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

THE CHEMISTRY OF FUNCTIONAL GROUPS

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

The chemistry of alkenes (published in 2 volumes)
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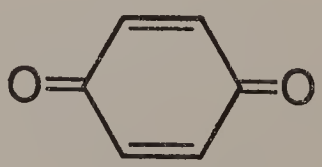

The chemistry of the quinonoid compounds

Part 2

Edited by

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Foreword

The present volume of the series 'The Chemistry of Functional Groups' is, like all other volumes of the series, organized according to the general plan described in the Preface printed in the following pages.

This volume differs somewhat from the others previously published in the series. The main dissimilarity lies in the fact that the quinonoid compounds do not have a functional group in the accepted sense, but rather the whole molecule is the carrier of the quinonoid properties and reactions. Moreover, the chemistry of quinones is inseparable in practice from the chemistry of the corresponding hydroquinones. In addition, some types of compounds belonging to this class are not quite accurately defined (e.g. 'non-benzenoid' quinones).

The original plan also included the following chapters which did not materialize: 'ORD and CD of quinones and related compounds' and 'Quinhydrone and semiquinone systems'.

Jerusalem, July 1973 SAUL PATAI

The Chemistry of Functional Groups
Preface to the series

The series 'The Chemistry of Functional Groups' is planned to cover in each volume all aspects of the chemistry of one of the important functional groups in organic chemistry. The emphasis is laid on the functional group treated and on the effects which it exerts on the chemical and physical properties, primarily in the immediate vicinity of the group in question, and secondarily on the behaviour of the whole molecule. For instance, the volume *The Chemistry of the Ether Linkage* deals with reactions in which the C—O—C group is involved, as well as with the effects of the C—O—C group on the reactions of alkyl or aryl groups connected to the ether oxygen. It is the purpose of the volume to give a complete coverage of all properties and reactions of ethers in as far as these depend on the presence of the ether group, but the primary subject matter is not the whole molecule, but the C—O—C functional group.

A further restriction in the treatment of the various functional groups in these volumes is that material included in easily and generally available secondary or tertiary sources, such as Chemical Reviews, Quarterly Reviews, Organic Reactions, various 'Advances' and 'Progress' series as well as textbooks (i.e. in books which are usually found in the chemical libraries of universities and research institutes) should not, as a rule, be repeated in detail, unless it is necessary for the balanced treatment of the subject. Therefore each of the authors is asked *not* to give an encyclopaedic coverage of his subject, but to concentrate on the most important recent developments and mainly on material that has not been adequately covered by reviews or other secondary sources by the time of writing of the chapter, and to address himself to a reader who is assumed to be at a fairly advanced post-graduate level.

With these restrictions, it is realized that no plan can be devised for a volume that would give a *complete* coverage of the subject with *no* overlap between chapters, while at the same time preserving the readability of the text. The Editor set himself the goal of attaining *reasonable* coverage with *moderate* overlap, with a minimum of cross-references between the chapters of each volume. In this manner, sufficient freedom is given to each author to produce readable quasi-monographic chapters.

The general plan of each volume includes the following main sections:

(a) An introductory chapter dealing with the general and theoretical aspects of the group.

(b) One or more chapters dealing with the formation of the functional group in question, either from groups present in the molecule, or by introducing the new group directly or indirectly.

(c) Chapters describing the characterization and characteristics of the functional groups, i.e. a chapter dealing with qualitative and quantitative methods of determination including chemical and physical methods, ultraviolet, infrared, nuclear magnetic resonance, and mass spectra; a chapter dealing with activating and directive effects exerted by the group and/or a chapter on the basicity, acidity or complex-forming ability of the group (if applicable).

(d) Chapters on the reactions, transformations and rearrangements which the functional group can undergo, either alone or in conjunction with other reagents.

(e) Special topics which do not fit any of the above sections, such as photochemistry, radiation chemistry, biochemical formations and reactions. Depending on the nature of each functional group treated, these special topics may include short monographs on related functional groups on which no separate volume is planned (e.g. a chapter on 'Thioketones' is included in the volume *The Chemistry of the Carbonyl Group*, and a chapter on 'Ketenes' is included in the volume *The Chemistry of Alkenes*). In other cases, certain compounds, though containing only the functional group of the title, may have special features so as to be best treated in a separate chapter, as e.g. 'Polyethers' in *The Chemistry of the Ether Linkage*, or 'Tetraaminoethylenes' in *The Chemistry of the Amino Group*.

This plan entails that the breadth, depth and thought-provoking nature of each chapter will differ with the views and inclinations of the author and the presentation will necessarily be somewhat uneven. Moreover, a serious problem is caused by authors who deliver their manuscript late or not at all. In order to overcome this problem at least to some extent, it was decided to publish certain volumes in several parts, without giving consideration to the originally planned logical order of the chapters. If after the appearance of the originally planned parts of a volume it is found that either owing to non-delivery of chapters, or to new developments in the subject, sufficient material has accumulated for publication of an additional part, this will be done as soon as possible.

The overall plan of the volumes in the series 'The Chemistry of Functional Groups' includes the titles listed below:

The Chemistry of Alkenes (*published in two volumes*)
The Chemistry of the Carbonyl Group (*published in two volumes*)
The Chemistry of the Ether Linkage (*published*)
The Chemistry of the Amino Group (*published*)
The Chemistry of the Nitro and the Nitroso Group (*published in two parts*)
The Chemistry of Carboxylic Acids and Esters (*published*)
The Chemistry of the Carbon–Nitrogen Double Bond (*published*)
The Chemistry of the Cyano Group (*published*)
The Chemistry of Amides (*published*)
The Chemistry of the Hydroxyl Group (*published in two parts*)
The Chemistry of the Azido Group (*published*)
The Chemistry of Acyl Halides (*published*)
The Chemistry of the Carbon–Halogen Bond (*published in two parts*)
The Chemistry of the Quinonoid Compounds (*published in two parts*)
The Chemistry of the Thiol Group (*in preparation*)
The Chemistry of the Carbon–Carbon Triple Bond
The Chemistry of Amidines and Imidates (*in preparation*)
The Chemistry of the Hydrazo, Azo and Azoxy Groups (*in preparation*)
The Chemistry of the SO, $-SO_2$, $-SO_2H$ and $-SO_3H$ Groups
The Chemistry of the $-OCN$, $-NCO$, $-SCN$ and $-NCS$ Groups
The Chemistry of the $-PO_3H_2$ and Related Groups

Advice or criticism regarding the plan and execution of this series will be 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, and who continues to help and advise me. 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.

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Contents

CHAPTER 12

Syntheses and uses of isotopically labelled quinones

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I. THEORETICAL INTRODUCTION

A. Absolute Rate Theory of Isotope Effects

According to equilibrium statistical mechanics[1-47], absolute rate theory of chemical reactions[2,3] and Redlich–Teller product rule[16,17], and in agreement with the Bigeleisen–Mayer reduced partition function ratios[4,18], the theoretical equation which relates through vibrational frequencies the ratio of rate constants of two isotopic molecules, k_1/k_2, with the force constants and geometry of reactants and of the transition complex has the form (1)[19,20]:

$$\frac{k_1}{k_2} = \frac{(\nu^{\ddagger})_{1L}}{(\nu^{\ddagger})_{2L}}\left[\prod_{i=1}^{3N-y}\frac{u_{2i}}{u_{1i}}\frac{\sinh(u_{1i}/2)}{\sinh(u_{2i}/2)}\left(\frac{\sigma_1}{\sigma_2}\right)\Big/\prod_{i=1}^{3N^{\ddagger}-(y+1)}\frac{u_{2i}^{\ddagger}}{u_{1i}^{\ddagger}}\frac{\sinh(u_{1i}^{\ddagger}/2)}{\sinh(u_{2i}^{\ddagger}/2)}\left(\frac{\sigma_1}{\sigma_2}\right)\right] \quad (1)$$

$$= (\mathrm{TIF})(\mathrm{TDF})$$

Here, $\sinh(u_i/2) = \frac{1}{2}[\exp(u_i/2) - \exp(-u_i/2)]$, $u_i = hc\omega_i/kT$, k is Boltzmann's constant, h is Planck's constant, c is the light velocity, ω_i is the fundamental (normal) frequency of the molecule, $\nu_{1L}^{\ddagger}$ is the imaginary frequency corresponding to the coordinate of the reaction, σ_1, σ_2 are symmetry numbers, $\ddagger$ denotes the transition state complex, N is the number of atoms in a polyatomic molecule, y equals 5 for linear molecules and 6 for nonlinear molecules, and the symbols (TIF) and (TDF) denote temperature-independent and temperature-dependent factors. In (1) the ratio of transmission coefficients is omitted and the motion of the reacting system along the reaction coordinate has been treated classically.

Equation (1) is valid for all isotopes and in the case of heavy isotopes with small differences between their masses it approaches the well-known Bigeleisen–Mayer expression (2)[3,4]:

$$\frac{k_1}{k_2} = \frac{(\nu^{\ddagger})_{1L}}{(\nu^{\ddagger})_{2L}}\left[1 + \sum_{i=1}^{3N-6} G(u_i)\,\Delta u_i - \sum_{i=1}^{3N^{\ddagger}-7} G(u_i^{\ddagger})\,\Delta u_i^{\ddagger}\right] \quad (2)$$

where $G(u_i) = \frac{1}{2} - 1/u_i + 1/[\exp(u_i) - 1]$, $\Delta u_i = (u_{1i} - u_{2i})$; the subscript 1 refers to the lighter molecule and $u_i = h\nu_{2i}/kT$ refers to the frequency of the heavier molecule. Function $G(u_i)$ was introduced and tabulated for different values of u by Bigeleisen and Mayer[3,18]. Expression (2) can be

further simplified[5, 21–23] for $u_i < 2\pi$, that is for small ν_i or high temperatures:

$$\frac{k_1}{k_2} = \frac{(\nu^{\neq})_{1L}}{(\nu^{\neq})_{2L}}\left[1+\frac{1}{24}\left\{\sum_{i=1}^{3N-6}(u_{1i}^2-u_{2i}^2)-\sum_{i=1}^{3N^{\neq}-6}(u_{1i}^{\neq 2}-u_{2i}^{\neq 2})\right\}\right]$$

$$= \frac{(\nu^{\neq})_{1L}}{(\nu^{\neq})_{2L}}\left[1+\frac{\hbar^2}{24(kT)^2}\{a_{ii}-a_{ii}^{\neq}\}(m_{1i}^{-1}-m_{2i}^{-1})\right] \tag{3}$$

Expression (3) has summation over $3N-6$ degrees of freedom both in the substrates and in the transition complex, since the Wigner tunnel correction (4) discussed in section A.2 has been included in the transition complex part of formula (3). It has also been presumed that the isotopic

$$Q_1/Q_2 = \left[1+\frac{1}{24}(u_{2iL}^{\neq 2}-u_{1iL}^{\neq 2})\right] \tag{4}$$

molecules are labelled in one position and $a_{ii} = (a^{xx}+a^{yy}+a^{zz})$ is the sum of the Cartesian force constants at the place of isotopic substitution. Approximate expression (3) results directly from more general expansion in powers of u of the logarithm of the reduced partition function f[5, 23].

From equations (1), (2) and (3) it follows that the k_1/k_2 ratio tends to the ratio of the frequencies of decomposition, $(\nu_{1L}^{\neq}/\nu_{2L}^{\neq})$, when $h \to 0$, since expressions $\sinh(u_{1i}/2)/\sinh(u_{2i}/2)$ both in numerator and denominator of (1) reduce to the ratios (ν_{1i}/ν_{2i}) and $(\nu_{1i}^{\neq}/\nu_{2i}^{\neq})$ correspondingly. From expression (3) it follows that the high-temperature kinetic isotope effect should approach the ratio $(\nu_{1L}^{\neq}/\nu_{2L}^{\neq})$ according to the $1/T^2$ law. At lower temperatures equations (1) and (2) require the kinetic isotope effect to diminish with temperature according to the $1/T$ law. Expression (3) shows that the kinetic isotope effects reflect the changes in force constants at the isotopic atom in going from the initial to the transition state of the reaction. Weakening of the force constants around the isotopic atom in the transition state makes the value in square brackets larger than unity and, consequently, the molecule possessing the lighter isotope (subscript 1) reacts faster than the heavier one ('normal isotope effect'). In the opposite situation of strengthening of the force constants around the isotopically substituted atom in the transition state, the numerical value of the expression in the square brackets is lower than unity and may outweigh the pre-exponential factor, thus leading to the 'inverse isotope effect'. The latter situation frequently occurs in the so-called 'secondary isotope effects' for which the theoretical pre-exponential factor $(\nu_{1L}^{\neq}/\nu_{2L}^{\neq})$

is very close to unity. Anomalous temperature dependences of theoretical isotope effects were discussed by Stern and Wolfsberg[7–10, 24].

I. Two- and three-centre reactions

a. Two-centre reactions. In the one-bond approximation[3, 4, 25, 26] the equations (1), (2) and (3) reduce to expression (5).

$$\frac{k_1}{k_2} \approx \left[\frac{\sinh(u_{1i}/2)}{\sinh(u_{2i}/2)}\right] \approx \left(\frac{\nu_{1L}^{\pm}}{\nu_{2L}^{\pm}}\right)[1+G(u_i)\,\Delta u_i]$$

$$\approx \left(\frac{\nu_{1L}^{\pm}}{\nu_{2L}^{\pm}}\right)\left[1+\frac{1}{24}\left(\frac{h}{2\pi kT}\right)^2 (f_{X-m_i})(m_1^{-1}-m_2^{-1})\right] \qquad (5)$$

where f refers to the force constant of the isotopic $X-m_i$ bond. From the one-bond treatment of isotope effects for the isotopes of hydrogen it follows that at relatively low temperatures the major portion of the effect arises from the difference of the zero-point energies of the harmonic X—H and X—D oscillators. Taking the value 2900 cm^{-1} for the stretching frequency of the C—H bond one finds 4·15 and 3·0 kcal/mole for the zero-point energies of the C—H and C—D bonds respectively. The difference $\Delta E_0 = (h\nu_H/2 - h\nu_D/2)$ equals 1·15 kcal/mole which in zero-point approximation leads to a factor of 7 in rate at 300 K[27]. Inclusion of the Boltzmann excitation term (sinh approximation) gives slightly lower values. For instance, taking $\omega_{C-H} = 2985$ cm^{-1} and $\omega_{C-D} = 2191{\cdot}68$ cm^{-1} one finds that at 273·2, 283·2 and 313·2 K the calculated values of k_H/k_D are respectively 8·07, 6·97 and 5·88. For tritium k_H/k_T are 19·65, 12·81 and 2·414 at 273·2, 313·2 and 998·2 K, respectively[20].

In many reactions the experimental deuterium and tritium kinetic isotope effects are in agreement with one-bond model calculations, but experimental kinetic deuterium isotope effects may vary in magnitude from 1 to 16 or even more. Some small hydrogen isotope effects have been explained by the assumption that the carbon–hydrogen bond is not broken in the rate-controlling step of the reaction, as, for example, in the nitration of toluene[60]. Other small experimental deuterium isotope effects have been explained by invoking a triangular transition state in which the A—H bond is not completely broken in the transition state but is bent, the hydrogen atom being at the same time attached to two skeletal carbon atoms in the molecule.

b. Three-centre reactions: $AH+B = A+HB$. Deuterium isotope effects smaller than those calculated according to the one-bond method are explained by considering the equilibrium between the one-bond oscillator

and a linear three-centre transition state in which only stretching vibrations are taken into account[27,28].

$$\begin{matrix} & k_1 & k_2 & \\ \mathrm{A} & \cdots & \mathrm{H} & \cdots \mathrm{B} \\ x_\mathrm{A} & & x_\mathrm{H} & x_\mathrm{B} \end{matrix}$$

(1)

Three-centre transition state model

Following the method of Herschbach, Johnston, Pitzer and Powell (H.J.P.P.)[27-29] one approximates the potential in which particles A, H and B move by the function (6) with the interaction term β, and one eliminates

$$V = \tfrac{1}{2}k_1(x_\mathrm{H}-x_\mathrm{A})^2+\tfrac{1}{2}k_2(x_\mathrm{B}-x_\mathrm{H})^2+\beta(x_\mathrm{H}-x_\mathrm{A})(x_\mathrm{B}-x_\mathrm{H}) \qquad (6)$$

from the general solution of the vibrational secular equation the antisymmetric stretching vibration, corresponding to the reaction coordinate, by putting $(k_1 k_2-\beta^2) = 0$. In the case of a symmetrical transition state, when $k_1 = k_2$, the central hydrogen atom does not participate in the motion in the symmetrical mode of vibration and the isotope effect is as large as in the one-bond approximation. If $k_1 \gg k_2$ or $k_2 \gg k_1$, that is when the transition state is substrate-like or product-like, and if, additionally, $\nu_\mathrm{s}^{\mp}$ is comparable to the frequency of the substrate one-bond oscillator, then the contribution of the temperature-dependent part to the total theoretical isotope effect might be negligible and the 'classical' isotope effect is caused mainly by the temperature-independent factor, which in the H.J.P.P.[29] approach to the problem is close to unity. When the ratio of the imaginary frequencies $(\nu_{1\mathrm{L}}^{\mp}/\nu_{2\mathrm{L}}^{\mp})$ is replaced by the ratio of 'zero frequencies' of the antisymmetric vibration (ν_1^*/ν_2^*) of two isotopic three-centre transition complexes, the value of the pre-exponential (TIF) factor for hydrogen isotopes is close to unity[27,28].

In the more detailed consideration of the reaction of the type[30]

$$\mathrm{AH}+\mathrm{B} \longrightarrow [\mathrm{A}\cdots\mathrm{H}\cdots\mathrm{B}]^{\mp} \longrightarrow \mathrm{A}+\mathrm{HB} \qquad (7)$$

where A and B are not atoms but molecular fragments, one takes into account also the two real bending vibrations in the initial state and two bending modes in the transition state: A···H···B. In the symmetrical 'hydrogen-bonded' transition state the two bending vibrations might be greater than in the initial normal molecule, their contribution to the zero-point energy differences $\Delta E_0^{\mp}$ might be large and $(E_\mathrm{D}-E_\mathrm{H}) = \Delta E_0-\Delta E_0^{\mp\prime}$ will be smaller than the value obtained for the stretching vibration alone. In the practical treatment of the deuterium and tritium isotope effects in

hydrogen transfer reactions one frequently takes into account three real vibrations in the initial state and only two bending vibrations in the transition state. Within the framework of such approximation the values of the pre-exponential factors permitted by equation (1) should be found in the case of deuterium to be between 0·5 and 1·41 and closer to unity than to the possible extreme values $(2)^{\frac{1}{2}}$ or $(\frac{1}{2})$. Calculation of isotope effects according to the simple equation (8) should reproduce the experimental isotope effects in reactions and experimental conditions in which

$$k_1/k_2 = \exp(\Delta E_0/RT) \tag{8}$$

the tunnel effects do not operate. Finally, the (highly unrealistic) upper extreme value of the deuterium isotope effect calculated according to the scheme which takes into account one stretching and two (in-plane and out-of-plane) deformation vibrations in the initial state, and neglects the negative contribution of the transition state, gives values for k_H/k_D equal 12·1 at 40·0°C and 18·5 at 0°C. Inclusion of terms corresponding to vibrations of the transition state of the hydrogen transfer reactions diminishes the theoretical deuterium isotope effect to a value close to the one obtained in the one-bond treatment of the kinetic isotope effects.

2. Tunnelling in isotopic chemical reactions[30–41]

According to quantum mechanics and numerous experimental observations[30–45], there is a certain probability that microscopic particles will penetrate the potential energy barriers when their individual energies, E_i, are less than the height of the barrier, V_0 (E_0) which they encounter on their path. Expressions for probability of crossing the barrier by the particle of mass m and energy E have been derived by solving the stationary Schroedinger equation (9) for different shapes of energy barriers, $V(x)$[30–45].

$$\frac{d^2\psi}{dx^2} + \frac{8\pi^2 m}{h^2}[E - V(x)]\psi = 0 \tag{9}$$

The expression for the likelihood of the particle penetrating through the one-dimensional, rectangular potential barrier of the width l in the simplest case when $2m(V_0 - E)l^2/\hbar^2 \gg 1$ is given by[42–45]

$$G(E) \approx \exp\{-(2/\hbar)\sqrt{[2m(V_0 - E)l^2]}\} \tag{10}$$

The expression for the likelihood of crossing the potential barrier approximated by an inverted parabola, $V(x) = V_0 - V_0 x^2/a^2$ whose base equals $2a$ is given by equation (11)[33, 43] while (12) defines the curvature of

$$G(E) = \{1 + \exp[2\pi(V_0 - E)/h\nu_i]\}^{-1} \tag{11}$$

the barrier at the top. Expression (11) follows also from the relations derived for the more realistic symmetrical Eckhart potential, more closely resembling the potential barrier found in chemical reactions[31, 35, 36]. From

$$\nu_i = E_0^{\frac{1}{2}}/\pi a(2m)^{\frac{1}{2}} \tag{12}$$

relations (10), (11) and the de Broglie relation assigning a wavelength $\lambda = (\hbar/mv)$ to a particle of mass m and velocity v it follows that the largest deviations from classical behaviour should be observed for particles of low masses (electron, proton, deuteron), narrow energy barriers and large $(V_0 - E)$ differences. Protons moving with thermal velocities (at ordinary temperatures) have the wavelength of 10^{-8}–10^{-9} cm which is similar to the width of the barriers found in chemical reactions. Substituting the value 0 for $\hbar$ in expressions (10) and (11) one obtains the classical value 0 for the permeability of the barriers for particles having energy E less than V_0.

a. Relations between the classical and quantum mechanical treatments of the reaction rates. Classically only those molecules $N(E_0)$ from the total assembly, N_{tot}, which have a total energy equal to or greater than its height $E_0(V_0)$ are able to pass the potential barrier. Therefore the classical expression for the reaction rate constant is obtained by multiplying the collision rate by the factor q equal to the fraction,

$$q = N(E_0)/N_{\text{tot}} = \exp(-E_0/kT)$$

of molecules with $E_i \geqslant E_0$ from the total number of molecules. The quantum mechanical expression for q (13) takes into account the finite value of the permeability, G, of the potential barrier for particles with energies $E < E_0$, as well as the partial reflexion of particles having $E > E_0$. Insertion of expressions for G into (13) and further integration leads to theoretical relations for the quantum mechanical reaction velocity

$$q = \frac{1}{kT}\int_0^\infty G \exp(-E/kT)\,\mathrm{d}E \tag{13}$$

constant. Integration of expression (13) in the case of a parabolic potential barrier, assuming that $G = 1$ for $E > E_0$ gives

$$q = \frac{1}{\beta - \alpha}(\beta \exp(-\alpha) - \alpha \exp(-\beta)) \tag{14}$$

where

$$\alpha = E_0/kT \quad \text{and} \quad \beta = 2\pi^2 a\sqrt{(2mE_0)}/h \tag{15}$$

The observed heat of activation E_0^* is given by equation (16) and expression (17) gives the ratio of E_0^* to the classical height of the barrier E_0.

$$E_0^*/R = -\mathrm{d}\log(q)/\mathrm{d}(1/T) \tag{16}$$

$$E_0^*/E_0 = [\beta/(\beta-\alpha)]$$

$$\times [(\beta-\alpha-1)\exp(-\alpha)+\exp(-\beta)]/[\beta\exp(-\alpha)-\alpha\exp(-\beta)] \tag{17}$$

When $\exp(-\alpha) \gg \exp(-\beta)$, equation (17) simplifies to

$$E_0^*/E_0 = 1-[1/(\beta-\alpha)] \tag{18}$$

One can solve the quantum mechanical problem of the reaction rate by deriving the first- and further-order quantum mechanical corrections to the corresponding classical and semiclassical relations[20, 33, 41]. The true rate constant will be the product of the classical rate constant k_{cl} and the quantum mechanical correction Q:

$$k_{\mathrm{qu}} = Qk_{\mathrm{cl}} \tag{19}$$

Then, by definition, the quantum correction to the reaction velocity constant equals

$$Q = \exp(E_0/kT)\int_0^\infty (1/kT[\exp(-E/kT)]\,G(E)\,\mathrm{d}E \tag{20}$$

Insertion of expression (11) into (20) and integration gives

$$Q = \frac{\pi\alpha/\beta}{\sin(\pi\alpha/\beta)} - \frac{\alpha\exp(\alpha-\beta)}{\beta-\alpha}\left\{1-\left[\frac{\beta-\alpha}{2\beta-\alpha}\exp(-\beta)\right]+\ldots\right\} \tag{21}$$

If $\exp(\alpha-\beta) \ll 1$, that is for small $\nu_t(u_t)$ or large (E/kT), the first term of (21) is used as a tunnel correction to the reaction velocity:

$$Q_t = (\pi\alpha/\beta)/\sin(\pi\alpha/\beta) = (u/2)/\sin(u/2) \tag{22}$$

where $u = (2\pi\alpha/\beta) = (h\nu_t/kT)$. The second part of expression (21) can be similarly expressed in terms of u_t:

$$\frac{\alpha}{\beta-\alpha}\exp(\alpha-\beta) = \frac{u_t}{(2\pi-u_t)}\exp\left[\frac{-E_0}{kT}\left(\frac{2\pi-u_t}{u_t}\right)\right] \tag{23}$$

One neglects the term (23) when $u \ll 2\pi$. Expansion of (22) into powers of u gives

$$Q = 1+u^2/24+7u^4/5760+\ldots \quad (u<2\pi) \tag{24}$$

The first two terms of the expansion (24) correspond to Wigner's quantum correction to the classical passage of a particle of mass m over a col in

the energy surface of n dimensions (25)[37]. The difference between the

$$Q = \frac{v_{qu}}{v_{cl}} = 1 - \frac{1}{24}\sum_{n}(hiv_i/kT)^2 \tag{25}$$

experimental (quantal) activation energy E^* and the classical activation energy E_0 can be found by differentiating (19):

$$(E^*_{qu} - E_{cl}) = kT^2\,\mathrm{d}(\ln Q)/\mathrm{d}T = kT[(u_i/2)\cot(u_i/2) - 1] \tag{26}$$

Similarly the departure of the apparent pre-exponential factor A^* from the classical one is found to be

$$\begin{aligned} A^*/A &= (k_{qu}/k_{cl})\exp[(E^* - E)/kT] \\ &= [(u/2)/\sin(u/2)]\exp[(u/2)\cot(u/2) - 1] \end{aligned} \tag{27}$$

From relations (17), (18), (22), (26) and (27) it follows that the experimental activation energy E^* should be less than the height of the barrier E_0 and should decrease with decreasing temperature. Also, the pre-exponential factor A^* should be less than the classical A due to the curvature of the plot $\log k_{exp}$ against $1/T$ [30, 40]. From expressions (10) and (11) it follows that the tunnel corrections are mass-sensitive and, therefore, deuterium and tritium kinetic isotope effects should be a good test of the theoretical quantum mechanical predictions for tunnelling and its consequences. The following general predictions can be made.

Experimental kinetic isotope effects k_H/k_D and k_H/k_T should be at low temperatures greater than theoretical isotope effects calculated with equation (1), which has no correction for tunnelling.

Differences of the activation energies $(E^*_D - E^*_H)$ and $(E^*_T - E^*_H)$ should be larger than the appropriate differences of zero-point energy.

The ratios (A^*_H/A^*_D) and (A^*_H/A^*_T) should be smaller than the limits predicted by the transition state theory in the absence of tunnelling. Abnormal low values for (A^*) are more marked for hydrogen than for deuterium compounds. Values of (A^*_H/A^*_D) smaller than 0·5 should serve as the evidence of tunnelling.

