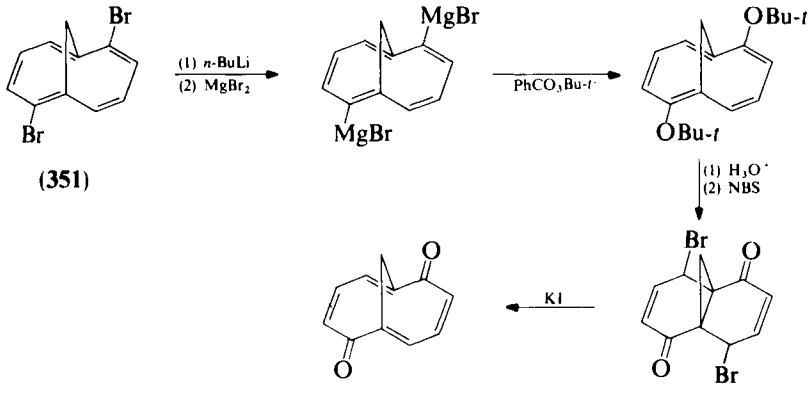
(346) (345) (347)

other hand, the ESR spectrum of the radical anion of **349** reflects some degree of quinonoid character in **349**.



(348) **(349)**

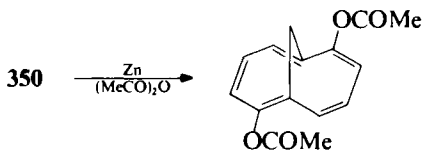
The synthesis of bicyclo[4.4.1]undeca-3,5,8,10-tetraene-2,5-dione (**350**) from 2,7-dibromo-1,6-methano[10]annulene (**351**) has also been reported[206]. Whether dione **350**



(351)

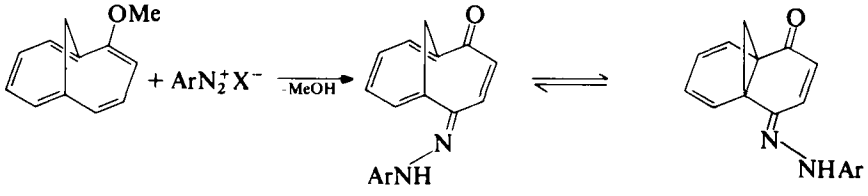
(350)

can be regarded as a quinone has not been settled on the basis of its spectral properties[206]. However, that **350** undergoes reductive acetylation to 2,7-diacetoxy-1,6-methano [10]annulene **352** gives an indication of its quinonoid property.

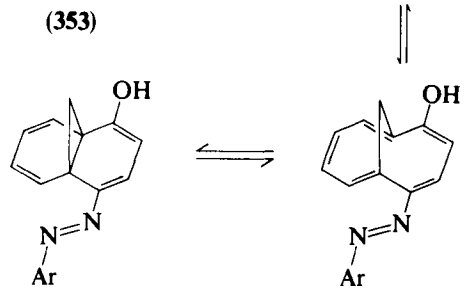


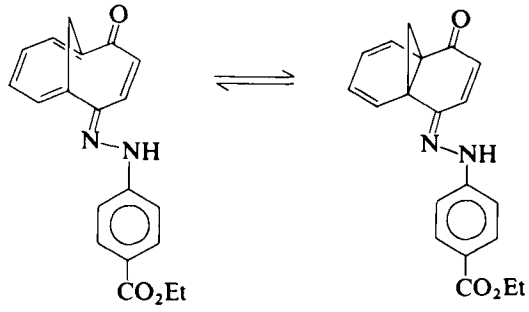
(352)

The monohydrazones of **345**, namely, compounds **353**, have been prepared[207-210] by coupling 2-methoxy-1,6-methano[10]annulene (**354**) with aryldiazonium salts. A combination of cycloheptatriene-norcaradiene valence tautomerization and hydrazone keto–azo enol tautomerization may lead to a total of four isomers in equilibrium. Both ^{13}C-NMR and IR data indicate that these compounds exist predominantly as quinone hydrazones[207]. However, if the aryl group in **353** carries an electron-withdrawing group at the 4-position, a slow isomerization can be observed by NMR spectroscopy[210]. For the

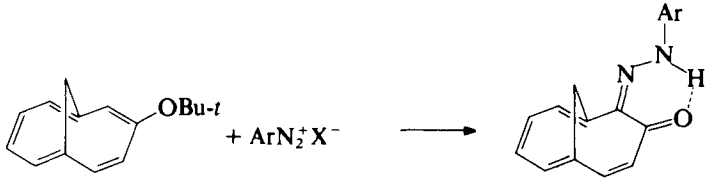


(354) (353)

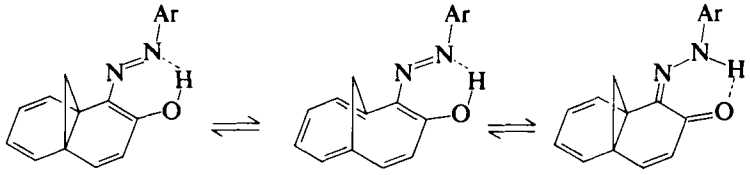




(355) (356)



(358) (357)



(359)

interconversion of **355** and **356**, the activation energy in either direction has been estimated to be $\sim 60\ KJ\ mol^{-1}$.

In a similar manner, hydrazones **357** have been prepared[207] from 3-*t*-butoxy-1,6-methano[10]annulene (**358**), although the parent bridged[10]annulene-2,3-dione, i.e. bicyclo[4.4.1]undeca-4,6,8,10-tetraene-2,3-dione, remains unknown. It has been suggested that a fast equilibrium exists between **357** and **359**.

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