3. Relative tritium and deuterium isotope effects

If we consider that the differences in zero-point energies of isotopic substrates and transition states determine the observed kinetic isotope effect then the numerical relation between deuterium and tritium isotope effects takes the form (28)[46, 47].

$$k_H/k_T = (k_H/k_D)^{1\cdot442} \tag{28}$$

Equation (28) is valid for relatively low temperatures (0–100°C), at which most of the $X—H_i$ oscillators are in their lowest vibrational state. Relation (28) neglects the pre-exponential entropy factor, the correction for tunnelling, the ratio $(\nu^{\ddagger}_{L,H}/\nu^{\ddagger}_{L,D,T})$ of frequencies of crossing over the potential barrier by light- and heavy-activated complexes and the fact that not all normal modes of vibration are shifted by $\sqrt{2}$ and $\sqrt{3}$ upon substitution of proton by deuterium and tritium respectively. Taking into account the neglected terms, the equation relating tritium and deuterium isotope effects can be written in the general form as[41]

$$k_H/k_T = (k_H/k_D)^r \tag{29}$$

where r equals $1{\cdot}442 \pm 0{\cdot}11$. The estimated departures $\pm 0{\cdot}11$ from the Swain value 1·442 also cover the uncertainties introduced by tunnel effects. The power s in equation (30), relating the tunnelling correction for tritium–protium and deuterium–protium has, in Wigner's approximation,

$$Q_H/Q_T = (Q_H/Q_D)^s \tag{30}$$

the value 1·333 for very small u_H and the value 1·58 for very large u_H. Thus departures of r from the value 1·442 are expected when the observed isotope effects k_H/k_D are determined mostly by the dependence of the tunnelling correction Q on the masses of the hydrogen isotopes.

B. *Experimental Methods of Determining Kinetic Isotope Effects*

In the ratio k_1/k_2 of the rate constants of two isotopic molecules with different isotopic composition k_1 usually refers to the molecule having the lighter isotope and k_2 refers to the molecule with the heavier isotope. Theoretically it is possible to determine the isotope effect by carrying out two reactions, one with molecules highly enriched with the isotope under consideration and the second with molecules with known natural isotopic composition. Because of the high cost of production of pure isotopes and the limited accuracy of absolute rate determinations, the direct method is practically limited to deuterium isotope effects. The most common methods used in kinetic isotope effect determinations are the competitive methods which were reviewed by Bigeleisen and Wolfsberg[4, 19, 20a]. Only methods which have been used in studies with quinones will be surveyed here.

1. Chemical competitive method

In this method two isotopic compounds, S_1 and S_2 both compete with a chemically different compound B, all three reacting with compound C.

Equations (31)–(33) are the simplest schemes illustrating this method.

$$S_1 + C \xrightarrow{k_1} X_1 \tag{31}$$

$$S_2 + C \xrightarrow{k_2} X_2 \tag{32}$$

$$B + C \xrightarrow{k_B} Y \tag{33}$$

If the reaction is first-order in each of the reactants, processes (31)–(33) are described by the differential equations (34)–(36), where s_{0i} and b_0 are

$$\mathrm{d}(x_1)/\mathrm{d}t = k_1(s_{01} - x_1)\,[c_0 - (x_1 + y)] \tag{34}$$

$$\mathrm{d}(x_2)/\mathrm{d}t = k_2(s_{02} - x_2)\,[c_0 - (x_2 + y)] \tag{35}$$

$$\mathrm{d}(y)/\mathrm{d}t = k_B(b_0 - y)\,[c_0 - (y + x_1,\, x_2)] \tag{36}$$

the initial concentrations of the species S_i and B, x_i and y are concentrations at time t_i of the product X_i and Y. In the experiment in which species S_1 and B are compared we have therefore

$$\mathrm{d}(x_1)/[k_1(s_{01} - x_1)] = \mathrm{d}(y)/[k_B(b_0 - y)] \tag{37}$$

For reactions (32) and (33) one obtains

$$\mathrm{d}(x_2)/[k_2(s_{02} - x_2)] = \mathrm{d}(y)/[k_B(b_0 - y)] \tag{38}$$

Integration of equations (37) and (38) and further transformations lead

$$\frac{k_1}{k_2} = \frac{\ln(1 - f_{B_{2\,exp}})}{\ln(1 - f_{B_{1\,exp}})} \frac{\ln(1 - f_{S_1})}{\ln(1 - f_{S_2})} \tag{39}$$

to (39), where the sign 1 or 2exp means first and second experiment,

$$f_{S_1} = (x_1/s_{01}), \quad f_{S_2} = (x_2/s_{02}) \quad \text{and} \quad f_{B_{i\,exp}} = (y_i/B_{i\,exp})$$

are the degrees of conversion of the species S_1, S_2 and B in the two competitive experiments and k_1 and k_2 are the rate constants defined by equations (31) and (32). When $f_{S_1, S_2} \ll 1$ and $f_{B_{i\,exp}} \ll 1$ then equation (39) simplifies to

$$k_1/k_2 = (f_{B_{2\,exp}} f_{B_{1\,exp}})(f_{S_1}/f_{S_2}) \tag{40}$$

Equation (40) is applied when S_1, S_2 and B are used in considerable excess.

2. Isotopic competitive methods

The isotopic competitive method is the most general method of kinetic isotope effect determinations. In this method two isotopic molecules, S_1 and S_2, compete with each other in reaction with other types of species B, C etc., or in their own unimolecular decomposition. The observed fractionation R_0/R_t of the isotopic molecules in the course of the reaction

can be related with the ratio of the rate constants k_1/k_2 and with the degree of decomposition or degree of the reaction of the isotopic compounds.

a. Analysis of the product after a known amount of conversion. In certain cases, for instance in decarboxylation processes[19], it is easy to separate the product from the reaction mixture at a known amount of reaction. If reactions (41) and (42) are first-order in the isotopic molecules,

$$S_1+B+C+\ldots \xrightarrow{k_1} X_1+Y+\ldots \tag{41}$$

$$S_2+B+C+\ldots \xrightarrow{k_2} X_2+Y+\ldots \tag{42}$$

S_i, and arbitrary-order in the other reactants, differential equations (43) and (44) will apply:

$$\mathrm{d}(x_1)/\mathrm{d}t = k_1(s_{01}-x_1)\,(B)^b(C)^c \tag{43}$$

$$\mathrm{d}(x_2)/\mathrm{d}t = k_2(s_{02}-x_2)\,(B)^b(C)^c \tag{44}$$

Dividing equation (43) by (44), integrating the differential equation obtained in the limits $0, x_2$ and $0, x_1$ and rearranging, one obtains (45)

$$\frac{k_1}{k_2} = \frac{\log\{1-[(1+R_0)/(1+R_t)]\,f\}}{\log\{1-[(1+R_0)/(1+R_t)]\,(R_t/R_0)\,f\}} \tag{45}$$

where $R_0 = (s_{02}/s_{01})$, $R_t = (x_2/x_1)$ and $f = (x_1+x_2)/(s_{01}+s_{02})$ is the fraction of the reaction. When $x_2 \ll x_1$ and $s_{02} \ll s_{01}$ equation (45) simplifies to (46):

$$k_1/k_2 = \log(1-f)/\log[1-(R_t/R_0)f] \tag{46}$$

When $f \ll 1$, (46) approximates to (47):

$$(k_1/k_2) \approx (R_0/R_t) \tag{47}$$

In this method it is recommended to work at small reaction percentages.

b. Analysis of the substrate after a high amount of conversion. Let us assume that the two isotopic species, S_i, disappear according to the exponential laws (48):

$$S_{t1} = S_{01}\exp(-k_1 t), \quad S_{t2} = S_{02}\exp(-k_2 t) \tag{48}$$

and the fraction-reacted f is given by the relation (49):

$$(1-f) = (s_{t1}+s_{t2})/(s_{01}+s_{02}) \tag{49}$$

Then the relation (50) can be derived:

$$(1-k_2/k_1) = \ln(R_{0s}/R_{ts})/\ln[(1-f)\,(1+R_{0s})/(1+R_{ts})] \tag{50}$$

where $R_{0s} = (s_{02}/s_{01})$ and $R_{ts} = (s_{t2}/s_{t1})$ are the isotopic ratios of the isotopic substrates under consideration at zero time of conversion and

after fraction f of the chemical species S has reacted. Equation (50) transforms into equations (51) or (52) when the isotopic species, S_2, is found in the reacting mixture at the tracer level†:

$$(1-k_2/k_1) = \ln(R_{0s}/R_{ts})/\ln(1-f) \tag{51}$$

$$k_1/k_2 = [\ln(1-f)]/[\ln(1-f)+\ln(R_{ts}/R_{0s})] \tag{52}$$

Equations (51) and (52) are used in studies with radioactive isotopes and with molecules containing ^{13}C, ^{15}N and ^{18}O at the natural abundance level. In the very precise works with ^{13}C and ^{18}O at the natural abundance level, formula (50) is used. In this method the reactions are carried to at least 50–60% of completion.

The equations relating kinetic isotope effects with the isotopic composition of substrates, products, or both as well as those applying for more complicated chemical processes where in the course of the reaction both intramolecular and intermolecular isotopic competition and fractionation occur, are given in references 4, 19, 20a and 60.

3. General remarks

If in the course of the reaction studied there are no isotopic exchanges between products, intermediates and reactants and the isotopic inhomogeneity within the molecule is easily determined, then the isotopic competitive methods are the most sensitive, since the two isotopic reactions are carried out in exactly the same physical conditions. Moreover, the precision of the mass spectrometric determinations of the isotopic composition of the samples is very high (in the case of $^{18}O/^{16}O$ and $^{13}C/^{12}C$ ratios sometimes better than 0·01‰[48–50]). In the case of samples containing ^{14}C, the composition can sometimes be determined with an accuracy approaching 0·2% but usually an error of 0·5% is considered acceptable[51]. In determinations of the relative specific activity of samples containing tritium the precision attained is sometimes 1–2% but measurements carried out with an accuracy better than 5% are still classified as good[52–55]. The problems of isotopic inhomogeneity[4,19], are important when working with compounds having natural isotopic abundances but do not exist with artificially labelled substances.

C. *Tracer Studies with Isotopes*

A rich literature[56–63b] covers the theory of tracer applications of isotopes and isotopically labelled compounds. A short formal description of the isotopic exchange reactions is given below.

† In this case: $s_{02} \ll s_{01}$; $s_{t2} \ll s_{t1}$; $(1+R_{0s}) \approx 1$; $(1+R_{ts}) \approx 1$ and the denominator of equation (50) approximates $\ln(1-f)$.

I. Kinetics of isotope exchange reactions

Consider the simple example of the exchange of isotopes X and X^* taking place between molecules AX and BX,

$$AX+BX^* = BX+AX^* \tag{53}$$

If there are no isotope effects and the transfer of isotope X^* from BX^* to AX and from AX^* to BX proceeds at the same rate, then at a tracer concentration of X^* in the system, the rate with which the concentration of X^* in chemical species AX changes is given by equation (54), where R

$$\mathrm{d}(ax)/\mathrm{d}t = Ry - Rx \tag{54}$$

is the rate, expressed in g atom/s, with which X exchanges at equilibrium between compounds AX and BX, $a = (AX)$ is the total concentration of AX molecules, $b = (BX)$ is the total concentration of BX molecules, $x = (AX^*)/[(AX)+(AX^*)]$ and $y = (BX^*)/[(BX)+(BX^*)]$ are fractions of the isotopically labelled species AX and BX. Integration of (54) leads to equation (55), where $F = (x/x_\infty) = x(a+b)/r$ is the degree of exchange, t is the time of exchange and $r = ax+by$.

$$-\ln(1-F) = [R(a+b)/ab]\,t = \rho t \tag{55}$$

Formula (55) has been derived without any particular assumption about the explicit functional dependence of R on concentrations of exchanging species and is of general validity. In the case of tritium and deuterium isotope exchanges, when the force constants in the chemical species AX and BX differ very much, $(x_\infty/y_\infty) = \alpha \neq 1$, and, at equilibrium, the relation

$$x_\infty = \left(\frac{ax+bx}{a+b}\right)$$

has to be replaced by

$$x_\infty = \frac{\alpha(ax+bx)}{\alpha a+b}$$

and the equation describing the exchange will be (56). Derivations of equations describing the kinetics of isotopic exchanges involving large kinetic and thermodynamic isotope effects are given in the monograph by Melander[60].

$$\ln[1-x/x_\infty] = -[R(\alpha a+b)/ab]\,t \tag{56}$$

II. SYNTHESES OF LABELLED QUINONES

A. Syntheses of ^{13}C-Labelled Quinones

Synthesis of ^{13}C-labelled quinones has been undertaken in connexion with interpretation of the low intensity lines present in the electron spin

resonance spectra of semiquinones, the ring-carbon atoms of which contain ^{13}C on the natural abundance level[64–71], and also for the elucidation of the nature of the electronuclear ^{13}C hyperfine interactions in the semiquinone ions[64, 65].

I. Synthesis of ^{13}C-labelled *p*-benzoquinones

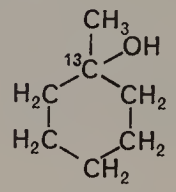
a. Synthesis of p-*benzoquinone*-1-^{13}C. Das and Venkataraman[66–68, 70] obtained (in 10 steps) labelled 1-^{13}C-benzoquinone with about 50 at% isotope abundance of ^{13}C in the 1-position in an overall yield of 2%, starting from $Ba^{13}CO_3$, enriched in ^{13}C to about 48%.

Ethyl acetate-1-^{13}C (**2**) was first prepared in four steps by adapting well-established preparative methods of ^{14}C-labelled compounds[19, 72, 73, 84, 85].

$$Ba^{13}CO_3 \xrightarrow{H_2SO_4} {}^{13}CO_2 \xrightarrow[\text{anhydrous ether}]{CH_3MgI} CH_3{}^{13}COOH$$
$$\xrightarrow{NaOH} CH_3{}^{13}COONa \longrightarrow CH_3{}^{13}COOC_2H_5 \qquad (57)$$
$$(2)$$

The labelled sodium acetate was converted to ethyl acetate by refluxing with triethyl phosphate[74] at 170–220°C (yield: 90·7%). 1-Methylcyclohexanol-1-^{13}C (**3**) was prepared in 53% yield from the Grignard reagent of pentamethylene dibromide with ethyl acetate-1-^{13}C[75].

$$CH_3{}^{13}COOC_2H_5 \xrightarrow[\text{anhydrous ether}]{BrMg(CH_2)_5MgBr} \qquad (58)$$

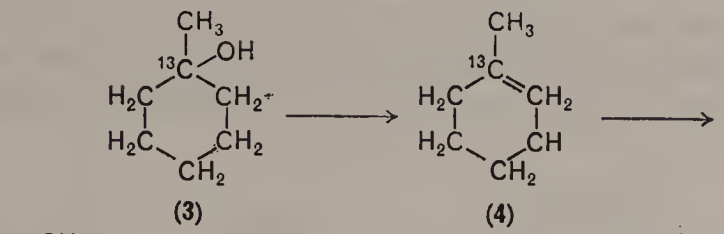


(3)

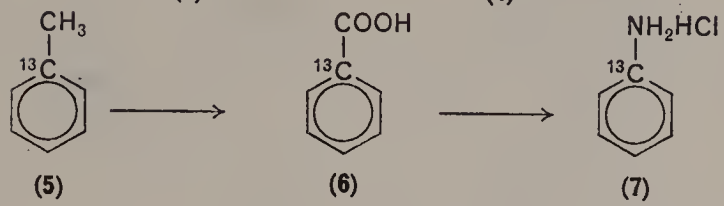
The iodine-catalysed dehydration of **3** to 1-methylcyclohexene-1-^{13}C (**4**) was carried out at 135–140°C using a Podbielniak column[75] with glass coils (yield: 40·1%). The dehydrogenation of **4** to toluene-1-^{13}C (**5**) was performed at 450°C using 30% platinum-on-asbestos (or palladium) catalyst in 67·7% yield. Toluene **5** was oxidized with an aqueous solution of potassium permanganate and sodium hydroxide to benzoic-1-^{13}C acid (**6**). This was converted to aniline-1-^{13}C hydrochloride (**7**) by Schmidt reaction using an excess of sodium azide (yield: 85·4%).

p-Benzoquinone-1-^{13}C (**8**) was obtained by oxidation of **7** with MnO_2 in dilute sulphuric acid (yield: 51·6%). The presence of one ^{13}C atom in the ring with an enrichment of about 50% was confirmed by observing the hyperfine structure[67] in the e.s.r. spectrum of the semiquinone ion prepared from the labelled *p*-benzohydroquinone-1-^{13}C (**9**).

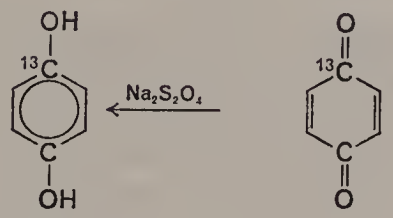
p-Benzoquinone-1-^{13}C was also synthesized in four steps with an overall yield of 16% by condensing acetone-2-^{13}C (**10**) with sodium



(3) (4)



(5) (6) (7)



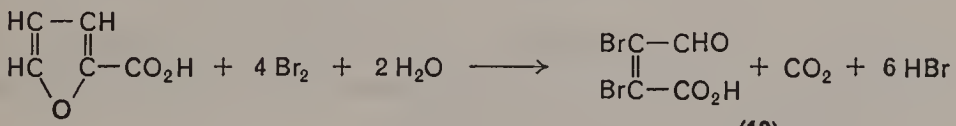
(9) (8)

(59)

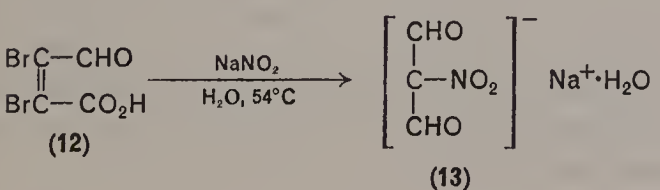
$$CH_3{}^{13}CO_2Ba \xrightarrow[490\text{–}510^\circ C]{\text{pyrolysis}} CH_3{}^{13}C(=O)CH_3 \qquad (60)$$

(10)

nitromalonaldehyde **13**[71,76–78]. Nitromalonaldehyde **13** was obtained from the aldehydo-acid **12** which in turn was prepared from furoic acid **11**. *p*-Nitrophenol-1-^{13}C (**15**) was prepared in 36·8% yield by condensing **10** with sodium nitromalonaldehyde monohydrate **13**. **14** was obtained from



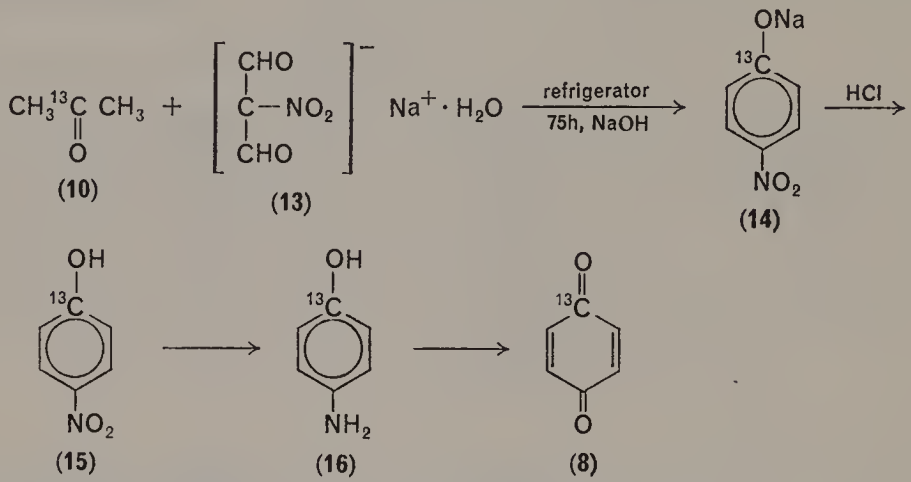
(11) (12)



(12) (13)

(61)

the reaction mixture by addition of NaOH pellets. *p*-Aminophenol **16** was prepared from **15** by reduction with Sn and HCl (yield: 96·4%). *p*-Benzoquinone-1-^{13}C was prepared from **16** by oxidation with sodium

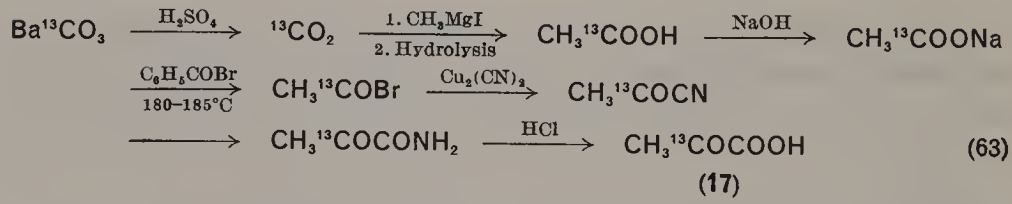


(62)

dichromate. The yield of the oxidation step was 47·4%, and the overall yield based on sodium acetate-1-^{13}C was 16%. The intensity measurements of the e.s.r. spectra of the semiquinone showed that the isotopic abundance of ^{13}C in the 1-position of the final product was 54 ± 3 at% in agreement with the 56·3 at% in the starting material sodium acetate-1-^{13}C.

b. Synthesis of p-*benzoquinone*-1,3,5-^{13}*C*. Synthesis of *p*-benzoquinone labelled with ^{13}C in positions 1, 3 and 5 was performed by condensation of pyruvic-2-^{13}C acid (**17**)[68,79–83].

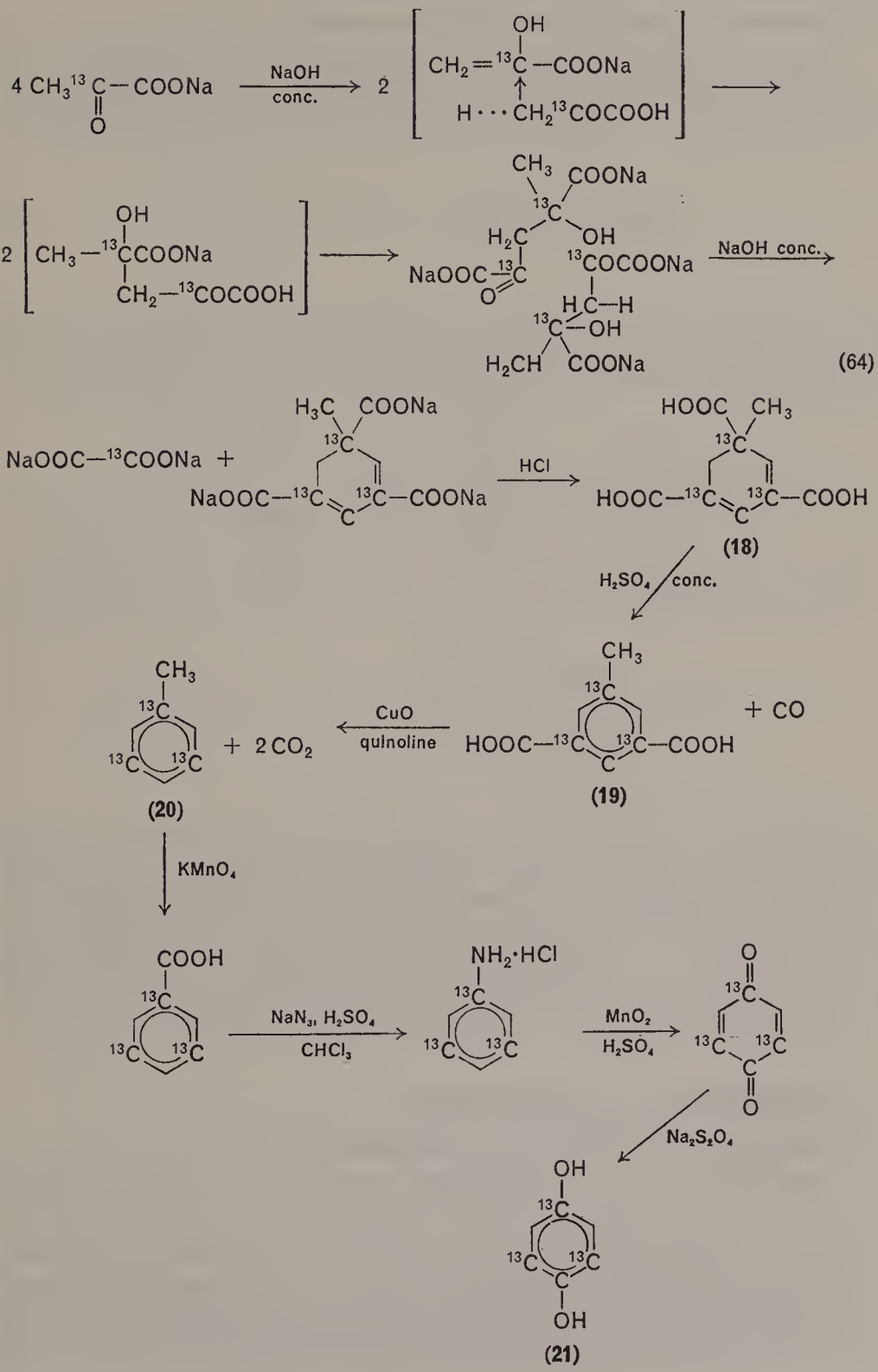
Pyruvic acid labelled in the keto-group was synthetized according to sequence (63):



(63)

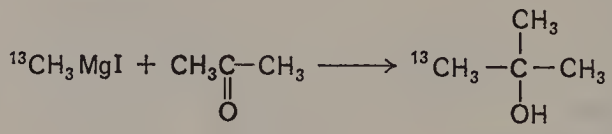
If in the last step the concentration of the hydrochloric acid was higher than 2N or if the pyruvamide was hydrolysed at a higher temperature than 70°C, acetic acid appeared as a side-product.

The condensation of the ^{13}C-labelled pyruvic acid (**17**) to methyl-dihydrotrimesic-1,3,5-$^{13}C_3$ acid (**18**) has been performed according to the method of Hughes and Reid[69], who also described the formation of uvitic-1,3,5-$^{13}C_3$ acid (**19**) and synthesis of toluene-1,3,5-$^{13}C_3$ (**20**) by decarboxylation of **19**. Transformation of **20** to *p*-benzohydroquinone-1,3,5-$^{13}C_3$ (**21**) has been carried out using the same sequence of reactions as in the case of *p*-benzoquinone-1-^{13}C.


4 CH3 13C COONa
O
NaOH
conc.
2
OH
CH2=13C—COONa
H···CH2 13COCOOH
2
OH
CH3—13CCOONa
CH2—13COCOOH
CH3 COONa
13C
H2C OH
NaOOC—13C 13COCOONa
O
H C—H
13C—OH
H2CH COONa
NaOH conc.
(64)
NaOOC—13COONa +
H3C COONa
13C
NaOOC—13C 13C—COONa
C
HCl
HOOC CH3
13C
HOOC—13C 13C—COOH
C
(18)
H2SO4 conc.
CH3
13C
HOOC—13C 13C—COOH
C
+ CO
(19)
CuO
quinoline
CH3
13C
13C 13C
+ 2 CO2
(20)
KMnO4
COOH
13C
13C 13C
NaN3, H2SO4
CHCl3
NH2·HCl
13C
13C 13C
MnO2
H2SO4
O
13C
13C 13C
C
O
Na2S2O4
OH
13C
13C 13C
C
OH
(21)

2. Synthesis of 2-t-[β-^{13}C]butylhydroquinone

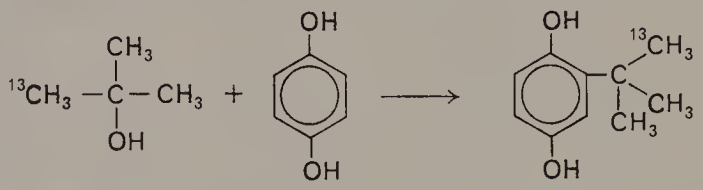
This has been performed[86–88] by alkylation of hydroquinone with *t*-butyl alcohol-β-^{13}C (**22**). The latter was obtained from the Grignard reaction of methyl iodide-^{13}C (having 48·1 at% excess of ^{13}C) with acetone:



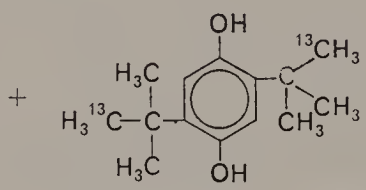
(65)

(22)

The method of Young and Rogers was used for the reaction of **22** with hydroquinone[89], adding an aqueous solution of the labelled alcohol to



(23)



(66)

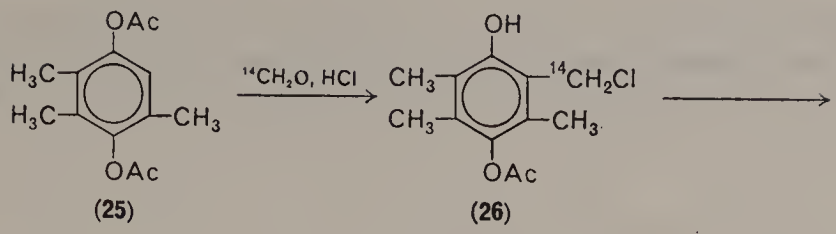
(24)

the vigorously stirred mixture of hydroquinone, phosporic acid and xylene heated to 115°C. After 30 min the hot xylene layer was removed and the hot acid phase was extracted with more xylene. The xylene was removed *in vacuo* to yield a crude mixture of 2,5-di-*t*-butylhydroquinone (27%) (**24**) and 2-*t*-butyl-β-^{13}C-hydroquinone (**23**) in 30% yield. The separation of the labelled compounds was achieved by chromatography on a silic acid–celite column using chloroform as the eluent.

B. Syntheses of ^{14}C-Labelled Quinones

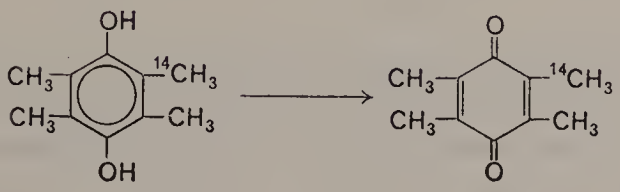
1. Synthesis of tetramethyl-$^{14}C_1$-*p*-benzoquinone (28)

Duroquinone-α-^{14}C was obtained according to reaction scheme (67)[72, 90, 91]. 2-Chloromethyl-^{14}C-3,5,6 trimethyl-4-acetoxyphenol (**26**), prepared in 89% yield by chloromethylation of trimethylhydroquinone diacetate (**25**) with formaldehyde-^{14}C[90–92] was reduced by lithium aluminium hydride to tetramethyl-^{14}C-hydroquinone (**27**). Oxidation of **27** with ferric sulphate gave a quantitative yield of duroquinone-α-^{14}C (**28**).



(25) (26)

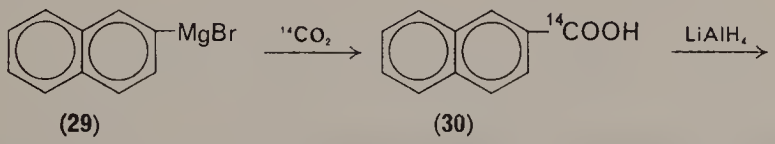
(67)



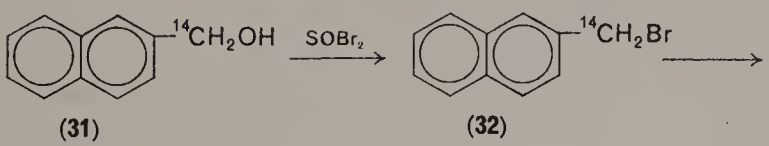
(27) (28)

2. Synthesis of ^{14}C-labelled naphthoquinones

a. Synthesis of 2-methyl-^{14}C-1,4-naphthoquinones. Synthesis of ^{14}C-labelled menadione (vitamin K_3) (**34**) has been achieved by the following scheme[93, 94]:



(29) (30)



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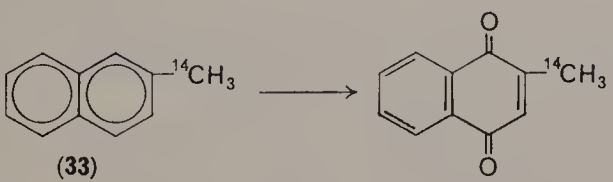
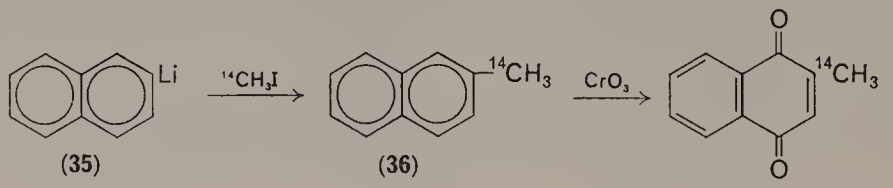


(33) (34)

(68)

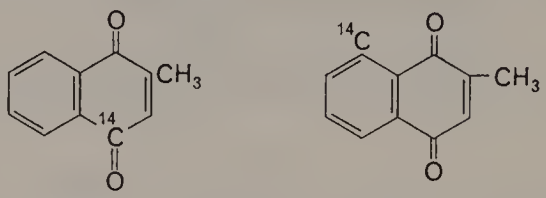
2-Naphthoic acid-carboxyl-^{14}C (**30**) was obtained in 70% yield from **29** and reduced to **31**, which in turn was converted to 2-bromomethyl-^{14}C-naphthalene (**32**). Reduction of **32** with $LiAlH_4$ yielded **33**, which was

oxidized with chromic oxide[94] to 2-methyl-^{14}C-1,4-naphthoquinone (**34**). The overall yield of vitamin K_3 was 23%. Vitamin K_3 (**34**) has also been synthesized using methyl-^{14}C iodide as a labelled starting material[72, 95].



(35) (36) (34) (69)

b. Synthesis of ring-labelled 2-methyl-1,4-naphthoquinones. The detailed directions for the synthesis of 2-methyl-1,4-naphthoquinone-4-^{14}C (**36**), using the method of Li and Elliot[96] and of 2-methyl-1,4-naphthoquinone-8-^{14}C (**37**) performed according to Collins[97], are given by Murray and Williams[72]. The reaction schemes have also been reviewed by Mikluhin[59] and by Crompton and Woodruff[73].

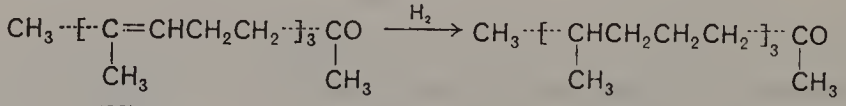


(36) (37)

3. Synthesis of vitamin K_1 labelled with ^{14}C

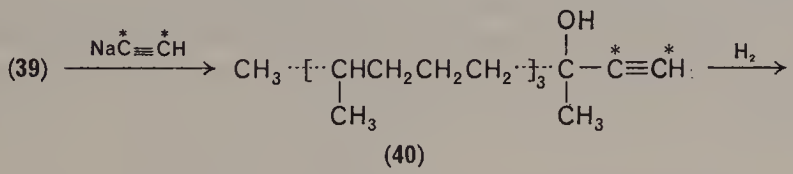
Labelled chemically pure compounds with vitamin K activity, especially vitamin K_1 and labelled menadione, are important tools for the elucidation of their functions, mode of action and metabolic pathways in living organisms[98–101]. Carbon ^{14}C can be introduced separately into vitamin K_1 either by the synthesis of a labelled naphthoquinone ring, or by introducing isotopic carbon into the 2-methyl group of the menadione used for the condensation reaction, or by labelling the phytyl chain in the 3-position. Reaction schemes used for the synthesis of simple naphthoquinones labelled with ^{14}C in various positions are described by Murray and Williams[72]. Methods used for the synthesis of labelled isoprenoid chains have been reviewed by Isler and coworkers[98].

a. Synthesis of ^{14}C-labelled isophytol. The reactions below illustrate the synthesis of isophytol labelled in the 1- and 2-position:

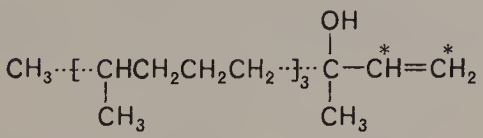


(38) (39) (70)

The unsaturated C_{18} ketone **38** was hydrogenated to give the saturated ketone **39**. Ethynylation of the latter with uniformly ^{14}C-labelled sodium acetylide in liquid ammonia followed by partial hydrogenation of the triple bond yields isophytol **41**. Phytol, **42**, can be prepared in three steps

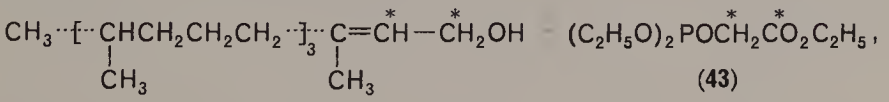


(40)

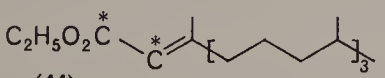


(41) (71)

from isophytol **41** or independently by reaction of **39** with the doubly labelled **43**, followed by reduction of the ester **44** with lithium aluminium hydride[98–102]:



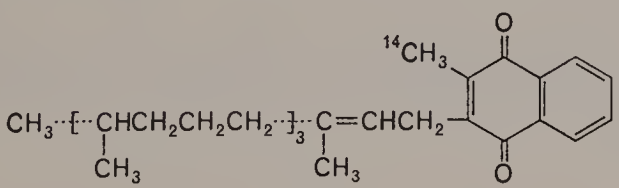
(42) (43)



(44)

The condensation of the isophytol with 2-methyl-1,4-naphthohydroquinone is catalysed by boron trifluoride. Oxidation of the condensation product by air or by silver oxide produces chain-labelled vitamin K_1.

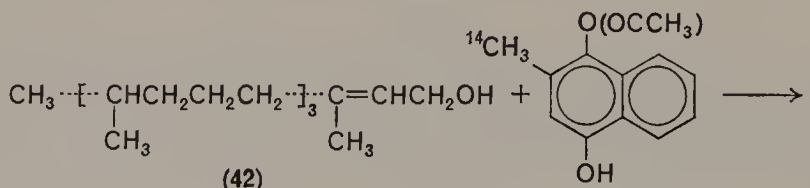
b. Synthesis of vitamin K_1 labelled in the methyl group. Racemic vitamin K_1 (**45**) labelled with ^{14}C in the 2-methyl group was synthesized by



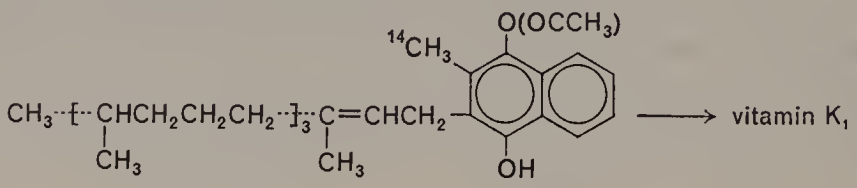
(45)

condensing 500 mg of 2-methyl-^{14}C-1,4-naphthohydroquinone (prepared from ^{14}C-labelled vitamin K_3) with 400 mg of isophytol **41** in dioxan with boron trifluoride as catalyst[103, 104]. Vitamin K_1 was obtained, by oxidation of the hydroquinone **49**, as a clear yellow oil, 20% based on **48**. The

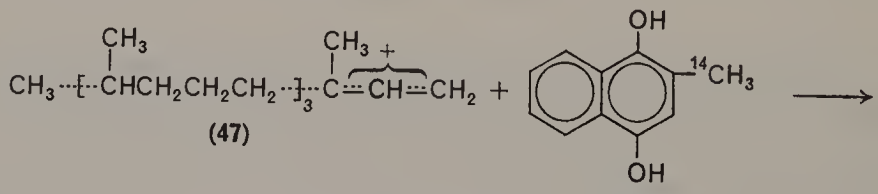
purity of the product has been tested by subjecting quinone to reductive acetylation[98–103] when the diacetate obtained accounted for 96·0% of the vitamin K_1 radioactivity used. Better overall yields of unlabelled vitamin K_1 (as high as 66%) were obtained[105] from menadiol 1-monoester (**45a**) using boron trifluoride etherate, aluminium chloride or potassium acid sulphate as catalysts. The condensation product **46**, dihydrovitamin K_1 1-monoacetate, was first hydrolysed and then oxidized to the quinone, vitamin K_1.



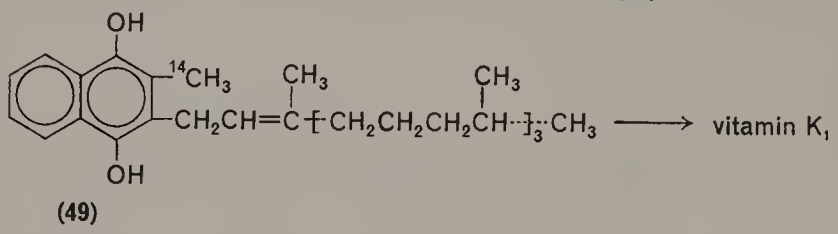
(72)



It is possible that electrophilic displacement by both phytol and isophytol may proceed through the same cationoid intermediate **47** yielding the hydroquinone of vitamin K_1, **49**.

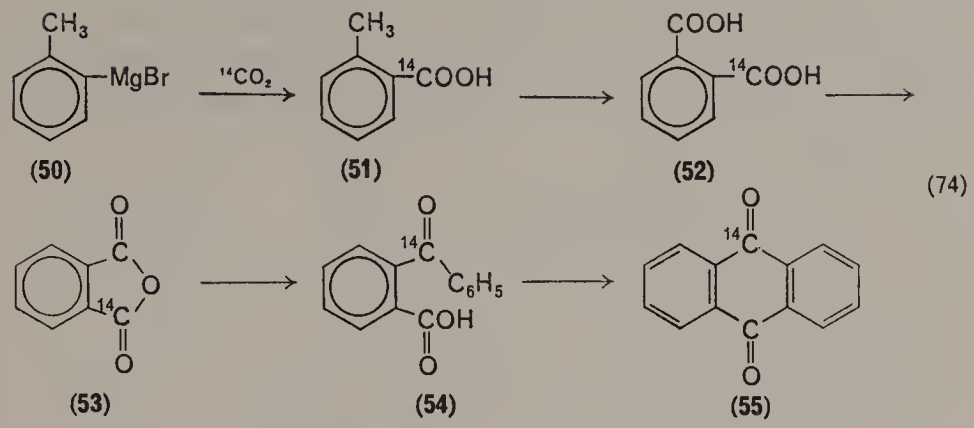


(73)



4. Synthesis of ^{14}C-labelled anthraquinones

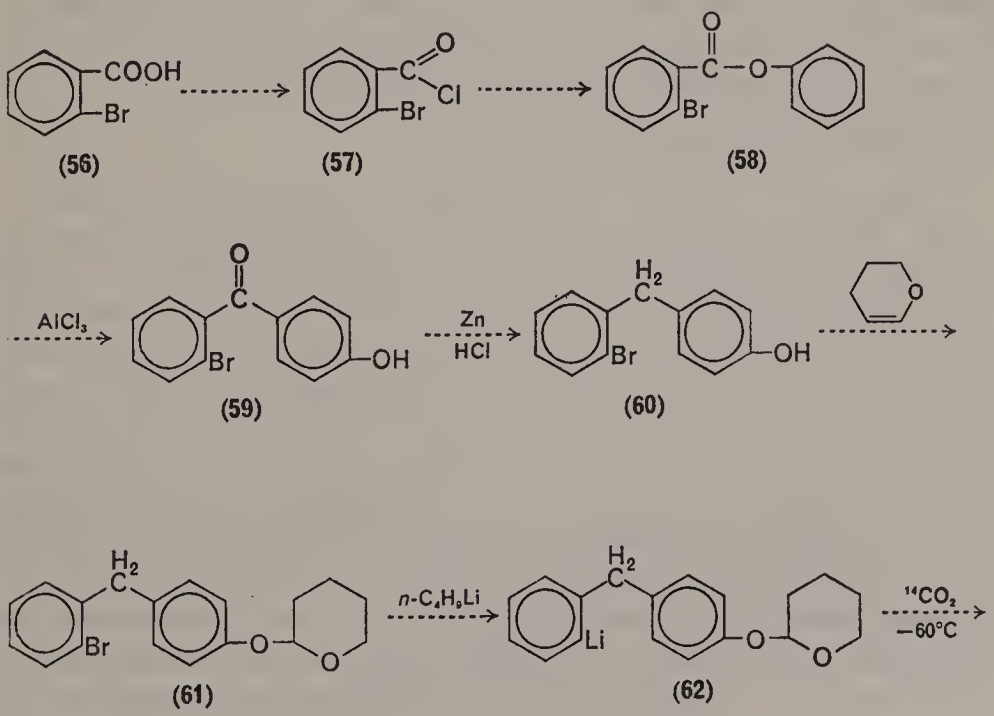
a. Synthesis of anthraquinone-9-$^{14}C_1$. Anthraquinone-9-$^{14}C_1$ (**55**) has been prepared as a labelled intermediate in the synthesis of anthracene-9-$^{14}C_1$[106]:

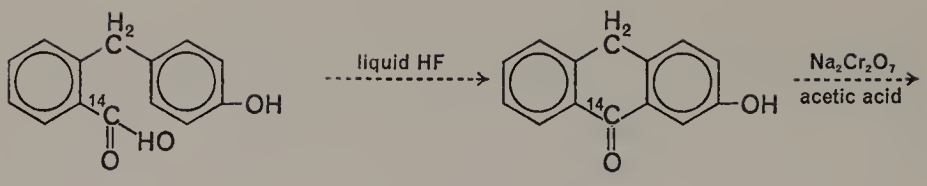


(74)

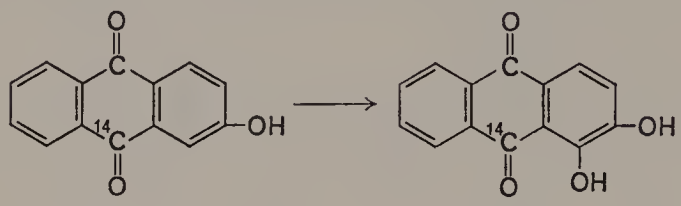
Carboxyl-labelled *o*-toluic acid (**51**) was prepared from **50** and oxidized to **52** by potassium permanganate. The anhydride **53** was obtained by refluxing **52** with thionyl chloride and gave **54** by Friedel–Crafts reaction. Ring closure to **55** has been achieved by heating **54** in 96% sulphuric acid at 120°C for 1 h[109].

b. Synthesis of 1,2-*dihydroxy anthraquinone*-9-^{14}C. The synthesis of labelled alizarin **66** is shown in the following reaction scheme[107]:





(63) (64)



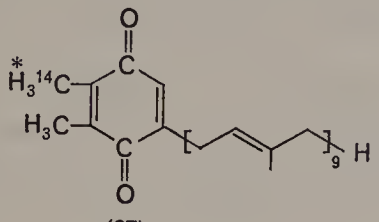
(65) (66) (75)

o-Bromobenzoyl chloride (**57**) is esterified with phenol. The Fries rearrangement[108] of **58** gave 2-bromo-4′-hydroxybenzophenone (**59**) which was reduced to 2-bromo-4′-hydroxydiphenylmethane (**60**). The hydroxyl group is protected in the next step by formation of a cyclic acetal with dihydropyran[110]. The halogen–metal interconversion with **61** and butyllithium yields the organolithium compound **62**, which was carbonated with labelled carbon dioxide. Ring closure of **63** gave 2-hydroxy-9-anthrone (**64**) in 88–100% yield[111], which was oxidized to 2-hydroxyanthraquinone (**65**) in practically quantitative yield. Conversion of **65** to alizarine **66** by hydroxylation has been achieved with high yield using an excess of potassium chlorate and sodium hydroxide.

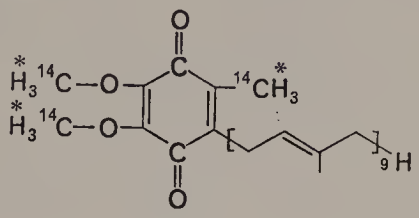
5. Biosynthesis of ^{14}C-labelled quinones

a. Biosynthesis of phytoquinones. Threlfall, Whistance and Goodwin[112] studied the incorporation of ^{14}C and tritium activity into terpenoid quinones synthesized by maize shoots, incubated during 24 h with continuous illumination, in water containing 50 Ci of L-Me-^{14}C methionine and 300 Ci of L-Me-^{3}H methionine[112]. They found that in the isolated plastoquinone **67**, ubiquinone **68** and phylloquinone **69** all the ^{14}C and tritium radioactivity was in the methyl or methoxyl groups on the quinonoid ring. Ubiquinone **68** contained 26% of the ^{14}C activity in the methyl group and the remaining activity in the methoxyl groups. Phylloquinone **69** also had the activity in the ring-attached methyl group which was formed by transfer of an intact $^{14}CH_3$ group from methionine. It is suggested that in the cases of phylloquinone and plastoquinone the methylation takes place in the chloroplast, whereas methylation of ubiquinone occurs elsewhere within the cell. Possible mechanisms for

C- and *O*-methylation have been proposed. Unfortunately, the yield of the labelled compounds based on the L-[Me-^{14}C, ^{3}H]–methionine radioactivity used is very low (under 1%).



(67)



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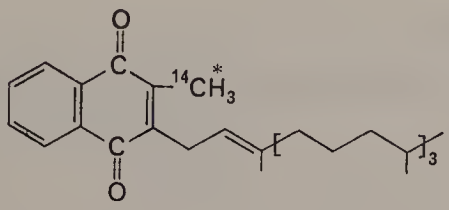
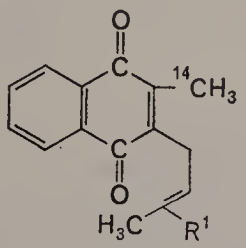
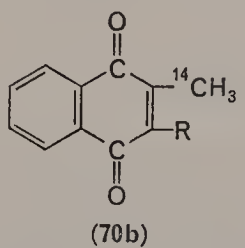


(69)

Guérin, Azerad and Lederer[113] have found that vitamin K_2(45)H (**70**) with ^{14}C-labelled 2-methyl group is synthesized by *Mycobacterium Phlei* from L-methionine-$^{14}CH_3$. It has been proved that the isoprenoid chain of the vitamin contains no radioactivity and that the total activity of the molecule is localized in the 2-methyl group. Phthalic acid obtained by oxidation of the labelled vitamin K_2(45)H showed only 0·24% of the total activity of the vitamin K_2(45)H. This excludes incorporation of the methyl group of the L-methionine-$^{14}CH_3$ into those eight atoms of the anthraquinone ring system which are transformed by oxidation into phthalic acid.



(70a)



(70b)

(In **70b** R is an isoprenoid chain consisting of 45 carbon atoms or 9 units of isoprene, one of which is saturated.)

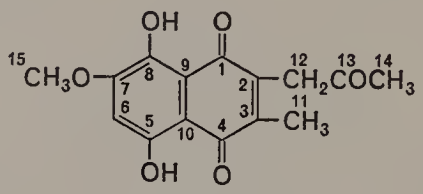
Martius and Billeter[114], using vitamin K_1 labelled with tritium in the nucleus, with ^{14}C in the side-chain, demonstrated that animals are able to replace the phytyl group of the vitamin K_1 by a geranyl–geranyl group, thus producing vitamin K_2(20).

Later Martinus and Leuzinger[114, 115] showed that the anaerobic heterotrophic bacteria *Fusiformis nigrescens* can use 1,4-naphthoquinone in the vitamin K synthesis, by transmethylation of a CH_3 group from methionine into the 2-position of naphthoquinone and attaching the isoprenoid chain in the 3-position.

b. Naphthaquinone biosynthesis[116]. Gatenbeck and Bentley[116] have shown that Me-^{14}C-methionine (**71**), 1-^{14}C acetate or 2-^{14}C malonate added to the growth medium of *Fusarium javanicum* are converted into labelled javanicin **72**. The percentages of incorporation are 0·83, 0·70 and 0·07%, respectively.

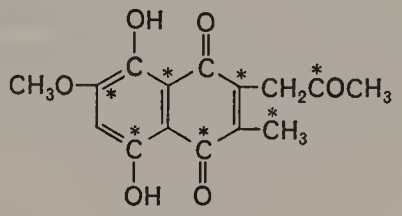
$^{14}CH_3SCH_2CH_2CH(NH_2)COOH$

(71)

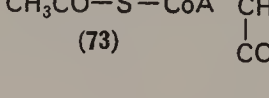


(72a)

Degradation of labelled javanicin revealed that the label is incorporate only in the methoxyl group (position 15). According to the authors the methyl group (position 11), is formed not by transmethylation but by the reduction of the carboxyl group. The remaining carbon atoms labelled with an asterisk in **72b** originate from the carbonyl groups of the labelled acetyl-CoA (**73**) and malonyl-CoA (**74**).



(72b)



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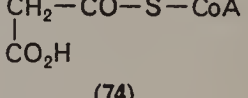
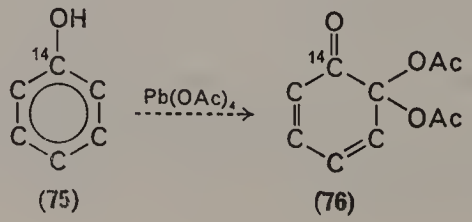


(74)

6. Synthesis of ^{14}C labelled o-benzoquinone diacetate

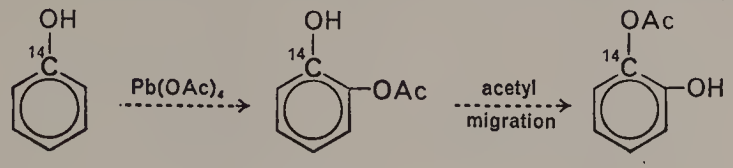
Billek, Swoboda and Wessely[117] synthesized *o*-benzoquinone diacetate (**76**) labelled with ^{14}C predominantly at the C-1-position by treating ^{14}C-labelled phenol with lead tetraacetate. Besides the main product



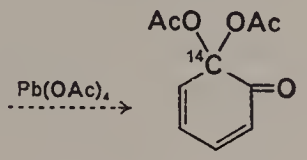
(75) (76)

(76)

2,2-diacetoxycyclohexa-3,5-dienon-1 (**76**), obtained in 95% yield, oxidation leads also to the formation of the 2-^{14}C isomer (**77**) in about 5% yield.



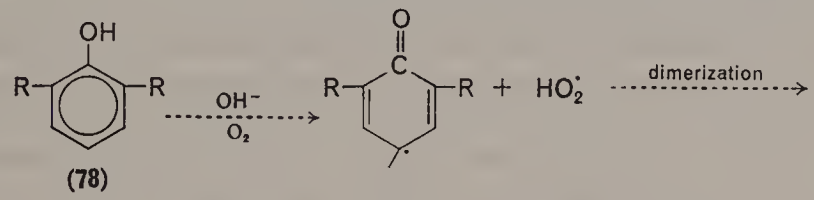
(77)



(77)

7. Synthesis of uniformly ^{14}C-ring-labelled 3,3′,5,5′-tetra-t-butyldiphenoquinone

Uniformly ^{14}C-ring-labelled diphenoquinone (**79**) was synthesized in the presence of oxygen from uniformly ^{14}C-ring-labelled 2,6-di-*t*-butylphenol (**78**). The reaction[118] takes place at 37°C in *t*-butyl alcohol solution



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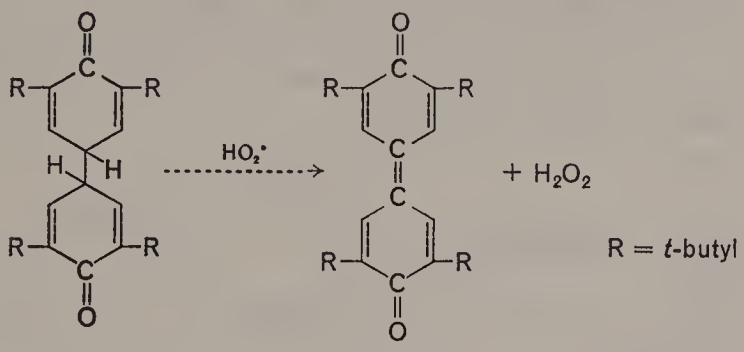


(79)

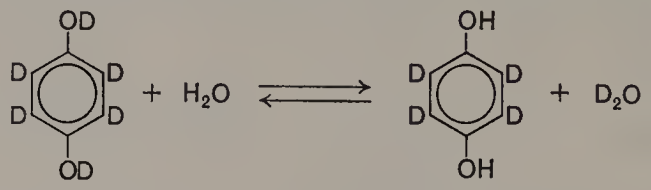
of KOH. The final yield of the purified dark-red crystalline product **79** was 64% having a specific activity of 2·4 mCi/mmole.

C. Synthesis of Tritium- and Deuterium-labelled Quinones

1. Synthesis of deuterium-labelled *p*-benzoquinone

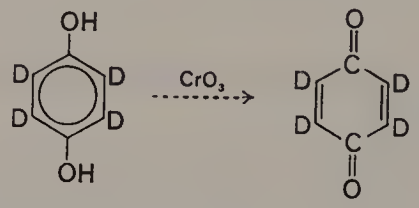
Deuterium-labelled 1,4-hydroquinone has been obtained[119, 120] by hydrogen exchange taking place between heavy water and *p*-benzohydroquinone at high temperatures (170°C, 40–50 h) in the presence of sodium

hydroxide. In the product so obtained the labile oxygen-bound deuterium was replaced by hydrogen through re-exchange (79a) at room temperature.



(79a)

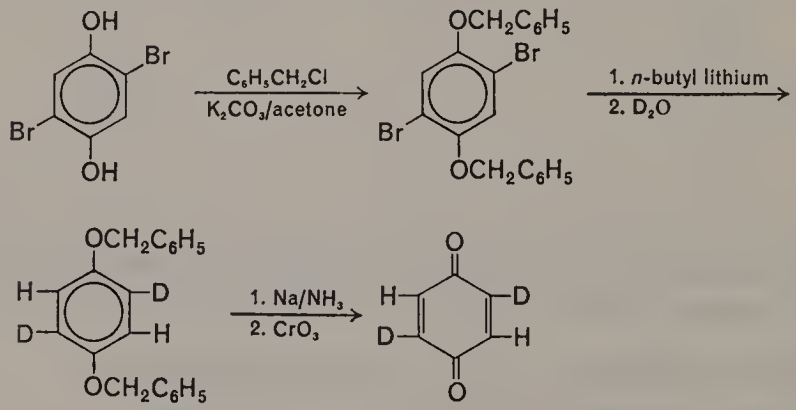
The heavy 1,4-benzoquinone was obtained by oxidation of the heavy hydroquinone with dichromate solution according to the usual method[121, 122]. The authors did not notice any transfer of deuterium from



(79b)

either the ring-labelled *p*-benzohydroquinone or the *p*-benzoquinone to the solvent during the oxidation process.

Charney and Becker[122b] prepared *p*-benzoquinone-d_4 by carrying out three subsequent isotopic exchange reactions between fully deuterated 3·4M sulphuric acid and hydroquinone at 100°C during 36 h. The labelled hydroquinone was oxidized with chromic oxide[122] to *p*-benzoquinone-d_4. The final yield of the purified *p*-benzoquinone was 55%. The authors[122c] have also obtained *p*-benzoquinone-2,5-d_2 and *p*-benzoquinone-2,6-d_2 by applying the reaction scheme (79c). *p*-Benzoquinone-d_1 was obtained[122c], starting from the commercially available monobromohydroquinone, by applying a similar sequence of reactions.

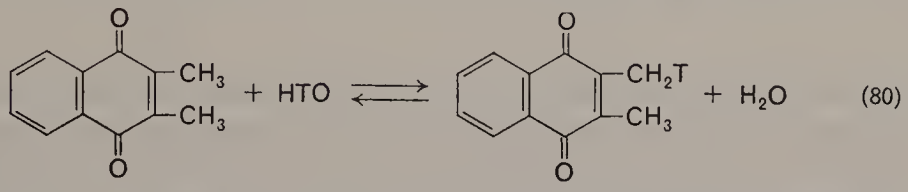


(79c)

2. Synthesis of deuterium- and tritium-labelled methylquinones

Clark and coworkers[123] and Lapidot and coworkers[125] investigated the base-catalysed hydrogen isotope exchange between methyl quinones

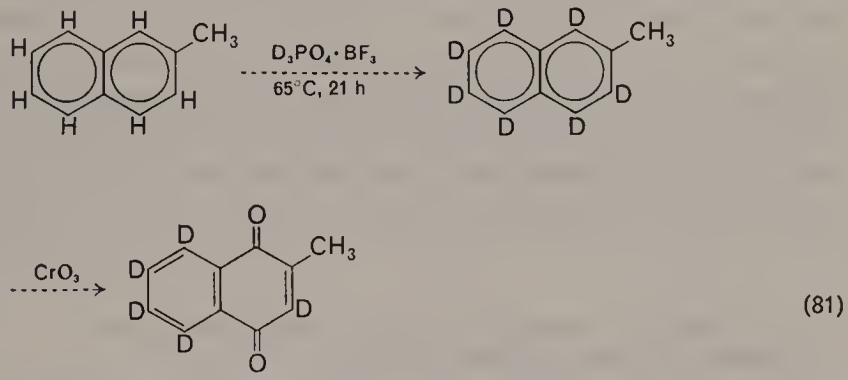
(duroquinone, 2,3-dimethylnaphthoquinone and other quinones including vitamin $K_1(20)$) and D_2O or tritiated water in dioxan solutions. Such studies can furnish data for choosing the best conditions for synthesis of labelled methylquinones. For example, in the case of a solution of 2,3-dimethylnaphthoquinone in a dioxan-tritiated water mixture using triethylamine as catalyst, isotopic equilibrium was reached after 10 h of refluxing. The dependence of the rate of the hydrogen exchange and the



(80)

dependence of the type of the side-reactions occurring during isotopic exchange on the nature of the base, temperature and pH have been observed.

Synthesis of 2-methyl-1,4-naphthoquinone-3,5,6,7,8-d_5 has been achieved by treatment of 2-methylnaphthalene with phosphoric acid-d_3-boron trifluoride reagent in cyclohexane and subsequent oxidation of the 2-methylnaphthalene-1,3,4,5,6,7,8-d_7 with chromic acid[93, 99] (reaction 81).



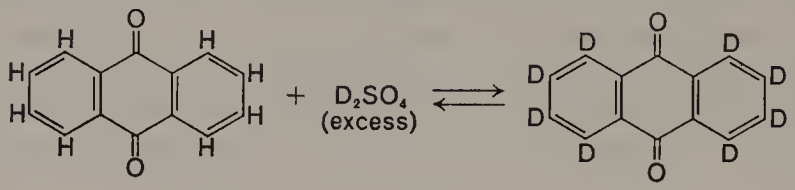
(81)

Condensation of the 2-methyl-1,4-naphthohydroquinone-3,5,6,7,8-d_5 with phytol catalysed with boron trifluoride gave vitamin $K_1(20)$-5,6,7,8-d_4[99, 124].

3. Synthesis of partially and fully deuterated 9,10-anthraquinone

Using sulphuric acid-d_2 as a deuterating agent, Lunelli and Pecile[126] prepared 9,10-anthraquinone-d_8 (**80**). The hydrogen exchange takes place to an appreciable extent at high temperatures and high concentrations of deuterated sulphuric acid. Under such severe experimental conditions sulphonation of the compound also occurs which, however, could be overcome by taking into account the reversibility of the sulphonation

reaction at low concentrations of sulphuric acid. Anthraquinone (2 g) in the form of a solid cylinder, deuterium oxide (5·4 ml) and deuterium



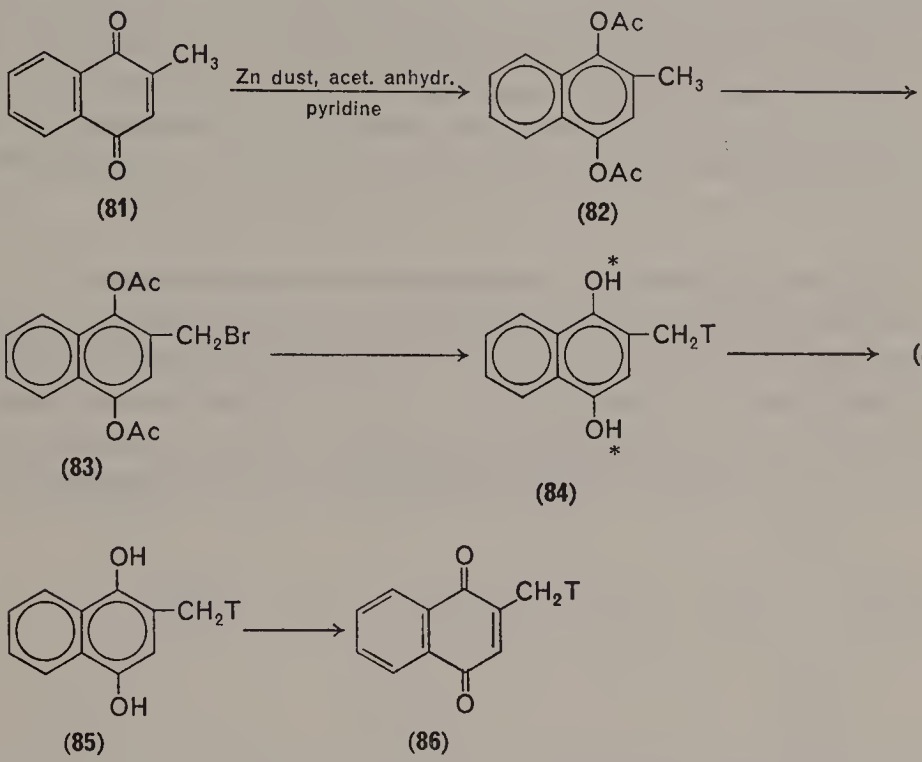
(80) (82)

sulphate (6·6 ml) are placed in a small glass apparatus filled with dry nitrogen in a dry box. The apparatus is then immersed in liquid nitrogen, evacuated, sealed and heated for 2·5 h with a small flame. The water evaporates during heating from the bottom (the reaction bulb) of the apparatus and condenses in a side-arm cooled by flowing water. The condensate flows down to the bottom through a thin tube connecting the side-arm with the reaction volume of the apparatus. In this way, after reaching a steady state, the circulation of the water causes the formation of a concentration gradient of the sulphuric acid as well as a temperature gradient in the reaction mixture moving from the bottom to the surface. Closer to the bottom, where the acid is concentrated, hydrogen exchange and sulphonation occur, while at the top of the reaction volume desulphonation of anthraquinone and exchange between sulphuric acid and water take place. After purification 1·8 g of the labelled product was obtained by Lunelli and Pecile[126]. The procedure was repeated two or more times to attain full deuteration and the final yield was 1·4 g (70%). Mass spectrometric analysis of the product showed 95·4% of anthraquinone-d_8 and 4·6% of anthraquinone-d_7.

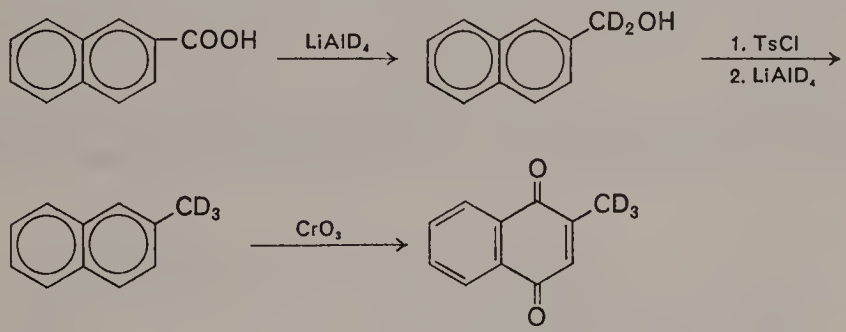
4. Synthesis of 2-methyl-T-1,4-naphthoquinone and 2-methyl-d_3-1,4-naphthoquinone

Synthesis of menadione labelled with tritium presumably in the 2-methyl group (**86**) has been carried out by Billeter and Martius[114]. The diacetate of 2-bromomethyl-1,4-naphthohydroquinone (**83**) was obtained by reduction of menadione **81** to menadiol diacetate **82** followed by side-chain bromination with *N*-bromosuccinimide and dibenzoyl peroxide. **83** was tritiated by a mixture of hydrogen and tritium, using a Pd-black catalyst in dioxan solution in the presence of triethylamine, and subsequently reduced by lithium aluminium hydride to give **85**, which in turn was oxidized with Ag_2O. The labelled product (**86**) was chromatographed, and 19% yield of tritium-labelled menadione was recovered with a specific activity of 46·5 μCi/μmole.

Introduction of deuterium into the 2-methyl group of the menadione[99] was achieved by Di Mari, Supple and Rapoport according to the reaction



scheme (83a). 2-Naphthoic acid was reduced with lithium aluminium deuteride[127]. 2-Naphthylmethanol-α-d_2 was converted to the *p*-toluenesulphonate, and directly reduced with $LiAlD_4$ to 2-methyl-d_3-naphthalene,



(83a)

the oxidation of which with chromic acid yielded 2-methyl-d_3-1,4-naphthoquinone.

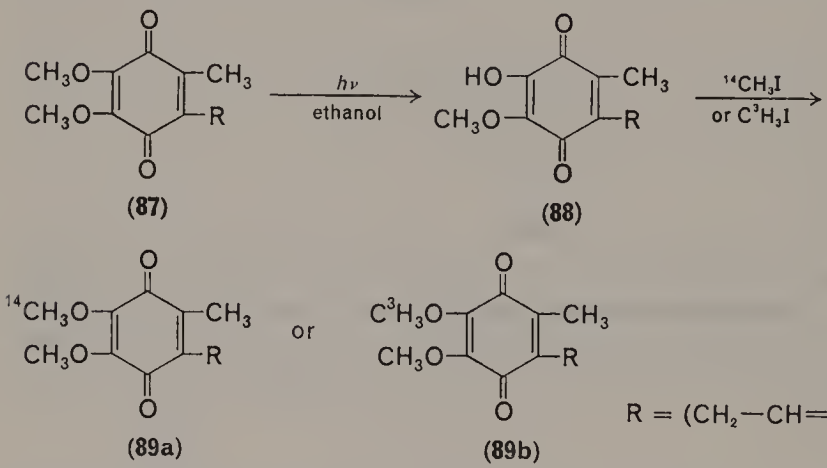
5. Synthesis of tritium-labelled vitamin K_1

Tritium-labelled vitamin K_1 was prepared by condensing tritium-labelled menadione with isophytol according to the method of Isler and Doebel[103]. Tritiated menadione (30 mg) was first hydrogenated over

palladium catalyst in dry dioxan solution and then mixed with 0·01 ml of BF_3-etherate in 0·5 ml of dry dioxan and 100 mg of isophytol in 0·5 ml of dry dioxan. All operations were carried out in an atmosphere of hydrogen. The reaction mixture was kept at 50°C for 10 min. The condensation product, hydroquinone of vitamin K, was oxidized with 100 mg of silver oxide for half an hour. After extraction with heptane, followed by chromatography, 35 mg of labelled phylloquinone were obtained (44% yield).

6. Synthesis of ^{3}H- and ^{14}C-methoxyl-labelled ubiquinone

2-Methoxyl-^{14}C- and 3-methoxyl-^{14}C-mixtures, and 2-methoxyl-^{3}H- and 3-methoxyl-^{3}H-mixtures of labelled ubiquinone (**89a, b**) have been obtained by methylation with labelled methyl iodide or labelled diazomethane[128], the photochemically obtained mixtures of approximately equal amounts of the 2- and 3-hydroxyubiquinone (**88**). Photolysis of ubiquinone **87** in

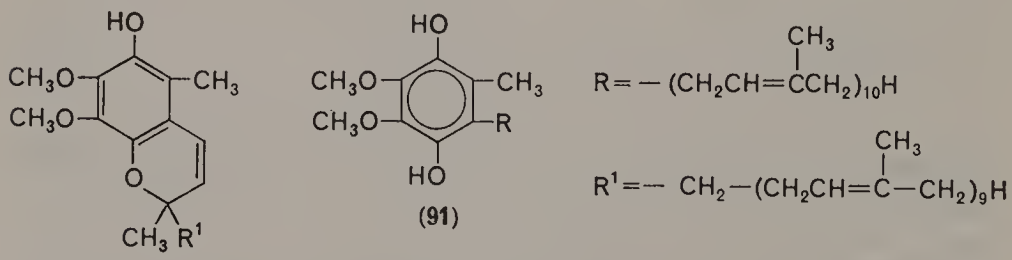


(87) (88) (89a) (89b)

(84)

$$R = (CH_2{-}CH{=}\overset{\displaystyle CH_3}{\overset{|}{C}}{-}CH_2)_{10}H$$

absolute ethanol yields at least eight products such as ubichromenol **90**, hydroubiquinone **91** and hydroxyubiquinone **88**. Hydroxyubiquinone **88**



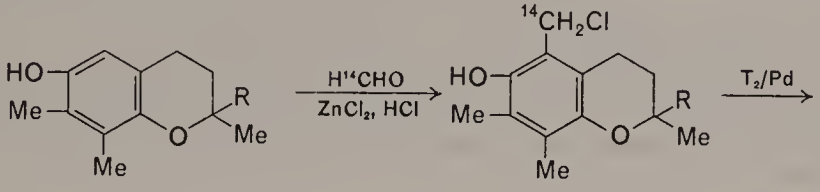
(90) (91)

was converted to methoxyl-^{3}H ubiquinone by reaction with methyl-^{3}H-iodide and anhydrous potassium carbonate in dry acetone.

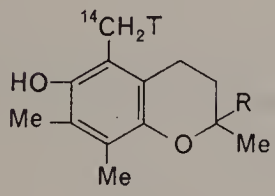
In similar experiments with methyl-^{14}C iodide the ubiquinone-methoxyl-^{14}C was obtained in 55% yield.

7. Synthesis of DL-α-tocopherol labelled with tritium and ^{14}C [129]

DL-α-Tocopherol-5-methyl-^{14}C was prepared by reduction of 5-chloromethyl-^{14}C-tocopherol, obtained by reacting DL-γ-tocopherol[129a] with ^{14}C-labelled paraformaldehyde and HCl. Tritium-labelled DL-α-tocopherol-5-methyl-T (**94**) of very high specific activity was synthesized using a modification in which the reduction of the unlabelled chloromethyl compound was carried out with tritium gas in dioxan using a mixed catalyst consisting of equal parts of palladium on charcoal and palladium on calcium carbonate.

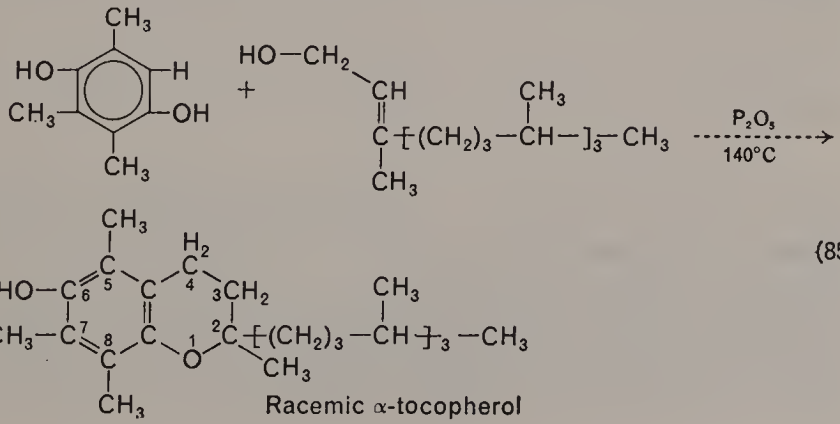


(92) (93)



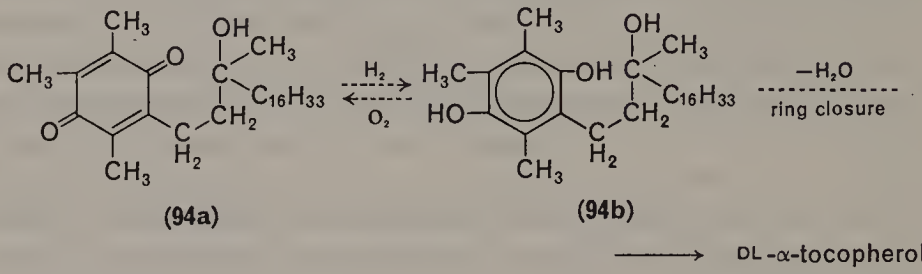
(94) (85)

Doubly labelled tocopherol was prepared by reduction of 5-*chloromethyl*-^{14}C-tocopherol with tritium gas according to scheme (85). Commercial synthetic tocopherols ('antisterility' vitamin E) are obtained by condensation of trimethylhydroquinone with phytol or phytylbromide according to reaction scheme (85a)[129b-g]. Oxidation of thetocopherol with



(85a)

ferric chloride ($FeCl_3$) or silver nitrate ($AgNO_3$) yields tocopherylquinone **94a** which in turn can be reduced to tocopheryl-hydroquinone **94b**[129g] with zinc in glacial acetic acid or palladium in alcohol. The original



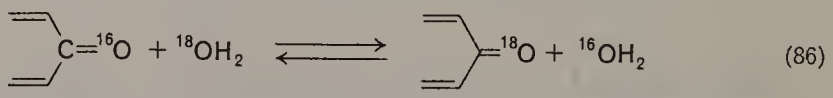
tocopherol can be regenerated by the reduction (and cyclization) of the quinone **94a** with reducing agent in strong acid solution[129g].

Condensation of phytylbromide with trimethylhydroquinone proceeds in benzene solution in the presence of $ZnCl_2$ or HCOOH. Better yields are obtained if monoesters of trimethyl hydroquinone are used for the reaction[129b, c, d].

D. Synthesis of Oxygen-labelled Quinones†

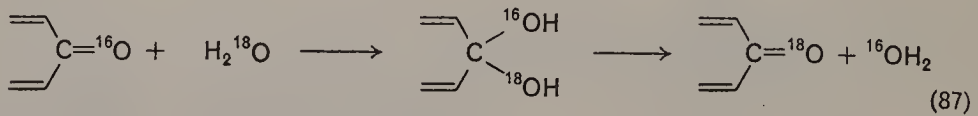
1. ^{18}O exchange in benzoquinones

It has been found that heavy oxygen of water exchanges with light oxygen of *p*-benzoquinone at room temperature[59, 130]:



(86)

The isotope equilibrium was reached after 10 days in neutral medium. (At the same time in acidic medium 70% exchange was found.) The exchange proceeds by addition of a molecule of water to the double bond of the carbonyl group:



(87)

† The reader of this section is referred to references A–H and 1–71 on oxygen isotope methodology, i.r., n.m.r. and e.s.r. spectroscopy, and also on ^{17}O and ^{18}O applications in physical and life sciences, in the catalogue of ^{18}O- and ^{17}O-labelled compounds edited by the Research Products Dept. of Miles Laboratories Inc., Elkhart, Indiana 46514, U.S.A.

I.r. spectra of deuterated and ^{18}O-labelled quinones are reviewed in the book of S. Pinchas and I. Laulicht, *Infrared Spectra of Labelled Compounds*, Academic Press, London and New York, 1971.

The isotope exchange reaction (86) can be used for synthesis of ^{18}O labelled quinones. Becker, Ziffer and Charney[122a] prepared *p*-benzoquinone-$^{18}O_2$ and *p*-benzoquinone-d_4-$^{18}O_2$ by shaking 1·3 ml of a benzene solution containing 100 mg of the quinone with 0·5 g heavy water enriched up to 90% in ^{18}O at room temperature for about 10 days[122a]. The relatively slow ^{18}O isotope exchange in the case of *p*-benzohydroquinone was studied quantitatively at 140–170°C in neutral, acid and basic solutions. In neutral and acid medium the exchange proceeds with an activation energy equal to 18 kcal/mole, while the base-catalysed exchange is stated to proceed with an activation energy of 27 kcal/mole[130].

2. Synthesis of ^{18}O-labelled naphthoquinones

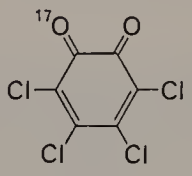
Di Mari, Snyder and Rapoport have established[100,101] that the initial rate of the acid-catalysed ^{18}O exchange between ^{18}O-enriched water and the 1,4-naphthoquinone is 50 times faster at room temperature than the ^{18}O exchange with 2,3-dimethyl-1,4-naphthoquinone. This difference between the unhindered and the hindered carbonyl–^{18}O-exchange was utilized for the synthesis of selectively labelled phylloquinones. *Phylloquinone*-4-^{18}O was prepared by condensing phytol with menadione-4-^{18}O, obtained by the direct exchange of 2-methyl-naphthoquinone with ^{18}O-enriched water in tetrahydrofuran solvent. The condensation reaction was catalysed by boron trifluoride-etherate and proceeded without loss of isotope. Synthesis of *phylloquinone*-1-^{18}O was achieved by preparing uniformly ^{18}O-labelled menadione at the temperature of refluxing tetrahydrofuran, preferential washing out of ^{18}O from the 4-position, and converting the 1-^{18}O-menadione into the corresponding phylloquinone[101]. Synthesis of *phylloquinone*-1,4-$^{18}O_2$ was carried out by direct ^{18}O-exchange of the phylloquinone itself with an $H_2{}^{18}O$–dioxan mixture at reflux during 3 h, when phylloquinone enriched up to 7·0% of ^{18}O was obtained.

^{18}O-labelled phylloquinones have been used subsequently by Snyder and Rapoport[101] to test the different mechanisms proposed to explain the role of these quinones in oxidative phosphorylation, to eliminate those mechanisms which involve the intermediacy of quinone methides and to impose additional restrictions on other allowable mechanisms[99–101].

3. Synthesis of ^{17}O-labelled quinones

Broze, Luz and Silver[131,132] prepared ^{17}O-labelled tetrachloro-*o*-benzoquinone (**95**), acenaphthenequinone (**96**), 9,10-phenanthraquinone (**97**), tetrafluoro-*p*-benzoquinone (**98**), tetrabromo-*p*-benzoquinone (**99**) and 2,3-dichloro-1,4-naphthoquinone (**100**) by exchange reactions between the parent quinones and ^{17}O-enriched water with 4–10 at% of

^{17}O. The isotope exchange of ^{17}O was carried out in dioxan–water (20 : 1). The concentration of the carbonyl compound was between 0·2 and 0·4M. Except in the case of compounds **95** and **96** HCl was added to the reaction mixture. The exchange with **95** and **98** was carried out at room temperature for 1 and 2 days respectively. The exchange with compounds **96**, **97**, **99** and **100** was performed at 60°C for 1–4, 3, 7 and 3 days, respectively. The kinetics of the ^{17}O exchange between water and the quinones **95–100** has not been studied, nor has the position of the equilibrium attained in the exchange been determined.



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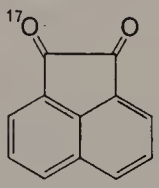

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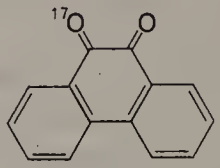

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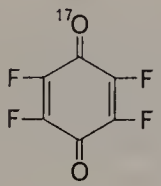

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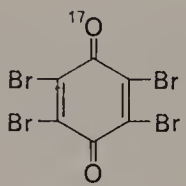

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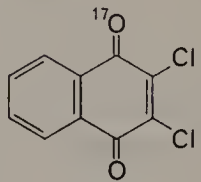
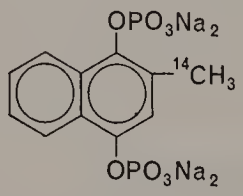


(100)

E. Synthesis of Labelled Drugs[133–158]

Introduction. Laboratory and clinical (metabolic) investigations[133–153] have shown that tetrasodium 2-^{14}C-methyl-1,4-naphthaquinol diphosphate (**101**, menadiol diphosphate), one of the earlier chemical radiosensitizers in the radiotherapeutic treatment of some malignant[134] tumours, enters

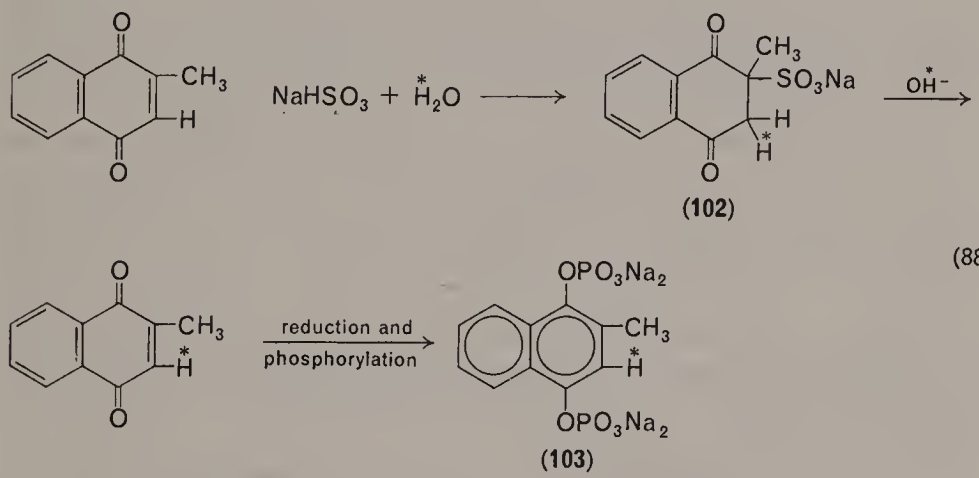


(101)

malignant cells to a much greater extent than normal cells. It localizes mostly along the growing edge of the tumours, and to a lesser extent in muscle and some other organs concerned with detoxification, excretion and vitamin K function. Uptake of the Synka-Vit (a synthetic K vitamin,

commercial name of **101**) by the bone marrow is less than by the tumour, by a factor of 5. This preferential concentration of compound **101** in some tumours and fast-growing tissues gave the idea to several research groups[62, 133–152] of further developing radioactive drugs which are already used for the hospital treatment of human malignancies and allied diseases. Tritium was found to be the most promising isotope for cancer internal radiotherapy. It is produced in nuclear reactors in practically 100% pure chemical T_2 form, is relatively cheap and readily available. Its low energy β-emission (maximum energy of the β-particles is $18{\cdot}7 \pm 0{\cdot}1$ keV, their mean energy is $5{\cdot}73 \pm 0{\cdot}003$ keV, the ranges in tissues corresponding to the mean and maximum energies are 1 and 6 μ respectively; the half-life is $12{\cdot}43 \pm 0{\cdot}04$ years) ensures that only the cell in which the labelled molecule was fixed will be affected by the radiation. In the next section some of the methods which have been used to incorporate tritium into the non-labile positions of Synka-Vit are described. Tritium-labelled compounds of specific activities as high as 83 Ci/mM have been synthesized for use in radiochemical therapy.

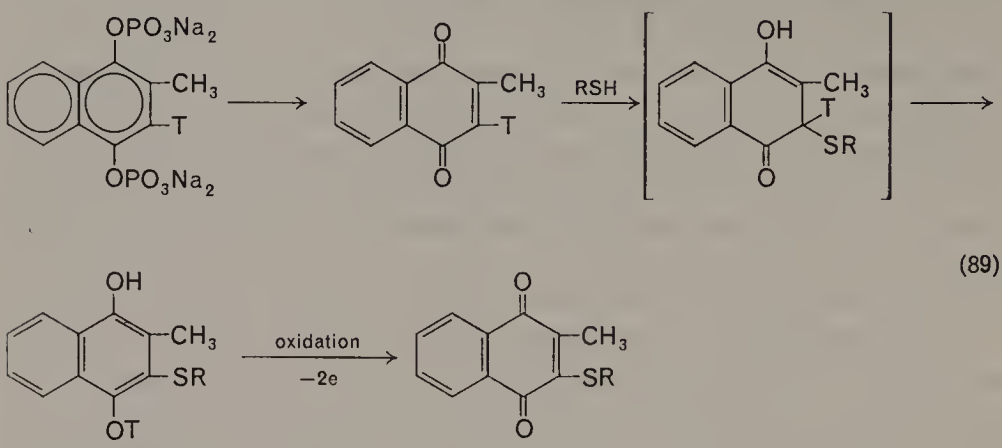
a. Synthesis of tetrasodium 2-methyl-1,4-naphthoquinol-3-T diphosphate[137, 140]. Synka-Vit (**103**), labelled with tritium in the 3-position of the hydroquinone system, was obtained by the intermediate formation of the adduct **102** with sodium hydrogen sulphite in the presence of tritiated water according to reaction scheme (88)[137]. Quinone was regenerated by



(88)

tritium-labelled alkali. The specific activity of the drug, **103**, labelled by this method was relatively low due to tritium–hydrogen exchange processes. Higher specific activity has been achieved by reductive dehalogenation of tetrasodium 2-methyl-3-bromo-1,4-naphthaquinol diphosphate in aqueous solution, using tritium gas in the presence of palladium–oxide

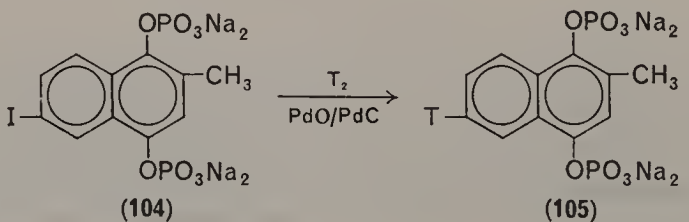
and palladium–charcoal. However, the atom in the 3-position is lost by the quinone during the fixation of the molecule to the cell, as shown in (89).



(89)

b. Synthesis of tritium-labelled Synka-Vit by the Wilzbach method[140,154–156]. Incorporation of tritium into the vitamin K substitute has also been achieved by direct exposure of the dry sodium salt **103** to practically pure tritium gas for a period of 1–3 weeks according to the Wilzbach exchange technique. Subsequent purification procedures showed that much of the original radioactivity of the vitamin K was associated mainly with the water of crystallization, and the tritium activity in non-exchangeable positions was relatively low. Moreover, some highly radioactive by-products associated with the vitamin gave toxic effects, especially damage to the bone marrow. The maximum specific activity obtained after 32 days of irradiation was less than 1 Ci/mM.

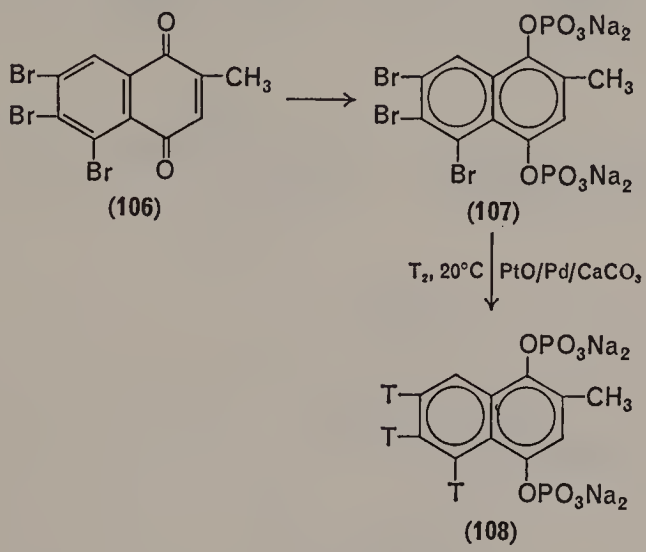
c. Synthesis of 2-methyl-6-tritio-1,4-naphthoquinol bis-disodium phosphate (TRA72)[140,142]. The radioactive drug TRA72 (**105**) was obtained by reductive dehalogenation of tetrasodium 6-iodo-2-methyl-1,4-naphthaquinol diphosphate (**104**). The reduction by tritium gas was rapid and quantitative. Radiochemically pure drug TRA72 of specific activity 28 Ci/mM was obtained. This corresponds to nearly 1 atom of tritium per molecule. Maximum theoretical specific activity for pure TRA72 equals 29·1 Ci/mM.



(104) (105)

(90)

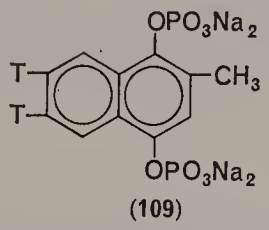
d. Synthesis of 2-*methyl*-5,6,7-*tritrito*-1,4-*naphthoquinol bis-disodium phosphate.* To fulfil the need for a drug with higher specific activity, the synthesis of 2-methyl-5,6,7-tritritio-1,4-naphthoquinol bis-disodium phosphate (**108**) was performed by reductive dehalogenation of the 5,6,7-tribromo-2-methyl-1,4-naphthoquinol bis-disodium phosphate (**107**)[141,142].



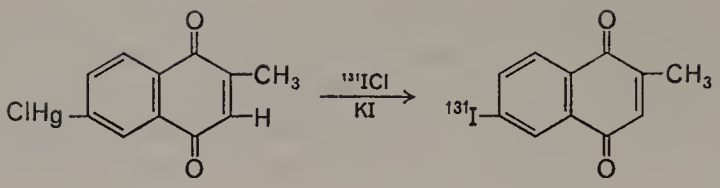
(91)

The specific activity of the drug (**108**, TRA119) was as high as 83 Ci/mM. The radiochemical purity of the product as determined by the dilution method and confirmed by chromatography was 100%[143].

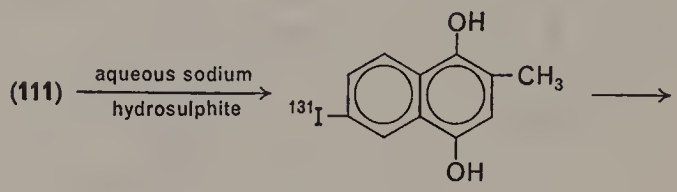
Since 1964 the radioactive drug of specific activity 58·2 Ci/mM, named TRK219, structure **109**[145,146,148,149], has also been produced.

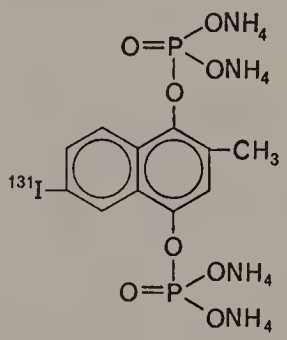


e. Synthesis of 6-^{131}*I-iodo*-2-*methyl*-1,4-*naphthoquinol bis-diammonium phosphate*[149–151]. This has been accomplished by treating 2-methyl-6-chloromercury-1,4-naphthaquinone (0·5 g) with 10 mCi of ^{131}I-iodine monochloride. The labelled product, 6-iodo-2-methyl-1,4-naphthaquinone (**111**) was used after purification for the preparation of the radioactive drug (**112**, 6-^{131}I-iodo MNDP) as shown in reaction (93). The compound **112** was used for the purpose of tumour localization by radioisotope scanning method.



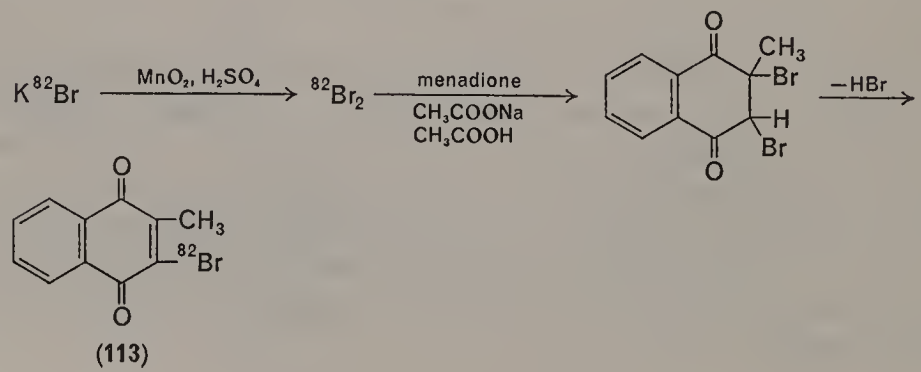
(110) (111) (92)





(112) (93)

f. Synthesis of 2-*methyl*-3-^{82}*Br-bromo*-1,4-*naphthoquinone*[135,136]. This has been carried out according to scheme (94). Radioactive bromine was added to menadione in the presence of sodium acetate and acetic acid at liquid air temperature. The contents were warmed to 50°C in a water bath and further acetic acid was added. After 3 h water was added to precipitate the labelled quinone **113**.

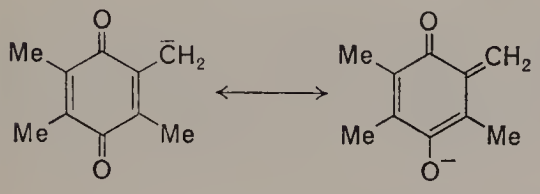


(113) (94)

III. TRACER APPLICATIONS OF LABELLED QUINONES

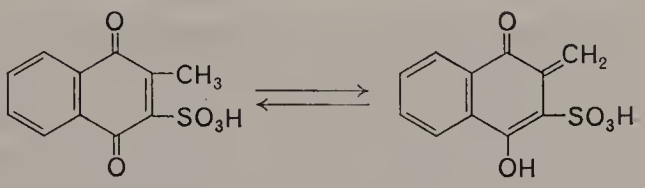
A. Hydrogen–Isotope Exchange in Methylquinones

Discussing the problems of reactivity of quinones and their derivatives[59,159–162], various authors included in the reaction schemes intermediate anions of the quinone methide type **114** as the transient species, or postulated the existence of the tautomeric forms such as **117**.



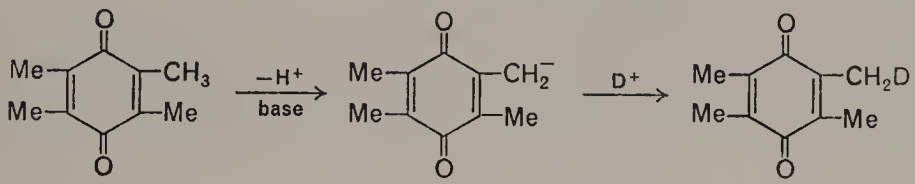
(114) **(115)**

(95)



(116) **(117)**

Formation of the intermediates **114** and **117** requires removal of a proton from the methyl group of the corresponding methyl quinones. Addition of deuterium to the methylene group of one of these intermediates should lead to the formation of methyl-labelled quinones. Experimental



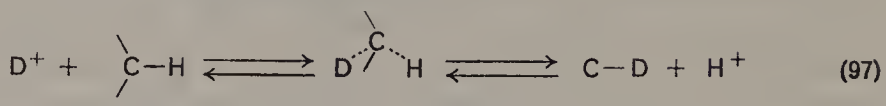
(96)

(118)

evidence[123] for such reaction schemes has been obtained in the case of duroquinone **118**, 2,3-dimethylnaphthoquinone and perhydrovitamin K, which were found to incorporate deuterium into C—H bonds when heated under reflux for several hours in dioxan–D_2O solutions with triethylamine or potassium carbonate as catalysts. Similar exchange reactions have been used for synthesis of tritium-labelled methyl quinones.

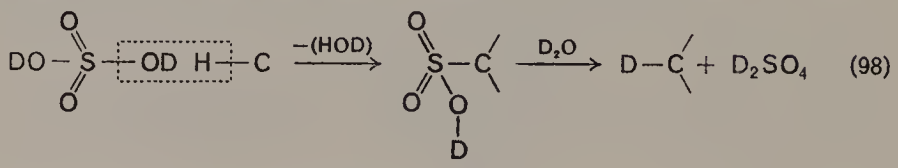
The multistep high-temperature exchange between concentrated deuterosulphuric acid, D_2SO_4, and 9,10-anthraquinone has been utilized for synthetic purposes; however, its kinetics and mechanism have not been studied in detail[126].

Exchange of ring hydrogens proceeds probably either through a bimolecular replacement mechanism (97):



(97)

or through sulphonation followed by desulphonation (98):

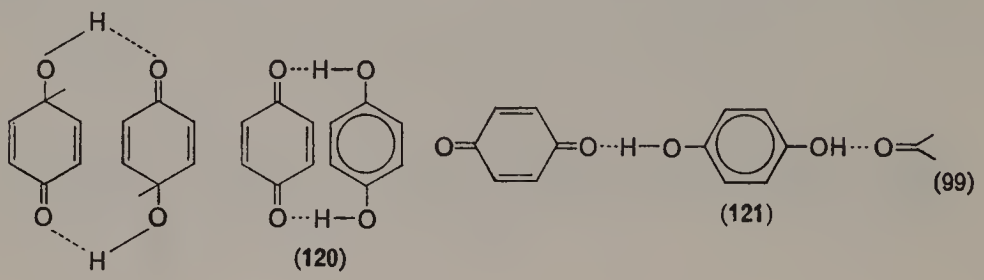


(98)

B. Quinone–Hydroquinone Exchange Reactions

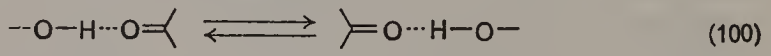
1. Hydrogen bonding in benzoquinhydrone[163, 164]

It was thought for some time that in the benzoquinhydrone complex the hydrogen bond binding the complex is symmetrical and that the two constituent molecules lose their identity through the formation of the symmetrical resonance hybrid **119**[90, 163]. Later it was found that in 'dimeric' structures such as **120**, or in long chains of the type **121**, the hydrogen is located closer to one of the oxygen atoms, but the potential energy curve may have two minima and hydrogen can jump from one



(119) (120) (121) (99)

minimum into another. In the latter case the transition (100) should be possible, and quinone nuclei are transformed into hydroquinone or *vice*



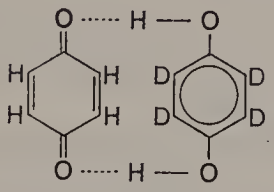
(100)

versa with a rate dependent on the potential barrier between the two minima. The final mixture should contain equal quantities of both indistinguishable forms. Gragerov and Miklukhin[119, 120] approached the problem of the hydrogen bond in the quinhydrone complex by studying the exchange between benzoquinone and hydroquinone-2,3,5,6-d_4 in the

labelled quinhydrone **122**. The authors found that there is no exchange between benzoquinone and the hydroquinone-2,3,5,6-d_4 nucleus in the

$C_6H_4O_2 \cdots C_6D_4(OH)_2$

(122)



(123)

solid quinhydrone complex kept at room temperature for 24 h or for 6 h at 70°C. Similarly, labelled quinhydrones **123** or quinhydrones with deuterium-labelled benzoquinone **124** when kept at 100°C for 3 h showed,

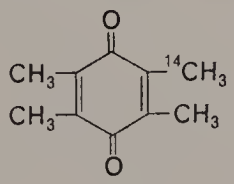
$C_6D_4O_2 \cdots C_6H_4(OH)_2$

(124)

after subsequent thermal decomposition *in vacuo* and separation by sublimation at 10^{-4} mm Hg into the two components, the retention of heavy hydrogen in the original positions. According to the authors, this shows that hydrogen is located in the quinhydrone complex near the oxygen of the hydroquinone moiety and that hence there is no nuclear deuterium exchange after the complex has been formed.

2. Exchange in duroquinhydrone

Bothner-By[90] investigated the problem of exchange in duroquinhydrone using tetramethyl-$^{14}C_1$-*p*-benzoquinone (**125**) or durohydroquinone-α-^{14}C as labelled molecules. The separation of the duroquinhydrone into its components after the exchange process has been completed was effected by thermal decomposition of the quinhydrone samples *in vacuo* and sublimation of the more volatile quinone at 90°C.



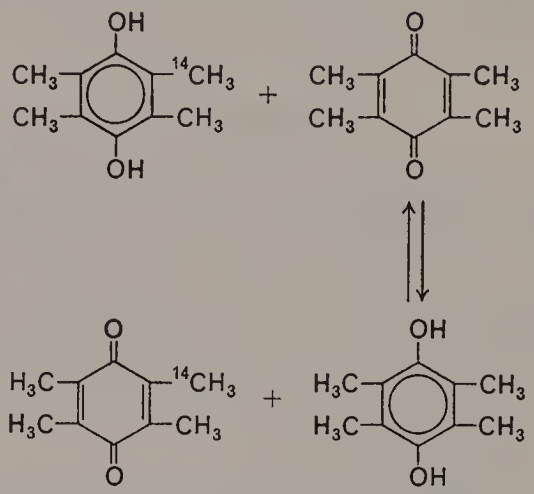
(125)

This author found that there is no detectable exchange of the total duroquinone moiety between duroquinone and durohydroquinone in the *solid* duroquinhydrone complex at 25°C during 24 hours but there is a rapid exchange between the quinone and the hydroquinone in *solution* prior to precipitation of the complex. The formulation of quinhydrones as

symmetrical resonance hybrids is incompatible with these experimental results and the earlier observations reported by Gragerov and Miklukhin are confirmed.

3. Duroquinone and durohydroquinone exchange in buffered methanol solution

A rapid electron and labile hydogen exchange reaction between duroquinone and durohydroquinone observed previously in the process of preparation of the quinhydrone complex has been studied quantitatively by Bothner-By at 25°C in methanol solution saturated with potassium biphthalate[91].



(101)

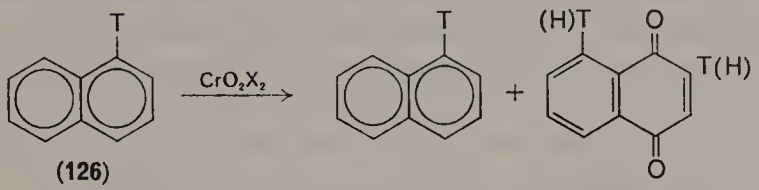
The exchange reaction (101) proceeds in methanol solution at a measurable rate with a half-life of the order of minutes. This solvent has been chosen because duroquinone can be partially extracted from it by means of pentane (after the addition of a few drops of water to cause immiscibility). The rate of the exchange reaction was found to be nearly independent of the quinone concentration and first-order with respect to the hydroquinone. The author has suggested that the exchange proceeds through the intermediate oxidation state, which is a 'semiquinone free radical' formed rapidly from duroquinone and doubly charged durohydroquinone anions. The proposed path of the exchange is represented in scheme (102), where H_2Q^* represents the radioactive durohydroquinone. Q represents inactive duroquinone, $^{\bullet}Q^-$ represents a semiquinone radical, etc. In the relatively acid solution the concentration of the doubly charged

$$H_2Q^* \rightleftharpoons HQ^{*-} + H^+$$
$$HQ^{*-} \overset{\text{slow}}{\rightleftharpoons} Q^{*2-} + H^+ \qquad (102)$$
$$Q^{*2-} + Q \rightleftharpoons \dot{Q}^{*-} + \dot{Q}^- \rightleftharpoons Q^* + Q^{2-}$$

anion would be extremely low, and its rate of formation may be assumed to be rate-controlling. Low initial concentrations of singly charged hydroquinone anions in the solution and the low second ionization constant for hydroquinones suppress the rate of the exchange reaction observed.

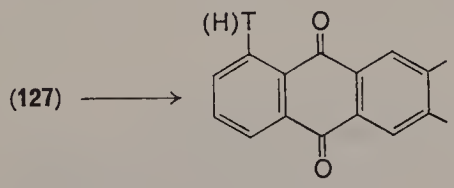
C. *Tritium Shift in the Oxidation of Naphthalene to 1,4-Napthoquinone with Chromyl Reagents*[165, 166]

Sharpless and Flood showed in a recent preliminary report[165] that the quinone **127**, obtained in the course of the partial oxidation of 1-^{3}H,1-^{14}C naphthalene (**126**) with chromyl acetate or chromyl chloride in CCl_4, contains tritium in the 2-position:



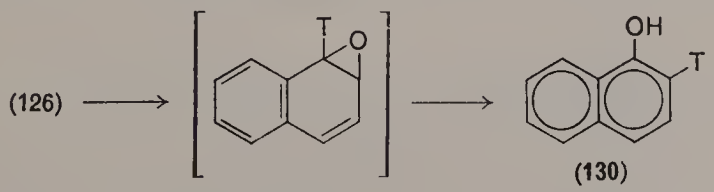
(126) (127) (103)

The location of the tritium has been determined by Diels–Alder reaction of the quinone **127** with 2,3-dimethylbutadiene, followed by air oxidation (reaction 104), when the hydrogen atoms bound to the 2- and 3-carbons of **127** are removed. The ratio of the total tritium radioactivity to the



(128) (104)

total ^{14}C radioactivity, ^{3}H/^{14}C, in the compound **128** was found to be 26–31% less than in the quinone **127**. In the absence of a tritium shift the ^{3}H/^{14}C ratio should be nearly the same in both **127** and **128** compounds. The authors have suggested that the migration of tritium proceeds through the intermediate of the epoxide type **129** without participation of a



(129) (130) (105)

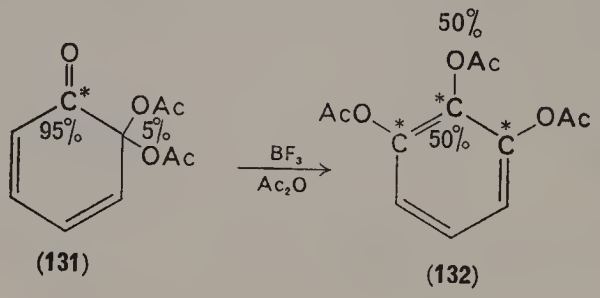
protonic exchange mechanism. They have found also that in the partial oxidative destruction of the naphthaquinone **127** by chromyl acetate (in CCl_4) the $^3H/^{14}C$ ratio in the unreacted quinone which was recovered decreased slightly (from 0·70 to 0·67).

D. ^{18}O Studies of the Oxidative Fission of Hydroquinone Ethers with Argentic Oxide

Silver(II) oxide (AgO) oxidizes selectively dimethyl ethers of naphtho- and benzohydroquinones in acidic media. *p*-Quinones are formed at room temperature in high yield. The reactions are accomplished most efficiently in dilute acidified aqueous dioxan solution[167]. When 2,3-dimethyl-1,4-dimethoxynaphthalene was oxidized with AgO in the presence of $H_2{}^{18}O$ and H_3PO_4, the product, 2,3-dimethyl-1,4-naphthoquinone, was found to be enriched with ^{18}O[167]. Carbon monoxide, obtained by the pyrolysis of the labelled naphthoquinone at 600°C, was only slightly less enriched with ^{18}O (1·65%) than the initial acidic water milieu which contained 1·70% of ^{18}O. A control experiment carried out with 2,3-dimethyl-1,4-naphthoquinone for 5 min in the same reaction conditions, including silver oxide, showed after isolation an unchanged content of ^{18}O (0·28%), close to the natural abundance[167,168]. Therefore it was assumed that the oxidative demethylation of hydroquinone ethers by AgO proceeds through *aryl–oxygen bond fission.*

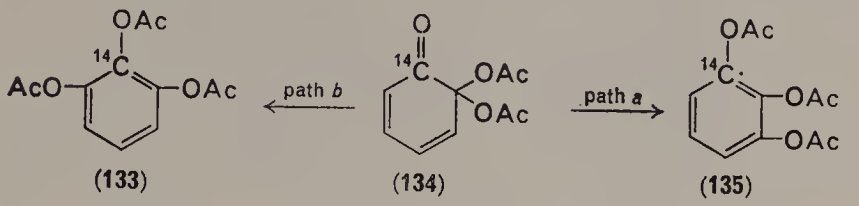
E. The Diketone–Phenol Rearrangement

The 2,2-diacetate of *o*-benzoquinone **131** undergoes in the presence of, for example, BF_3 in ether or in acetic acid anhydride the diketone–phenol rearrangement[117,169,170]. Localization of the ^{14}C activity in the resulting pyrogallol triacetate (**132**) revealed[117] that the C-1 and C-3 atoms together contain 50% of the labelled carbon while the remaining 50% of the activity was found at the C-2 carbon atom:



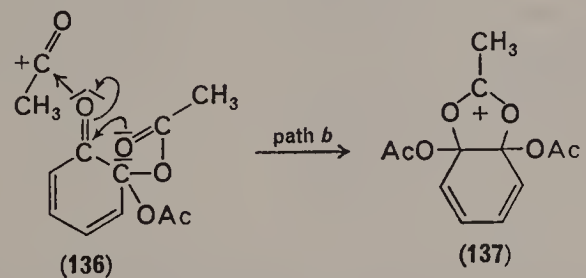
(131) (132) (106)

Thus, in the presence of BF_3 the rearrangement proceeds in two directions:

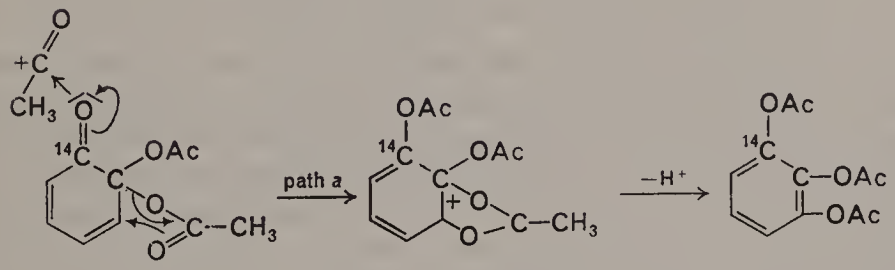


(133) (134) (135) (107)

It is suggested[117, 170] that the rearrangement is initiated by attack by arc acetylium cation $CH_2\overset{+}{C}O$ on the carbonyl oxygen and formation of positive charges at the ring carbons. In the next step, intramolecular migration of the acetyl group takes place through the formation of an 'acetate bridge'. Accepting the possibility of the formation of an intermediate acetoxonium-ion (**137**) it follows that the acetoxy group can migrate in both directions with equal probability[117].



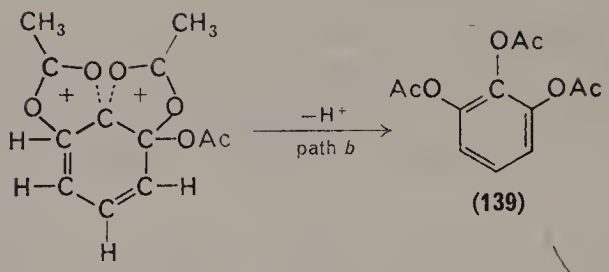
(136) (137) (108)



(109)

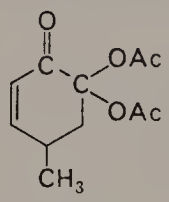
One can visualize also a reaction scheme in which attack by the $CH_3\overset{+}{C}O$ cation on the carbonyl oxygen leads to the transient species **138**, which then transforms into isotopic isomer **139** upon proton abstraction. Aromatization ends the migration process similarly as in the case of path *a*[117].

When $Ac_2{}^{18}O$ was used to convert 4-methyl-*o*-benzoquinone diacetate (**140**) and 5-methyl-*o*-benzoquinone diacetate (**141**) into 5-methylpyrogallol (**142**) in both cases one-third of the ^{18}O enrichment was found in the central hydroxyl group and two-thirds in the two peripheral hydroxyl groups[171]. In view of the absence of kinetic and tracer studies



(138) (139) (110)

concerning the inter- and intra-molecular acetoxy exchange in the reacting mixture and the preliminary state of the research itself[170,171], the interpretation of this distribution of the label in the pyrogallol triacetate obtained should be postponed.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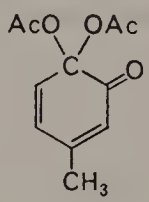
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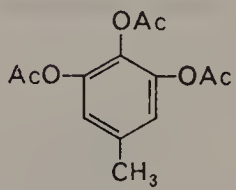
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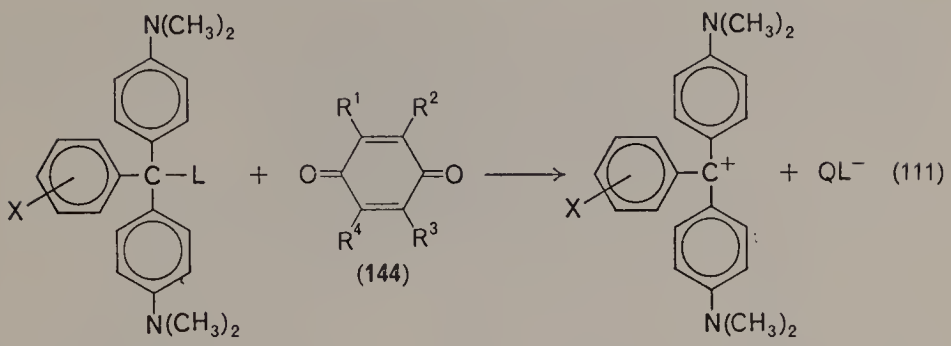
IV. ISOTOPE EFFECT STUDIES WITH QUINONES

So far isotope effect studies with quinones have been directed mainly towards the elucidation of the structure of the transition states of hydrogen transfer processes. The possibilities of the method are, however, much broader. For instance, ^{13}C-isotope effect studies of the mechanism of the catalytic reduction of quinones by carbon monoxide are currently being investigated by Russian groups[172–176]. Many other as yet untouched problems could be investigated using isotopic techniques. The results presented in this section are very promising and indicate that in spite of experimental difficulties the fundamental problems of quantum mechanics concerning the motion of hydrogen in the course of chemical changes can be treated by studying deuterium and tritium isotope effects.

A. *Isotope Effects in the Quinone Oxidation of Leuco-Triphenylmethane Dyes*

Lewis and his students[177–180] studied the oxidation of substituted leuco-malachite greens **143** by chloranil and other quinones **144**.



(143) (144) (145) (111)

The following substituents, both in **143** and **144**, have been investigated:

(1a) X = *p*-$N(CH_3)_2$, L = H or D
(1b) X = *o*-(OCH_3), L = H or D
(1c) X = *m*-Cl, L = H or D
(1d) X = H, L = H or D
(1e) X = *p*-NO_2, L = H

(2a) $R^1 = R^2 = R^3 = R^4 = Cl$
(2b) $R^1 = R^2 = R^3 = R^4 = Br$
(2c) $R^1 = R^2 = R^3 = R^4 = I$
(2d) $R^1 = R^2 = Br$, $R^3 = R^4 = Cl$
(2e) $R^1 = R^4 = Br$, $R^2 = R^3 = Cl$
(2f) $R^1 = R^3 = Br$, $R^2 = R^4 = Cl$
(2g) $R^1 = R^4 = Cl$, $R^3 = R^2 = F$
(2h) $R^1 = R^2 = Cl$, $R^3 = R^4 = CN$

The reaction was found to be first-order in each of the reagents[177], independent of acid concentration and, in the case of acetonitrile solvent, also independent of water or oxygen content. The authors have concluded that the oxidation by quinones takes place by a one-step hydride-transfer mechanism ('although the argument lacks rigour'). Only in the case of methanol solvent was the oxidation process complicated by the solvolysis of tetrachloro-*p*-benzoquinone.

Chloranil is quite stable in acetonitrile and the overall oxdiation rate follows second-order kinetics almost up to completion. When excess of chloranil was used the reaction was first-order. Some of the data characterizing the temperature-dependence of the deuterium isotope effect observed in the oxidation of the leuco-crystal violet (1a) by chloranil (2a) in methanol solvent are given in Table 1. The data obtained fit quite precisely the Arrhenius equation (112), but side-reactions introduced into the experiment result in a substituent-, isotope- and temperature-dependent error, so that the authors could draw no conclusions concerning the structure of the transition complex.

$$k_H/k_D = 0{\cdot}345\,[\exp(1933/RT)] \qquad (112)$$

The oxidation reaction was also investigated in acetonitrile, which is a better solvent than methanol (regarding both solubility and stability) of

TABLE 1. Deuterium isotope effects in the oxidation of 4,4′,4″-tris(dimethylamino)triphenylmethane (1a) by tetrachloro-*p*-benzoquinone (2a) in methanol

T (°C)	$k_H \times 10^2$ ($M^{-1} s^{-1}$)	k_H/k_D
2·7	9·68	11·3
14·7	19·8	9·9
29·9	43·2	8·2
44·7	89·5	7·1

all reagents and products. The effect of substituents on the rate constants in the oxidation of leuco-triphenylmethane dyes with chloranil (2a) and bromanil (2b) is shown in Table 2. Rate constants and deuterium isotope

TABLE 2. Rate of oxidation of substituted leuco-malachite greens by chloranil and bromanil in acetonitrile, at 25°C

X in compound **143**	Oxidant	k_H ($M^{-1} s^{-1}$)	k_H/k_D
H	Chloranil	$2·05 \times 10^{-2}$	11·4
H	Bromanil	$1·26 \times 10^{-2}$	—
o-OCH_3	Chloranil	$1·81 \times 10^{-2}$	11·9
o-OCH_3	Bromanil	$1·40 \times 10^{-2}$	12·7
m-Cl	Chloranil	$1·06 \times 10^{-2}$	11·8
p-$(CH_3)_2N$	Chloranil	$1·27 \times 10^{-1}$	11·4
p-$(CH_3)_2N$	Bromanil	$8·14 \times 10^{-2}$	13·4

effects in the oxidation of leuco-crystal violet (1a) with different substituted quinones at 25°C in acetonitrile are shown in Table 3. The first five reactions listed in Table 3 give experimentally satisfactory kinetic results while the other entries are less reliable because of side-reactions, too fast kinetics or other experimental difficulties. The value 6·96 obtained for the deuterium isotope effect in the oxidation of the leuco-dye with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (2h) was determined by two different methods which gave nearly coincident data. Partial oxidation (up to 68·2%) of a mixture of deuterated and undeuterated leuco-crystal violet with quinone and analysis of the residual leuco-dye for protium content by the kinetic method (using oxidation with excess of chloranil) resulted in the value $k_H/k_D = 6·99 \pm 0·07$. It should be noted that the competitive method should give good results even with fast reactions because both

deuterated and undeuterated compounds are reacting in exactly the same experimental conditions. The deuterium isotope effect in the same reaction was determined also by the chemical competitive method (see section

TABLE 3. Rates of oxidation of leuco-crystal violet (1a) with substituted quinones in acetonitrile, at 25°C

Substituted *p*-benzo and other quinones	k_H ($M^{-1} s^{-1}$)	k_H/k_D
Tetrachloro (2a)	$1{\cdot}27 \times 10^{-1}$	11·4
Tetrabromo (2b)	$8{\cdot}14 \times 10^{-2}$	13·4
2,3-Dibromo-5,6-dichloro (2d)	$9{\cdot}29 \times 10^{-2}$	11·8
2,5-Dibromo-3,6-dichloro (2f)	$8{\cdot}07 \times 10^{-2}$	11·8
2,6-Dibromo-3,5-dichloro (2e)	$8{\cdot}46 \times 10^{-2}$	12·0
2,5-Dichloro	1×10^{-2}	—
2,5-Dichloro-3,6-difluoro (2g)	$2{\cdot}1 \times 10^{-2}$	13·2 ± 2·5
Tetrachloro-*o*-benzoquinone	3·21	3·1
2,3-Dichloro-5,6-dicyano (2h)	10^5	6·96
$OCl_2H_2C_6—C_6H_2Cl_2O$ [181-2]	$7{\cdot}5 \times 10^{-1}$	9·8
$OBr_2H_2C_6—C_6H_2Br_2O$ [181-2]	3·23	12·9
Tetraiodo (2c)	$4{\cdot}4 \times 10^{-2}$	11·6

I.B.1). In the particular case under consideration, the comparison of the relative rates of the oxidation of two leuco-dyes, leuco-crystal violet (1a, L = H) and lecuo-4″-nitro malachite green (1e, L = H), on the one hand, and the deuterated analogue (1a, L = D) and the nitro compound (1e, L = H), on the other, yielded a value of k_H/k_D equal to 6·96, in agreement with the first set of experiments. The relative rates of reaction have been determined by a spectrophotometric method not requiring the direct analysis of the isotopic composition of the material used.

The data shown in Table 4 illustrate the temperature dependence of the separate constants as well as the temperature dependence of the

TABLE 4. Temperature dependence of the rate constant and of the deuterium isotope effect in the oxidation of leuco-crystal violet with chloranil

T (°C)	$k_H \times 10^2$ ($M^{-1} s^{-1}$)	$k_D \times 10^2$ ($M^{-1} s^{-1}$)	k_H/k_D
9·96	5·23 ± 0·22	0·380 ± 0·004	13·7
14·88	7·45 ± 0·02	0·515 ± 0·007	14·7
19·83	9·96 ± 0·37	0·738 ± 0·012	13·1
24·91	12·7 ± 0·4	1·08 ± 0·05	11·8
29·84	15·4 ± 0·3	1·40 ± 0·01	11·01
35·44	19·4 ± 0·7	1·96 ± 0·006	9·9

deuterium isotope effect in the oxidation of leuco-crystal violet (1a) by tetrachloroquinone in acetonitrile.

The results obtained in methanol solution presented in Table 1 show that the observed isotope effect is large, strongly temperature-dependent and indicates the existence of large tunnelling in the process studied. The quantitative interpretation of the data was not undertaken by the authors because of the relatively large spread of the experimental data, the temperature dependence of which was approximated by the linear relationship:

$$\log(k_H/k_D) = -0{\cdot}4622 + 0{\cdot}4226(10^3/T) \tag{113}$$

The data listed in Table 2 indicate that the solvent does not introduce drastic effects. The temperature dependence of the experimental rate constants of the oxidations of leuco-crystal violet in methanol and acetonitrile solvents are expressed correspondingly by the Arrhenius equations (114):

$$\left.\begin{aligned} k_H^{MeOH} &= 1{\cdot}8 \times 10^6 \exp(-9180/RT) \\ k_D^{MeOH} &= 5{\cdot}0 \times 10^6 \exp(-11080/RT) \\ k_H^{MeCN} &= 1{\cdot}2 \times 10^5 \exp(-8130/RT) \\ k_D^{MeCN} &= 2{\cdot}92 \times 10^6 \exp(-11520/RT) \end{aligned}\right\} \tag{114}$$

The temperature dependence of the observed deuterium isotope effect obeys (with the exception of the value at the lowest temperature) the Arrhenius equation (115) and suggests even larger tunnelling than in the

$$k_H/k_D = 0{\cdot}041\,[\exp(3390/RT)] \tag{115}$$

case of the oxidation carried out in methanol solution. The pre-exponential factor, $A_H/A_D = 0{\cdot}041$, is estimated with an experimental error of about 40%. Thus it has been demonstrated that experimental data in acetonitrile deviate strongly from the 'classically' allowed temperature dependence of the primary deuterium isotope effect (116) where $A_H/A_D \geqslant 0{\cdot}5$.

$$\log(k_H/k_D) = \log(0{\cdot}5) + \frac{1904}{2{\cdot}303}\Big/RT \tag{116}$$

The estimated low value of the pre-exponential factor, $A_H/A_D = 0{\cdot}0415$, is as small as in the fluoride-catalysed bromination of 2-carbethoxycyclopentanone[183]. The value $\log_{10} A_D^*/A_H^* = 1{\cdot}38 \pm 0{\cdot}07$, obtained by Bell and coworkers[183], corresponds to the ratio $A_H/A_D = 0{\cdot}0417$.

The existence of tunnelling in the chloranil oxidation of leuco-crystal violet was also documented[41] by Lewis and coworkers by determining the

tritium isotope effect in the oxidation of the tritium compound (1a; L = T) at 35·5°C and comparing the obtained value with the deuterium isotope effect at the same temperature. The tritium isotope effect, (k_H/k_T), equals $20{\cdot}4 \pm 1{\cdot}3$; the deuterium isotope effect, (k_H/k_D), equals 9·90 at this temperature. Equation (117), correlating the tritium and deuterium isotope effects, thus gives the value $r = 1{\cdot}31$, which deviates from the value $r_s = 1{\cdot}442$ in the direction expected for tunnelling. However, it is

$$(k_H/k_T) = (k_H/k_D)^r \tag{117}$$

frequently stated that the tunnel effect can be extensive without much deviation from the Swain equation (28). Lewis and coworkers[184] deduced from the rate and isotope effect data obtained in the studies of the oxidation of the leuco-triphenylmethane dyes the imaginary frequency $\nu_{iH}^{\neq} = 1080\text{–}1150\ \text{cm}^{-1}$ which corresponds to a correction of about 3 in the deuterium isotope effect. The authors assumed in the course of their calculations that $\nu_{iH}^{\neq} = (2)^{\frac{1}{2}} \cdot \nu_{iD}^{\neq}$. The ratio (Q_H/Q_D) calculated with Wigner's approximate first quantum correction (118) amounts at 0°C to

$$Q_H/Q_D \approx 1 + \tfrac{1}{24} h^2 \Delta(\nu^2)/(kT)^2 \tag{118}$$

the value $Q_H/Q_D = 1{\cdot}679$ if the frequency $\omega_H = 1080\ \text{cm}^{-1}$ is used. If this frequency, describing the potential energy barrier, is also used for the calculation of the shape of the one-dimensional truncated parabola with a height corresponding to $E = 8{\cdot}150$ kcal/mole then the formula (119), relating the imaginary frequency $\omega_i^{\neq}$ with the parameters of the inverted

$$\omega_{il} = (E_0^{\frac{1}{2}})/\pi a (2m)^{\frac{1}{2}} c \tag{119}$$

parabola, gives the width $2a = 0{\cdot}8087 \times 10^{-8}$ cm. The reaction barrier in the leuco-dye oxidation is therefore narrower than the barrier in the proton transfer reactions. This is so because in hydride transfer reactions the electron-deficient atom can approach the transferable hydrogen without electron repulsion (characteristic of nucleophilic substitution)[179].

The data presented in Table 3 show the relative insensitivity of the isotope effect to substitution in the leuco-dye, in agreement with the experimental and theoretical rules suggested by Swain[185] for hydride transfer reactions. Lewis noted nevertheless[184] a slight increase of the isotope effect on replacing the hydrogen in the *o*-position by an *o*-methoxy group and replacing the chloranil by bromanil, thus revealing a small steric influence on the deuterium isotope effect. The data presented in Table 3 indicate that the more powerful oxidizing agents react more rapidly and the results show smaller deuterium isotope effects. This is clearly seen in the case of oxidation with dichlorodicyanoquinone, for which the ratio $k_H/k_D = 6{\cdot}96$ was found. Faster rates of oxidation and

smaller deuterium isotope effects are caused by markedly reduced activation energies in the oxidation process. According to equation (21) of section I.A.2 the tunnel correction Q diminishes with reduction of the reaction potential barrier E_0.

Conclusions. The experimental deuterium and tritium isotope effects presented in this section show that the carbon–hydrogen bond is broken in the rate-determining step of the oxidation of triarylmethanes by quinones. The observed large isotope effects are consistent with the nearly symmetrical transition state in which the hydrogen is transferred about half the distance to the product[180] (although an alternative suggestion was presented by Lewis[179]). Faster oxidation reactions are accompanied by slightly smaller isotope effects. This can be explained in terms of increasing reagent-like character of the transition state resulting in a lower activation energy and, consequently, in smaller kinetic isotope effects.

The unusual behaviour of the low-temperature Arrhenius plot of the experimental deuterium isotope effects leading to differences in the activation energy of 3·35 kcal/mole and a very low ratio of the pre-exponential factor (0·041) can hardly be accounted for in terms of the usual absolute rate theory. The large value, 10–13, of the deuterium isotope effect and the unusually large differences in the activation energy would require one to consider all three frequencies in the initial state and their complete loss in the transition state of the oxidation reaction. But this extreme assumption about the change in bonding on passing from reactants to the transition state cannot explain the very low ratio of the Arrhenius pre-exponential factor $(A_H/A_D) = 0{\cdot}041$. Therefore it is necessary to reject the 'classical transition state' explanation and admit the existence of the large quantum-mechanical tunnelling in the oxidation of triarylmethanes. Assuming that the potential barrier separating substrates and products of the reaction has the form of a truncated two-dimensional parabola and using Bell's method one finds from the amount of tunnelling the barrier dimensions given by Perry[180] (Table 5).

TABLE 5. Barrier dimensions in the oxidation of leuco-crystal violet by chloranil

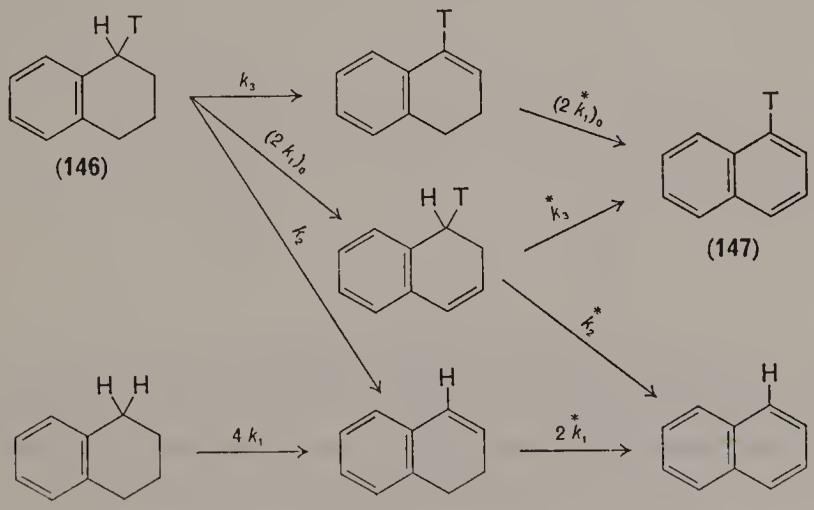
E_H (kcal/mole)	E_D (kcal/mole)	a (Å)	E_H^*/E_H	E_D^*/E_H
12·21	12·45	0·485	0·72	0·95

E_H^* and E_D^* are the observed Arrhenius (experimental) activation energies; E_H and E_D are the classical true potential barrier heights for hydrogen and deuterium.

Other observations, such as, for example, the tendency towards increasing the deuterium isotope effect with decrease in the rate constant, are also consistent with the presence of a large amount of tunnelling in the quinone oxidation reactions studied.

B. *Tritium Isotope Effects in the Oxidation of 1,2,3,4-Tetrahydro-1-^{3}H Naphthalene to 1-^{3}H Naphthalene by 2,3-Dichloro-5,6-Dicyano-Quinone (DDQ)*

Fast kinetics caused some difficulties in determination of the parameters characterizing the hydrogen isotope effects of deuterium and tritium in the course of the oxidation of the triphenylmethane dyes (reaction 111) with 2,3-dichloro-5,6-dicyanoquinone (2 h). An attempt was made recently[186] to determine the hydrogen isotope effect in the oxidation of tritium-labelled tetralin (1,2,3,4-tetrahydro-1-^{3}H-naphthalene, (**146**) and of 6-^{3}H-tetralin with DDQ at reflux temperature of the benzene solvent. The authors did not notice any measurable tritium isotope effect in the quinone oxidation of 6-^{3}H-tetralin to 2-^{3}H-naphthalene. Measuring tritium enrichment of the recovered starting tetralin in the course of its conversion to naphthalene, it has been found that the unlabelled tetralin molecules react 1·42–1·66 times faster than tetralin molecules labelled with tritium in the 1-position. The authors also found that 1,2-dihydro naphthalene with natural isotopic composition oxidizes with DDQ to naphthalene in refluxing benzene medium $2{\cdot}44 \pm 0{\cdot}11$ times faster than the 1,2-dihydro-1-^{3}H-naphthalene. It is suggested that the oxidation of tetralin to naphthalene proceeds according to the approximate reaction scheme (120) which takes into account the hydrogens in the 1- and 4-positions of the tetralin molecule. Besides the reactions presented in scheme (120) some side-processes also probably occur, since the authors did not

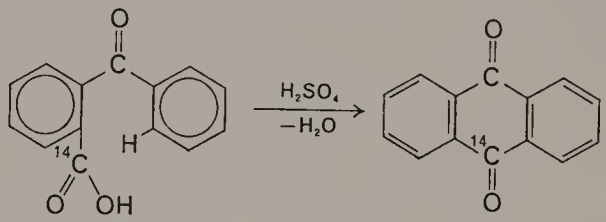


(120)

obtain the material balance in their experiments and total recovery was only about 80%. The lack of quantitative yields and the analytical difficulties introduce large uncertainties in the determination of the degree of conversion of the labelled tetralin into the intermediate dihydronaphthalene and into the final product, naphthalene. Moreover, the separation method used might itself also change the isotopic composition of labelled chemicals. The quantitative interpretation of the experimental results presented by the authors is therefore difficult. Nevertheless, some qualitative conclusions can be drawn. For instance, one obtains for the intramolecular tritium isotope effect, defined by the ratio of rate constants k_3/k_2 or k_3^*/k_2^*, the value 16·6 at 80°C, neglecting in the first approximation the departure of the values of the secondary isotope effects of tritium from unity. The deuterium isotope effect k_H/k_D calculated according to the Swain or Lewis relation should be about 8·54–7·02 at 80°C. This means that the rupture of the carbon–hydrogen bond takes place in the rate-determining step of the oxidation of tetralin with 2,3-dichloro-5,6-dicyanoquinone and that the hydrogen abstraction is accompanied by large tunnelling. The above qualitative conclusions should be confirmed by quantitative studies of the deuterium isotope effects in the quinone oxidation reactions of the tetralin labelled with deuterium in different positions.

C. ^{14}C Isotope Effect in the Condensation of o-Benzoylbenzoic Acid-Carboxyl-^{14}C to Anthraquinone-9-^{14}C

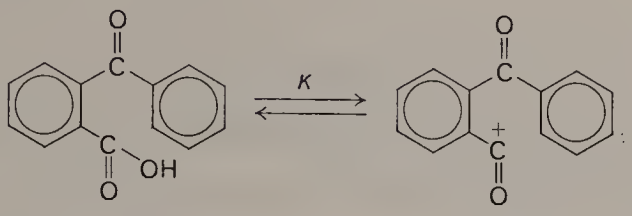
Ropp studied the ^{14}C isotope effect in the condensation of carboxyl-labelled *o*-benzoylbenzoic acid **148** to anthraquinone **149**[187]. The author



(148) (149) (121)

has found that at 80°C the experimental isotope effect, k_{12}/k_{14}, in reaction (121) is 1·03–1·04. This value is much smaller than the theoretical ^{14}C isotope effect in the $^{14}C—O$ bond rupture. Ropp explains the small value of the experimental ^{14}C isotope effect by suggesting that the condensation step leading to ring closure and formation of the new $^{14}C—^{12}C$ bond is

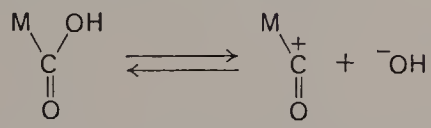
preceded by an equilibrium between the *o*-benzoylbenzoic acid and the corresponding acylium ion **150**:



(122)

(150)

The isotope effect on the equilibrium constant K of such a reaction can be calculated by considering the model (123):



(123)

Ropp makes the first step in the approximate theoretical treatment of equilibrium (123) by assuming that the isotopic equilibrium constant for ^{14}C in this process is equal to the ratio of the partition functions f_i corresponding to the isotopic C_i—OH bond, lost during the formation of the ionic structure **150**. Assuming a rather low frequency (850 cm^{-1}) for the C—OH bonds he finds that the K_{12}/K_{14} ratio equals 1·035 at 80°C in agreement with the reported experimental isotope effect. Ropp stated further that there are no (or only very small) isotope effects in the subsequent formation of the new C—C bond. The explanation presented by Ropp is very plausible but it is not a decisive one. Strict calculation in harmonic approximation gives at 80°C the value $1{\cdot}035_2$ for the ratio of the reduced partition functions of the isotopic ^{12}C—^{16}O and ^{14}C—^{16}O bonds. However, the experimental error with which the ^{14}C isotope effect has been determined is too large to be used for a quantitative test. A more complete theoretical approach to the problem would require one to consider also the four-centre coordinate of the reaction[188] which takes into account the simultaneous C—H and C—OH bond rupture and C—C and H—OH bond formations in the elimination of the water molecule.

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CHAPTER 13

Biological reactions of quinones

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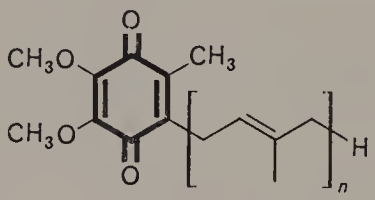
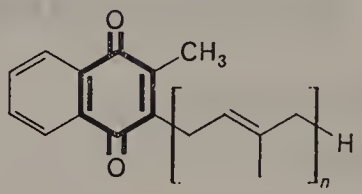
I. INTRODUCTION

Biologists are well acquainted with the meaning of the term 'quinone'. It connotes to them materials such as the ubiquinones, **1**, the menaquinones, **2**, alizarin, **3**, and diosquinone, **4**, which contain in their

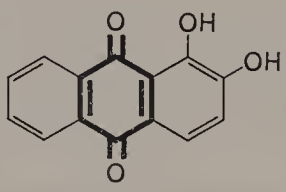
constitution either a 1,4-diketocyclohexa-2,5-dienoid moiety or a 1,2-diketocyclohexa-3,5-dienoid moiety (note emphasized portions of structures **1–4**). An excellent compendium of the structures and chemical properties of the naturally occurring substances of this type has been provided by Thomson[1].



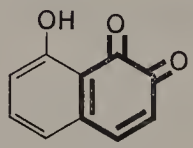
(**1**), $n = 0 \rightarrow 10$



(**2**), $n = 0 \rightarrow 12$



(**3**)



(**4**)

Less evident is the meaning of the term 'biological reaction'. Formally, an article on the 'biological reactions of quinones' would comprise a record of all the chemical transformations that could be wrought on each and every known quinonoid compound by any whole cell or cellularly derived system. Such a record would be enormously bulky, however, and would not necessarily increase our understanding of the fundamental biological significance of quinones. A more productive approach would be to focus only on those quinonoid materials which biological systems synthesize themselves, and then set out the functional roles these materials play *in the system that produces them*. Such will be the approach used in this chapter. We will start by reviewing the pathways used by cells to make quinonoid materials. Since this is an area wherein much is known and to which the present authors have contributed, it will be covered quite extensively. Thereafter, we will attempt to gather together what is known about the biological ends these syntheses serve. Apart from a few isolated areas, data on this topic are scant. Indeed, it is one of the goals of this chapter to stimulate biosynthetic chemists to think more teleologically. One final introductory comment—since we plan to consider only those situations in which the quinone is functionally involved in the cell that produces it, we will not be dealing with several important topics such as

menaquinones (vitamin K) and blood clotting, tocoquinone and ageing, the mode of action of the various quinonoid drugs, and microbial and insect controlling agents. Fortunately, the first two items have been the subject of recent reviews[2–4].

II. THE BIOSYNTHESIS OF QUINONES

Nature has devised a surprising number of biosynthetic routes to quinones. Chemists and biochemists have risen to the challenge of elucidating these pathways with great success. A limited number of typical examples of these achievements will be covered in this chapter. For the sake of classification, three major categories will be considered. The distribution of each pathway in nature will be summarized at the beginning of each heading or sub-heading.

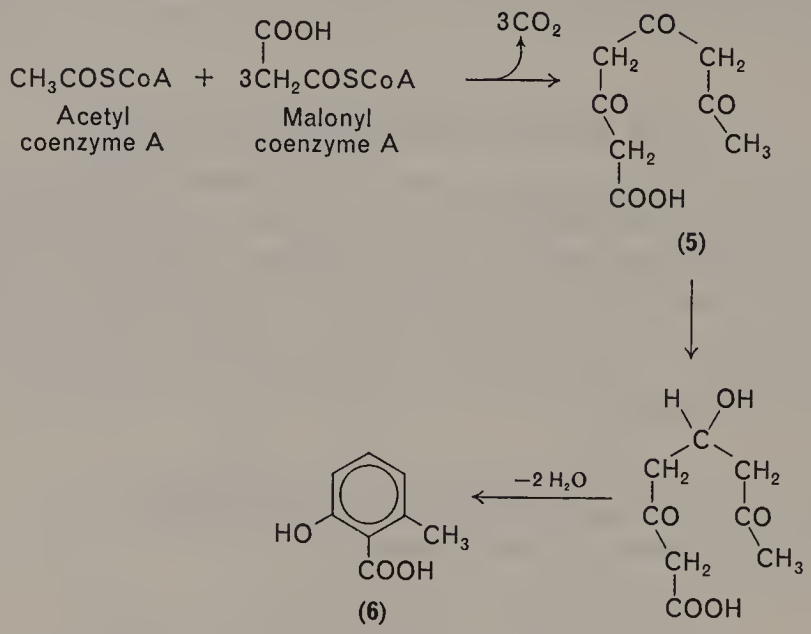
A. De Novo *Quinonoid Synthesis from Simple Aliphatic Acids ('Polymalonate' Condensations)*

Benzoquinones:	fungi, insects
Naphthoquinones:	fungi, plants, sea urchins
Anthraquinones:	fungi, plants
Miscellaneous:	fungi, *Streptomyces*

A well-explored pathway for the biosynthesis of aromatic compounds consists of the formation of a 'polyketomethylene' chain (e.g. **5**) which then undergoes cyclization and subsequent modification (for review, see references 5 and 6). Construction of the chain is usually initiated by a molecule of acetic acid, probably activated as its coenzyme A (CoA) derivative, which condenses in sequence with a number of molecules of malonic acid, again probably as the CoA derivative*. Each malonate molecule loses one CO_2. The prototypic reaction is the formation, from one acetate and three malonate units, of 6-methylsalicylic acid (**6**), a typical 'secondary metabolite' of fungi. This whole process is catalysed by a multi-enzyme system, 6-methylsalicylic acid synthase, which has

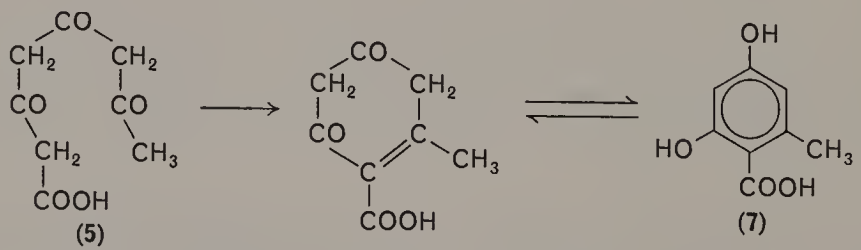
* The malonyl CoA is generally regarded as being derived through the action of acetyl CoA carboxylase: that is, the biotin-dependent carboxylation of acetyl CoA. However, in *Penicillium islandicum* (which also produces acetate-polymalonate-derived anthraquinones), the malonate moiety of the acidic polysaccharide, islandic acid (glucose : malonic acid, ca. 1 : 1), can be derived by oxidative α-decarboxylation of oxaloacetate[7]. It is not clear whether this 'alternate' route to malonate is generally employed for synthesis of the acetate-polymalonate products.

been extracted from *Penicillium patulum* in a stable form and has been studied in detail by Lynen and coworkers[8].



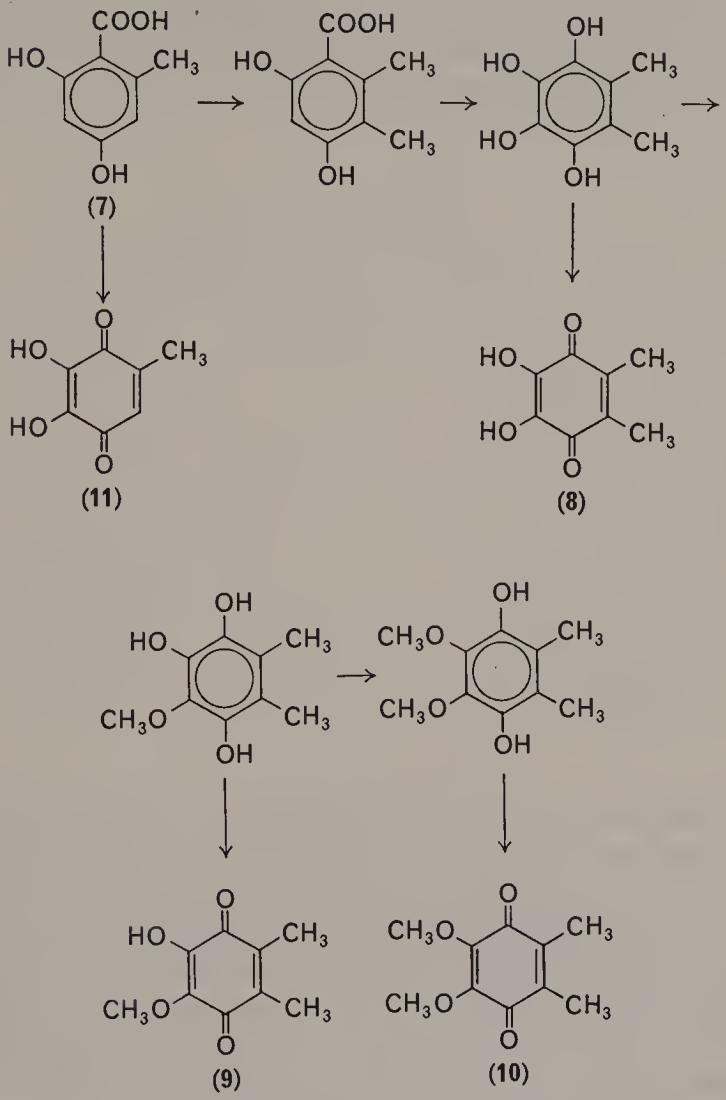
Assembly of aromatic compounds by this pathway does not take place in animals, but, to take the case of 6-methylsalicylic acid, this compound is formed by the 'acetate-polymalonate' pathway in a variety of fungi, in the bacterium *Mycobacterium phlei*[9], and in chloroplasts of dark-grown barley leaves[10].

If the polyketomethylene intermediate **5** does not undergo a reductive step, simple cyclization leads to orsellinic acid **7**, another commonly found mould secondary metabolite.



A frequently encountered feature of secondary metabolism and one that gives rise to many quinones is the modification of a basic skeleton by further biosynthetic manipulation. Thus, by methylation (in which *S*-adenosyl methionine serves as the methyl donor), hydroxylation and

oxidation, simple benzoquinones such as 2,3-dihydroxy-5,6-dimethyl-1,4-benzoquinone (**8**) and 2-hydroxy-3-methoxy-5,6-dimethyl-1,4-benzoquinone (**9**) and aurantiogliocladin (**10**) are produced from orsellinic

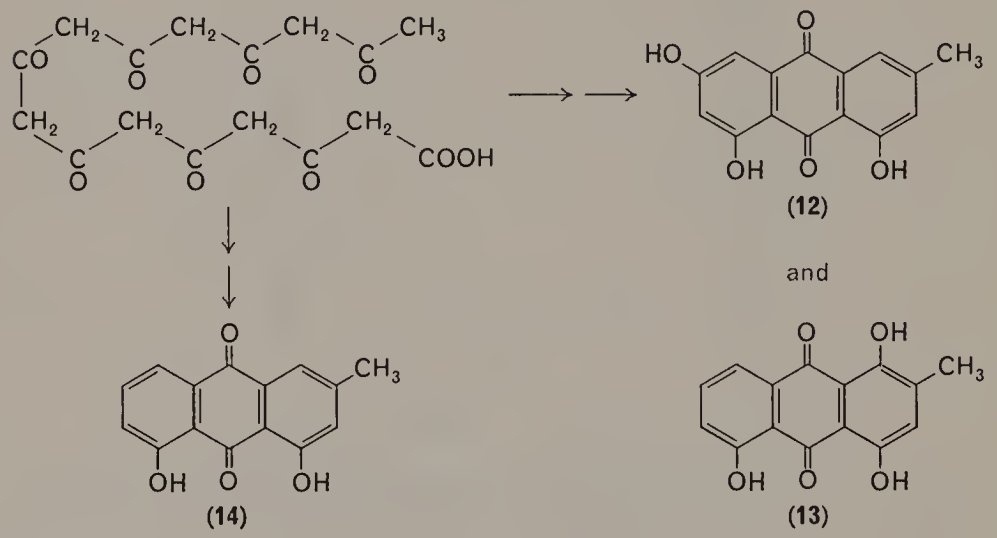


acid **7** by the fungus *Gliocladium roseum*[11,12]. 3,4-Dihydroxy-2,5-toluquinone (**11**) and its 3-methyl ether (fumigatin) are also examples of benzoquinones derived from orsellinic acid[11].

Cyclization of polyketomethylene chains and subsequent oxidation, etc., are not restricted to the formation of benzenoid compounds. In fact, some very early experiments substantiating the 'polyacetate' hypothesis*

* The need for malonate as the chain-extending unit was not recognized until 1961. Before that date the simple term 'polyacetate' was used.

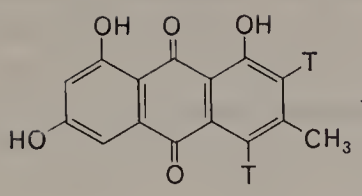
were concerned with anthraquinone biosynthesis*. Thus, in *Penicillium islandicum*, a chain of 16 carbons eventually gives rise to emodin **12**, its dimer skyrin, and islandicin **13**[14]. At some unknown stage the terminating carboxyl group is lost, hence these compounds contain only 15 carbons. This type of process also goes on in plants. Thus chrysophanol **14** and emodin **12** are acetate-polymalonate products of *Rumex alpinus*, *Rumex obtusifolius* and *Rhamnus frangula*[15–17].



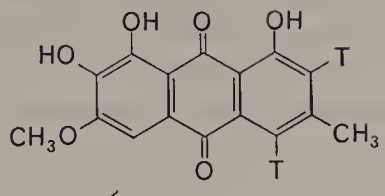
In an interesting study which sheds light on the decarboxylation reaction so frequently found in anthraquinone biosynthesis, Steglich[18,19] has used intact young sporophores of *Dermocybe sanguinea* to study the late stages of anthraquinone biosynthesis in this mushroom. The 6-mono-β-D-glucoside of emodin **15** labelled with tritium was well converted to dermoglaucin **16** and dermocybin **17** whereas endocrocin (**18**, ^{14}C-label) was converted to dermolutein **19** and dermorubin **20**. There was apparently no decarboxylation of endocrocin to the neutral compounds; thus decarboxylation may occur at a pre-aromatic stage.

Simple fungal naphthoquinones such as javanicin, **21**, are also derived from polyketomethylene compounds, the reduction of the terminal carboxyl to methyl being a unique feature in this case[20]. In plants, plumbagin **22** and 7-methyljuglone **23** arise from acetate[21] (presumably by

* Anthraquinones are often produced in very substantial amounts, e.g. the dry mycelium of *Helminthosporium gramineum* contained 30% of its weight of a mixture of polyhydroxyanthraquinones[13].



(15)
(as 6-β-glucoside)



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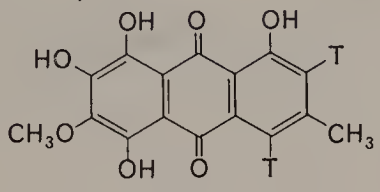

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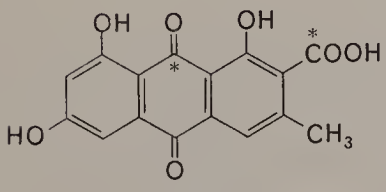

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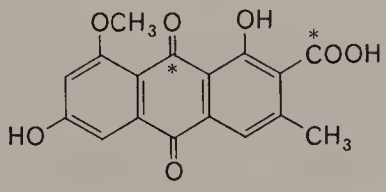

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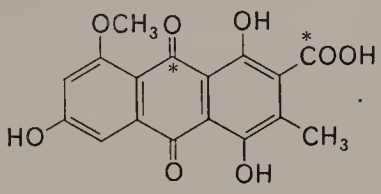
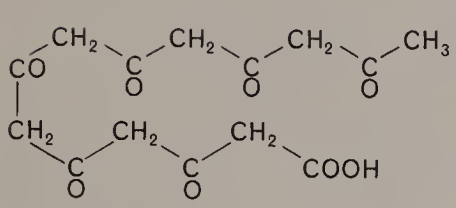
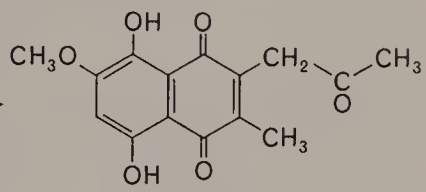


(20)

* = ^{14}C





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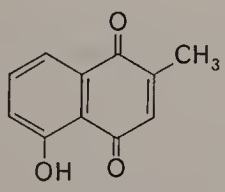

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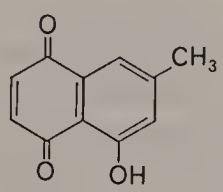
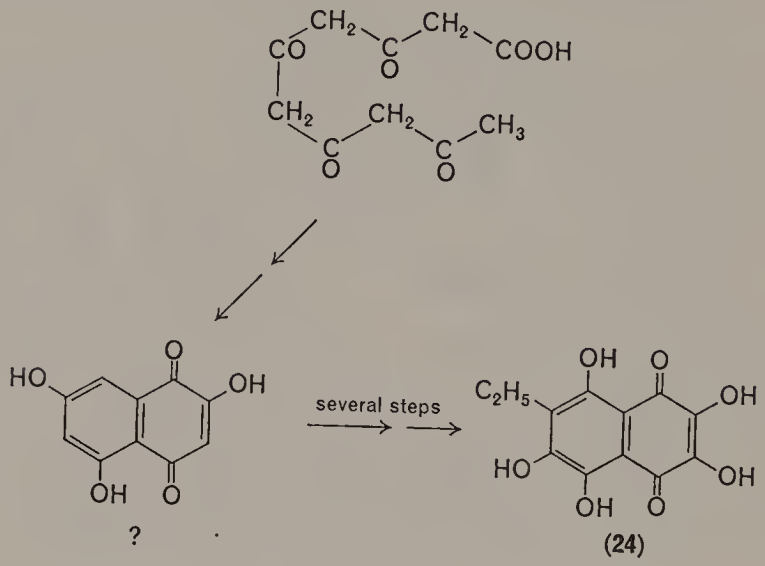
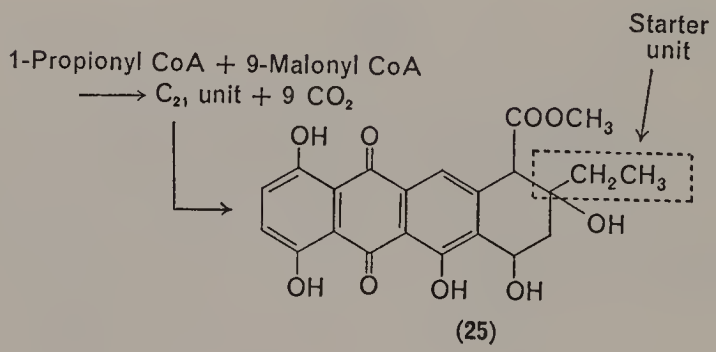


(23)

the acetate-polymalonate mechanism) and there is good evidence that echinochrome A, **24**, is derived in the sea urchin, *Arbacia pustulosa*, from a basic acetate skeleton[22].

A variation of this basic pathway is the use of 'starter' units other than acetate. For example, condensation of one propionyl and nine malonyl units gives rise to ε-pyrromycinone (**25**) in various Actinomycetes[23]. A

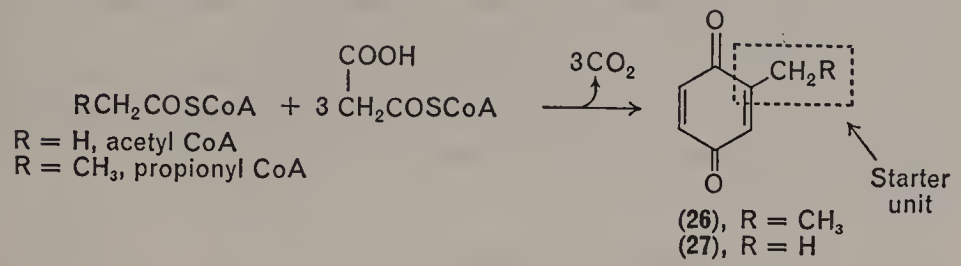




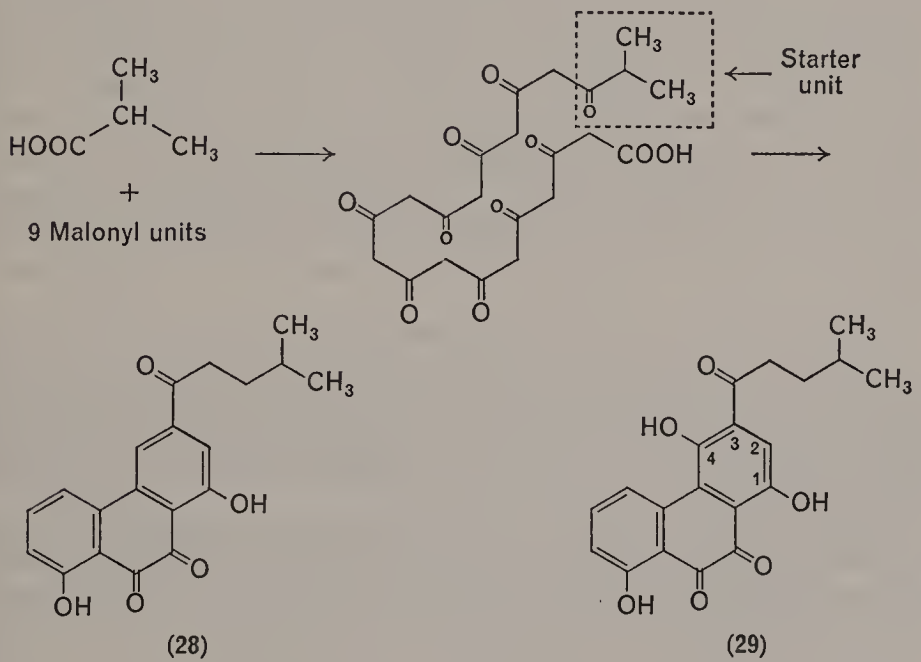
simpler case is the use of a propionate-polymalonate pathway in the biosynthesis of ethyl *p*-benzoquinone (**26**) in the defensive secretion of the beetle *Eleodes longicollis* (for more details, see p. 728). In this same secretion, methyl *p*-benzoquinone (**27**) is apparently derived by the acetate-polymalonate pathway, while, remarkably, benzoquinone itself is biosynthesized from the aromatic ring of tyrosine or phenylalanine[24] (see

section II.B.1 for details of this pathway)*. It is not clear whether symbiotic micro-organisms play a role in these syntheses.

In another case of quinone biosynthesis, this time an *ortho* system, isobutyrate apparently functions as the starter of a chain, extended



presumably by malonate units. The quinone is the *ortho*-phenanthrene-quinone, piloquinone (**28**), produced by *Streptomyces pilosus*. Valine also functions as a source of the branched starter unit[26, 27]. The accompanying 4-hydroxy-piloquinone (**29**) has the extra OH group in correct alignment for the proposed pathway.



* Also note the use of a propionate plus methylmalonate condensation in the biosynthesis of macrolide antibiotics[25].

B. *Quinones Derived from Aromatic and Pre-aromatic Cyclic Precursors*

Many quinones can be traced back to shikimic acid and hence finally to carbohydrate. Shikimate is the key compound for the biosynthesis of many aromatic compounds which are 'primary' metabolites (e.g. the amino acids, phenylalanine, tyrosine, tryptophan) and, in addition, serves as a precursor for many secondary metabolites.

There are several pathways to quinones, all of which diverge from shikimate. For ease of discussion, they will be identified by means of critical intermediates: *p*-hydroxybenzoate, homogentisate, *o*-succinylbenzoate and phenylpyruvate.

1. The role of *p*-hydroxybenzoate

Benzoquinones:	animals, plants, bacteria, fungi, insects, *Tetrahymena*
Naphthoquinones:	plants

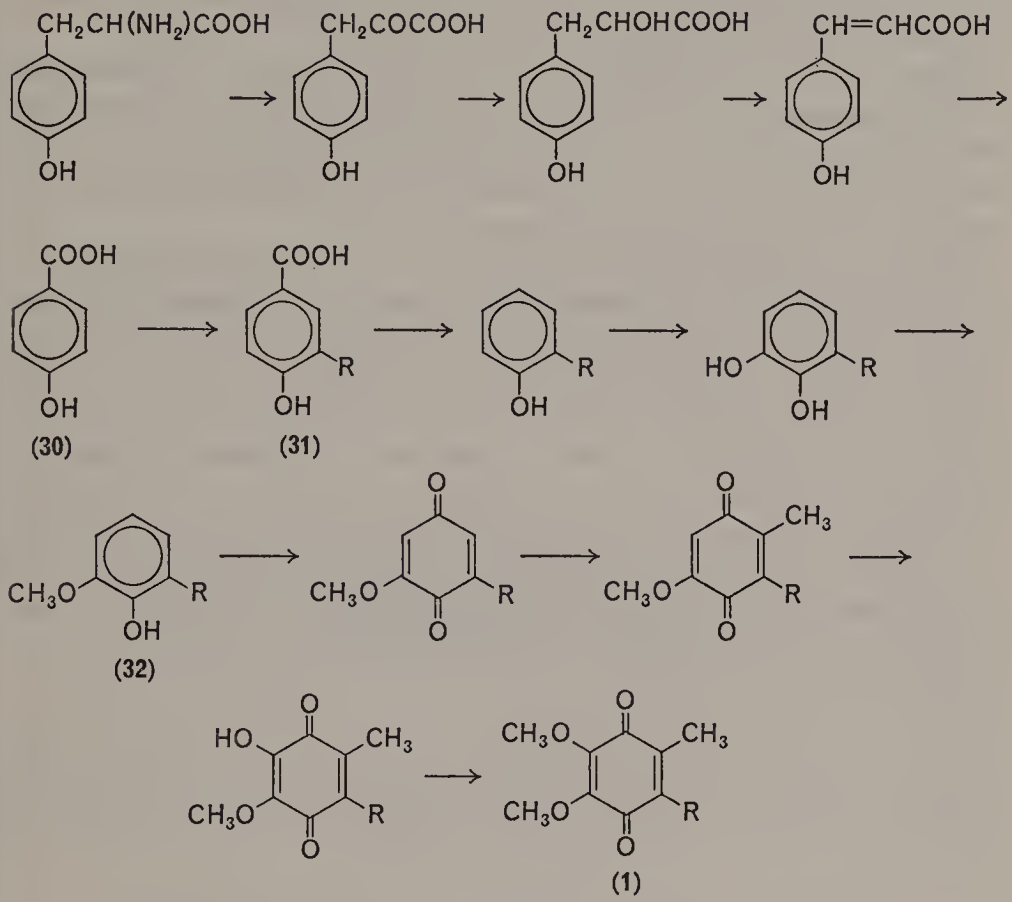
The discovery of ubiquinone **1** and related isoprenyl quinones and the elucidation of their biological function[28] stimulated considerable interest in the role of quinones in mammalian metabolism. Isoprenoid naphthoquinones had, of course, been investigated at a much earlier date in connexion with the menaquinone (vitamin K) problem. Despite the general structural resemblance of vitamin K and ubiquinone, it soon became apparent that ubiquinone was not a vitamin in mammals; unlike vitamin K, it could be biosynthesized by animal tissues*. Since animals do not have the capability for *de novo* synthesis of aromatic compounds†, it was logical to suspect a role for the 'essential' aromatic acids‡. Phenylalanine and tyrosine were shown to be precursors of ubiquinone in

* Several reviews have covered the subject of the biosynthesis of ubiquinone and other isoprenoid quinones[29–33]. Morton's classic text[33] covers much of the basic (pre-1965) material relating to the biologically active quinones and related compounds. For this reason, only early references of particular interest will be cited here. An effort will be made, however, to cover the most recent literature.

† They are unable to make shikimate or other hydro-aromatic derivatives to serve as precursors to the aromatics. On the other hand, hydro-aromatic compounds such as cyclohexanecarboxylate if added to the diet can be dehydrogenated (to benzoate in this case). The one exception to this statement is the ability to form by dehydrogenation (aromatization) of ring A of a steroid oestrogen.

‡ Since tyrosine, phenylalanine and tryptophan are important protein components and cannot be synthesized by the animal these amino acids have to be supplied in the diet as 'essential' components.

animals; however, only the ring-carbon atoms were used[34]. A similar situation was found for *p*-hydroxybenzoate (**30**)[35]. Our present understanding[36-40] of the pathway from phenylalanine and tyrosine through *p*-hydroxybenzoate is shown*. As would be expected from general



biosynthetic considerations the *O*- and *C*-methyl groups were found to be derived from the methyl group of methionine and the isoprene side-chain from mevalonate. In the course of the reactions from *p*-hydroxybenzoate the carboxyl group is lost and three other oxygen atoms are introduced onto the benzenoid nucleus. In the bacterium *Pseudomonas desmolytica* the oxygen atoms which carry the methyl groups are derived from oxygen gas[42].

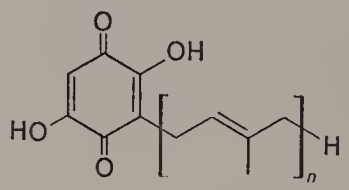
* Cyclohexanecarboxylic acid has been found to serve as a precursor of the quinone ring of ubiquinone in rat liver slices; this presumably involves dehydrogenation to benzoate which is also known to function as a ring precursor in the same way as *p*-hydroxybenzoate[41].

The pathway in animals is beginning to be clearly defined. Radioactivity from *p*-hydroxybenzoate is incorporated into 3-polyprenyl-4-hydroxybenzoate (**31**) in rat liver homogenates or slices[43]. In addition, 6-methoxy-2-nonaprenylphenol (**32**) has been well-characterized from neutral lipids of rat liver and when labelled with tritium was converted to ubiquinone by intact rats[44].

Olson and his colleagues have also completely characterized 5-demethoxyubiquinone-9 from rat liver slices, refuting a suggestion that their earlier reports were in error[45,46]. Although alternatives to the route shown above may exist, both in bacteria and animals, it appears to be generally correct in the major features.

While the *p*-hydroxybenzoate required as an ubiquinone precursor is derived from the essential amino acids in animals, it is generally assumed to arise directly from shikimic and chorismic acids in bacteria[47–49] and fungi[50]. Much of the bacterial work has centred on *Rhodospirillum rubrum*, a photosynthetic anaerobe which does not readily assimilate shikimate. However, this latter compound is efficiently utilized by *Escherichia coli* and, as will be seen later, radioactivity is incorporated into both ubiquinone and menaquinone.

It will be of interest to see whether this biosynthetic pathway is used in the formation of the recently discovered 2,5-dihydroxy-1,4-benzoquinones (**33a** and **b**) which have relatively short prenyl side-chains[51–52].

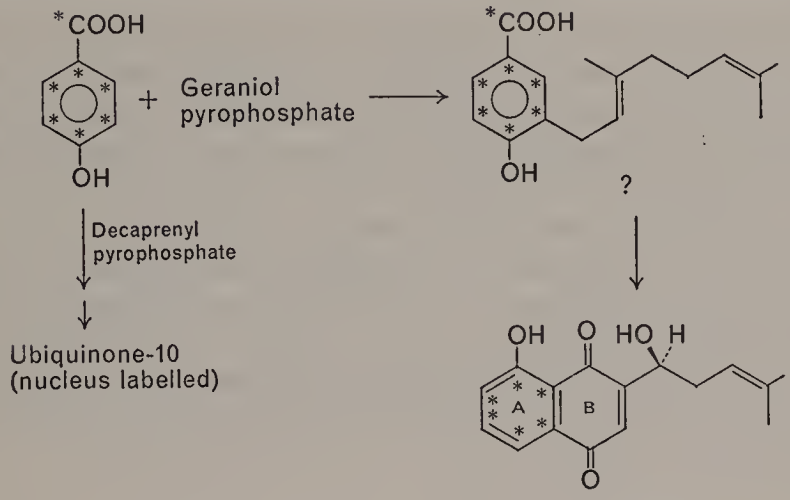


(33)

(**a**), $n = 3$, helveticone (fruiting bodies of *Chroogomphys helveticus*)
(**b**), $n = 4$, bovinone (fresh sporophores of *Boletus* [*Suillus*] *bovinus*)

Although the major biological role of *p*-hydroxybenzoate is presumably as a precursor to the ubiquinones, it also has a restricted role in the biosynthesis of the plant naphthoquinone, alkannin **34**. The side-chain of this material contains 6 carbon atoms rather than the 5 that would be expected from addition of mevalonate to a preformed naphthoquinone nucleus. However, it has been shown in *Plagiobothrys arizonicus* that the A-ring is derived from *p*-hydroxybenzoate, and *all* of the remaining carbons from 2 moles of mevalonate[53]. Possibly the *p*-hydroxybenzoate is first alkylated by a C-10 side-chain (i.e. by geraniol pyrophosphate), this

step then corresponding in essential detail to the ubiquinone biosynthetic pathway.

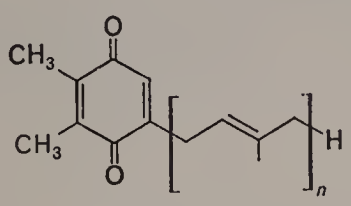


(34)

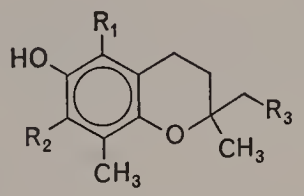
2. The role of homogentisate

Benzoquinones: plants
Naphthoquinones: plants

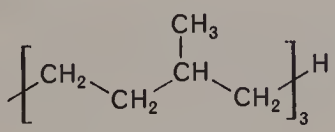
Kofler in 1946 isolated a quinone (Kofler's quinone) from alfalfa which was later rediscovered and named plastoquinone[54]. The plastoquinones are a group of 2,3-dimethyl-5-polyprenyl-1,4-benzoquinones (**35**) found in higher plants and algae. They share a common biosynthetic pathway with the tocopherols (**36a–39a**) and tocotrienols (**36b–39b**). Although

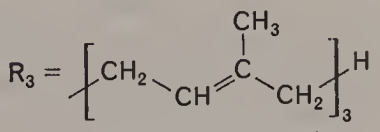


(**35**), $n = 4$



(**36**)–(**39**)

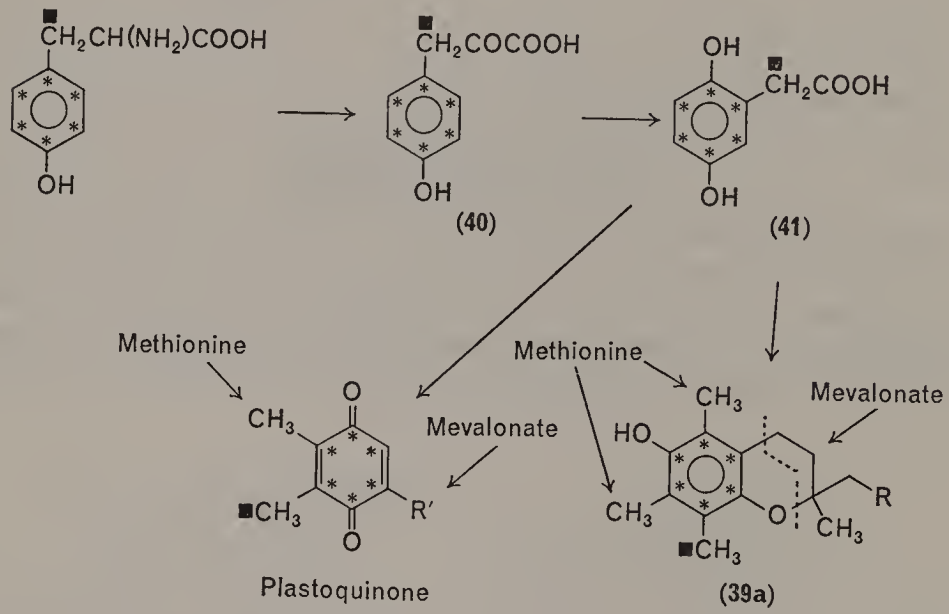
R_1	R_2	R_3 = 
(**36**), H	H	(**a**), δ-Tocopherol
(**37**), CH_3	H	(**a**), β-Tocopherol
(**38**), H	CH_3	(**a**), γ-Tocopherol
(**39**), CH_3	CH_3	(**a**), α-Tocopherol

R_3 = 

(**b**), δ-Tocotrienol
(**b**), β-Tocotrienol
(**b**), γ-Tocotrienol
(**b**), α-Tocotrienol

these latter materials are chromanols rather than quinones, they will be considered briefly here since they are probably derived from quinones.

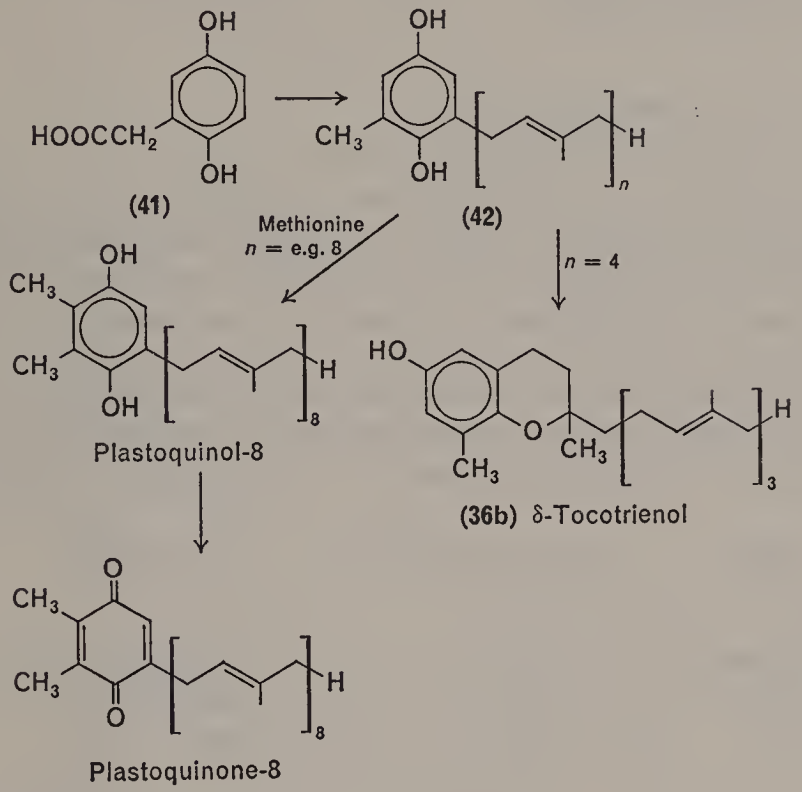
A key observation in the investigation of the biosynthesis of these two groups of compounds was the finding that one methyl group was derived from C-3 of the side-chain of tyrosine or phenylalanine[55]; a sharp contrast to ubiquinone biosynthesis where *all* of the side-chain carbons of tyrosine are lost. Furthermore, the benzenoid ring was derived from the ring system of either phenylalanine or tyrosine so that these amino acids contribute a C_6–C_1 fragment. Evidence that *p*-hydroxyphenylpyruvate **40** and homogentisate **41** are also involved has been obtained in a variety of plants[56]. The second methyl group of a plastoquinone and the second and/or third methyl of a tocopherol are derived from methionine[31]. Hence, the biosynthetic origins of these materials are, in outline, as follows*:



The exact sequence between homogentisate and the first intermediate with the methyl group (derived from the side-chain) is not known. The following materials, and their glucosides, are said not to be involved: gentisate, gentisaldehyde, gentisylalcohol and toluquinol[31]. The first step,

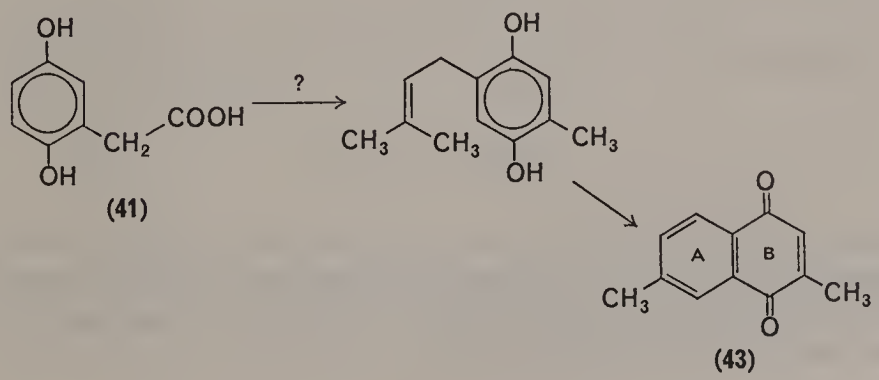
* The results summarized here for two labelling patterns were, of necessity, obtained in separate experiments.

therefore, may be sequential or concomitant prenylation and decarboxylation to form 3-polyprenyltoluquinols (**42**). Thus:



The chromanol (**36b**; δ-tocotrienol) may be regarded as the parent of both the tocotrienol and tocopherol series; alternate pathways are possible and for a more comprehensive discussion reference 31 should be consulted.

An apparently related pathway leads to the naphthoquinone, chimaphilin **43** in *Chimaphila umbellata*[57, 58]. In this case, the quinonoid ring and attached methyl arise from a C_6–C_1 unit derived from tyrosine, as discussed

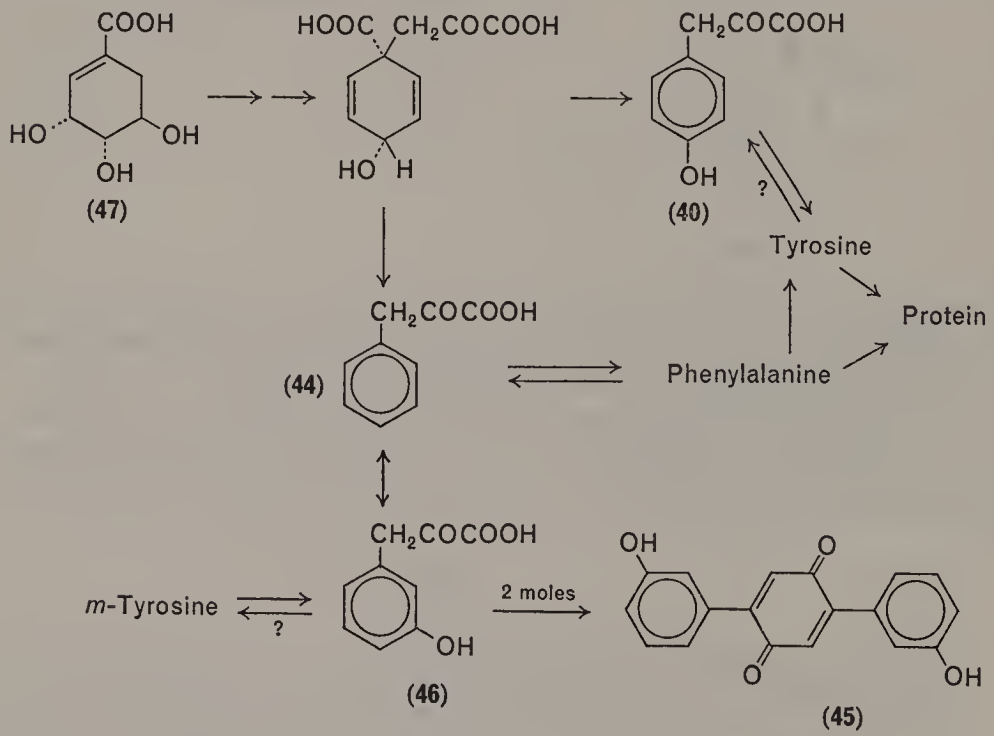


above, while the four atoms of the A-ring and the attached methyl originate in mevalonate. Note that in chimaphilin, the single prenyl unit must be added *para* to the CH_2COOH group, rather than *meta* as in plastoquinone biosynthesis.

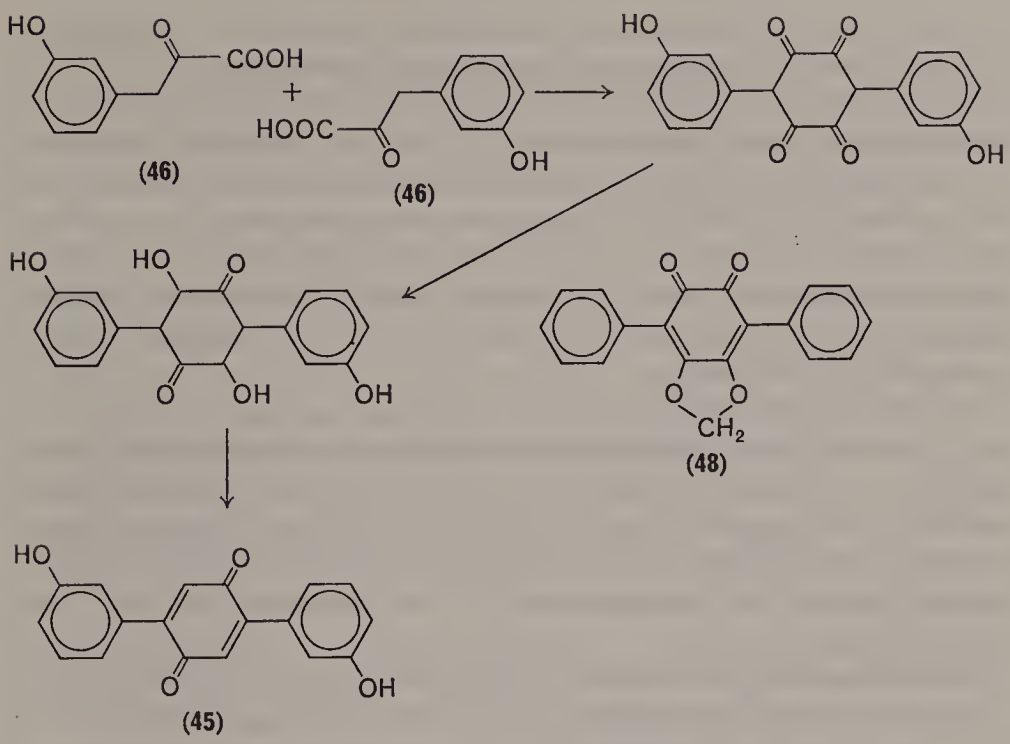
3. The role of phenylpyruvate

Terphenylquinones: fungi

Although *p*-hydroxyphenylpyruvate **40** is a precursor for homogentisate, as indicated in the previous section, some quinones are apparently formed directly from phenylpyruvate **44**. This is the case for the terphenylquinone, volucrisporin **45**, produced by cultures of the Imperfect Fungus, *Volucrispora aurantiaca*[59]. The results of feeding experiments with a variety of labelled precursors are consistent with the following biosynthetic map. An essential step in it is the hydroxylation reaction leading to the formation of *m*-hydroxyphenylpyruvate (**46**). The intermediate stages



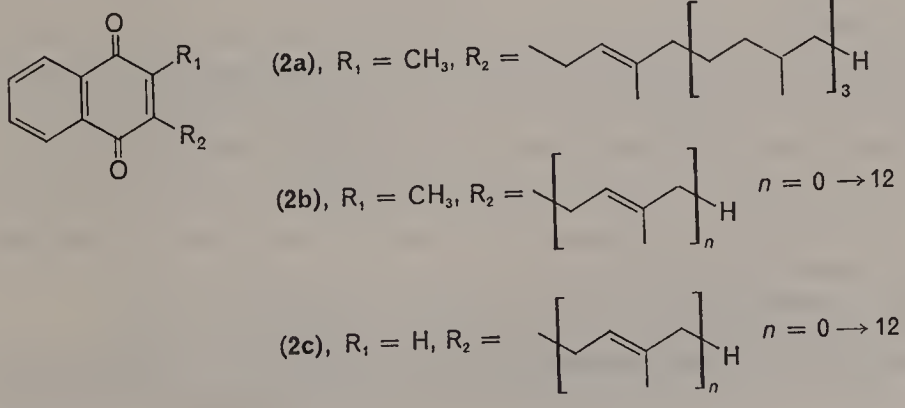
between *m*-hydroxyphenylpyruvate and the final product are not completely understood, but indirect evidence supports the scheme as shown. The related substance, phlebiarubrone **48**, is biosynthesized in a similar fashion from phenylalanine[60].



4. The role of succinylbenzoate in biosynthesis of naphthoquinones and anthraquinones

Naphthoquinones: bacteria, plants
Anthraquinones: plants

A novel pathway leading to naphthoquinones and anthraquinone biosynthesis has emerged as a result of interest in the biosynthesis of phylloquinone (**2a**, ≡vitamin K_1) and the menaquinones (**2b**, ≡vitamin K_2). The natural occurrence of, and structural variation possible in, these materials have been reviewed[1].

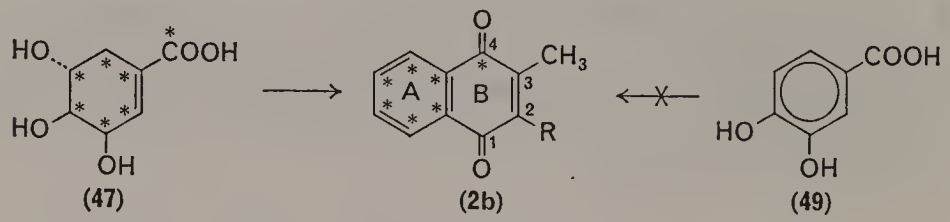


Three broad structural aspects have to be recognized in considering the biosynthesis of phylloquinone or a menaquinone type.

(i) *The methyl group at C-3.* The occurrence of desmethylmenaquinones (**2c**) suggested that these materials could act as substrates for methyl transferases. Direct evidence for the utilization of labelled methionine has been obtained for MK-9 * in *Bacteroides melaninogenicus* (= *Fusiformis nigrescens*)[61], for MK-9 (II-H_2) in *Mycobacterium phlei*[62] and *Mycobacterium smegmatis*[63], and for MK-8 in *E. coli*[64]. Furthermore, labelled DMK-9 has been converted to MK-9 (II-H_2) in a cell-free extract prepared from *M. phlei*[65].

(ii) *The isoprene side-chain at C-2.* With the realization of the prime role of mevalonate in the biosynthesis of isoprenoid compounds, it was logical to assume this material was the precursor for the side-chains of materials such as plastoquinone, ubiquinone, phylloquinone and menaquinone. The utilization of mevalonate for the production of the isoprenoid portions of phylloquinone[67,68] and menaquinone[69] has been demonstrated.

(iii) *The naphthalene nucleus.* Tentative evidence for a role of shikimate **47** in menaquinone biosynthesis in *E. coli* was obtained in 1964[70,71]. At that time, it was also suggested that protocatechuate **49** was involved. Independent work with *E. coli* and *M. phlei* confirmed the role of shikimate and provided unambiguous proof that all seven carbon atoms of this acid were incorporated[72,73]. No evidence has been obtained, however, to support a role for protocatechuate or its aldehyde in menaquinone



(47) (2b) (49)

biosynthesis[72–77]. The utilization of shikimate has also been studied in *Bacillus megaterium* with analogous results[74], and work in *M. phlei* with [1,2-^{14}C]- or [5-^{3}H]-shikimate shows that the ring junction of the naphthoquinone system originates from the ethylene carbons of shikimate, as shown previously[75,76]. In those bacteria such as *E. coli* which contain both

* In accordance with recommended practice[66], the following abbreviations will be used in this section:

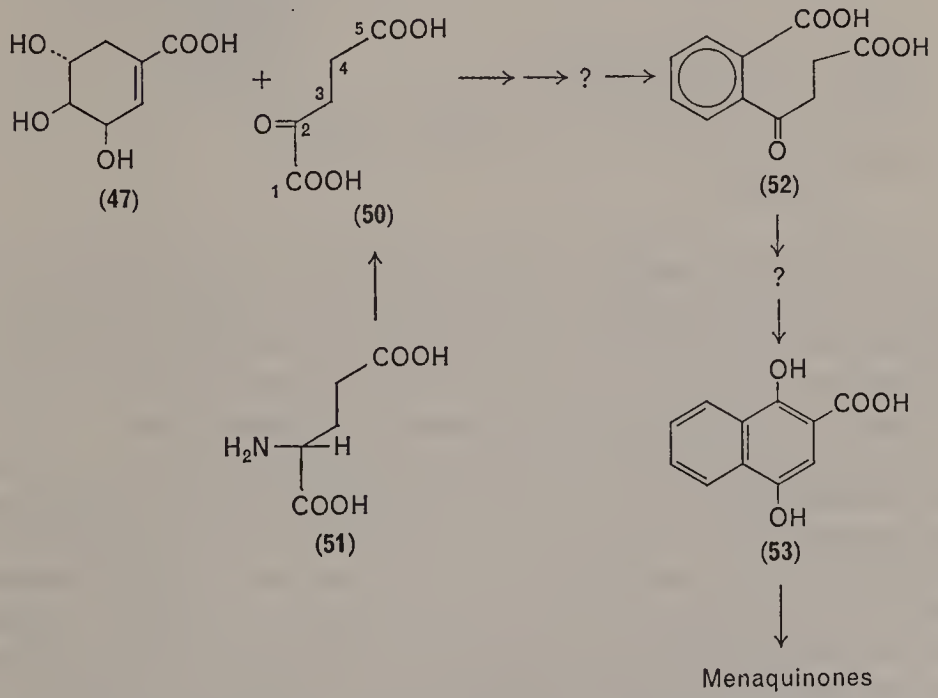
MK = menaquinone; DMK = desmethylmenaquinone at C-3.

MK-*n* = menaquinone with side-chain of *n*-prenyl units at C-2.

MK-*n* (II-H_2) = dihydromenaquinone with side-chain of *n*-prenyl units in which the second, counting from the nucleus, is saturated.

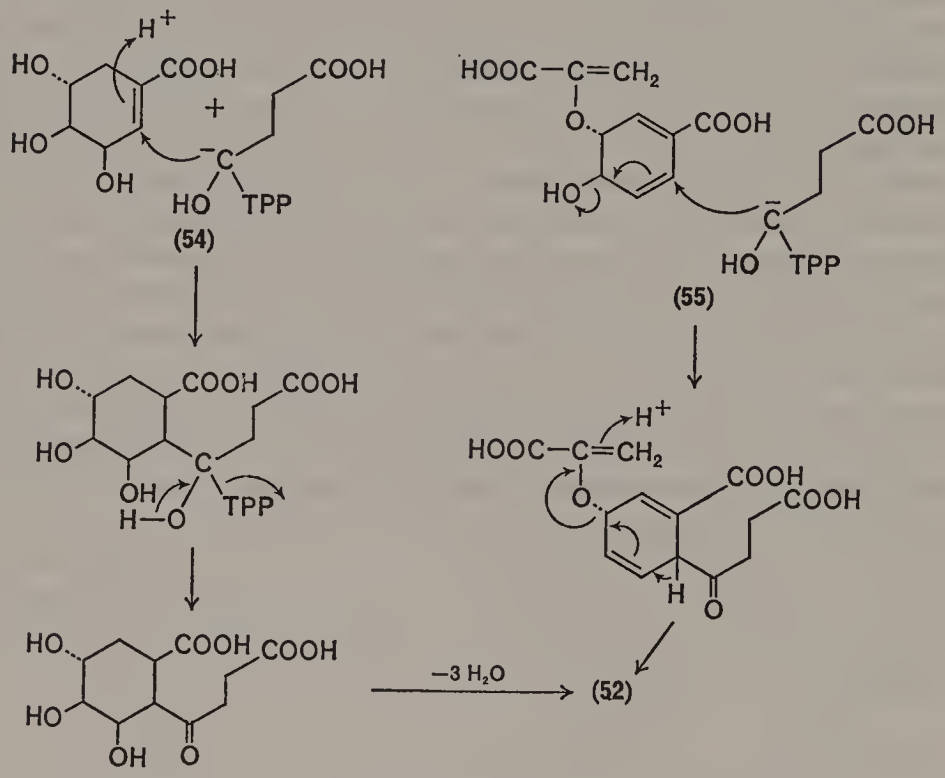
ubiquinone and menaquinone, administration of labelled shikimate leads to label incorporation into both types of compound.

To complete the menaquinone structure a precursor for the remaining three carbon atoms, C-1, C-2 and C-3, of the B-ring had to be discovered. After considerable effort, indirect evidence that the 'missing' three carbon atoms originate in 2-ketoglutarate (**50**) was obtained, both for lawsone biosynthesis in plants[78] (see later) and for menaquinone biosynthesis in bacteria[73,79]. This conclusion depended on tracer experiments with labelled glutamate, **51**, a substance which was presumed to undergo deamination to the keto compound. Thus, the general outline for biosynthesis of the naphthalene nucleus of menaquinones appears to involve a novel condensation of shikimate and 2-ketoglutarate. At some stage both the carboxyl groups of the ketoglutarate component are lost, leaving behind the original C-2, C-3 and C-4 of 2-ketoglutarate. Furthermore, succinylbenzoate (4-[2′-carboxyphenyl]-4-oxobutyrate) (**52**) has been shown to function as a menaquinone precursor in bacteria[73,80]. It seems likely that this oxobutyrate derivative could undergo a cyclization to 2-carboxy-1,4-naphthoquinol (**53**) as indicated below; compound **53** would then be decarboxylated, prenylated, methylated and oxidized to give the final menaquinone.



In the mechanism of decarboxylative coupling of the shikimate/ketoglutarate moieties originally postulated, 2-ketoglutarate is first converted

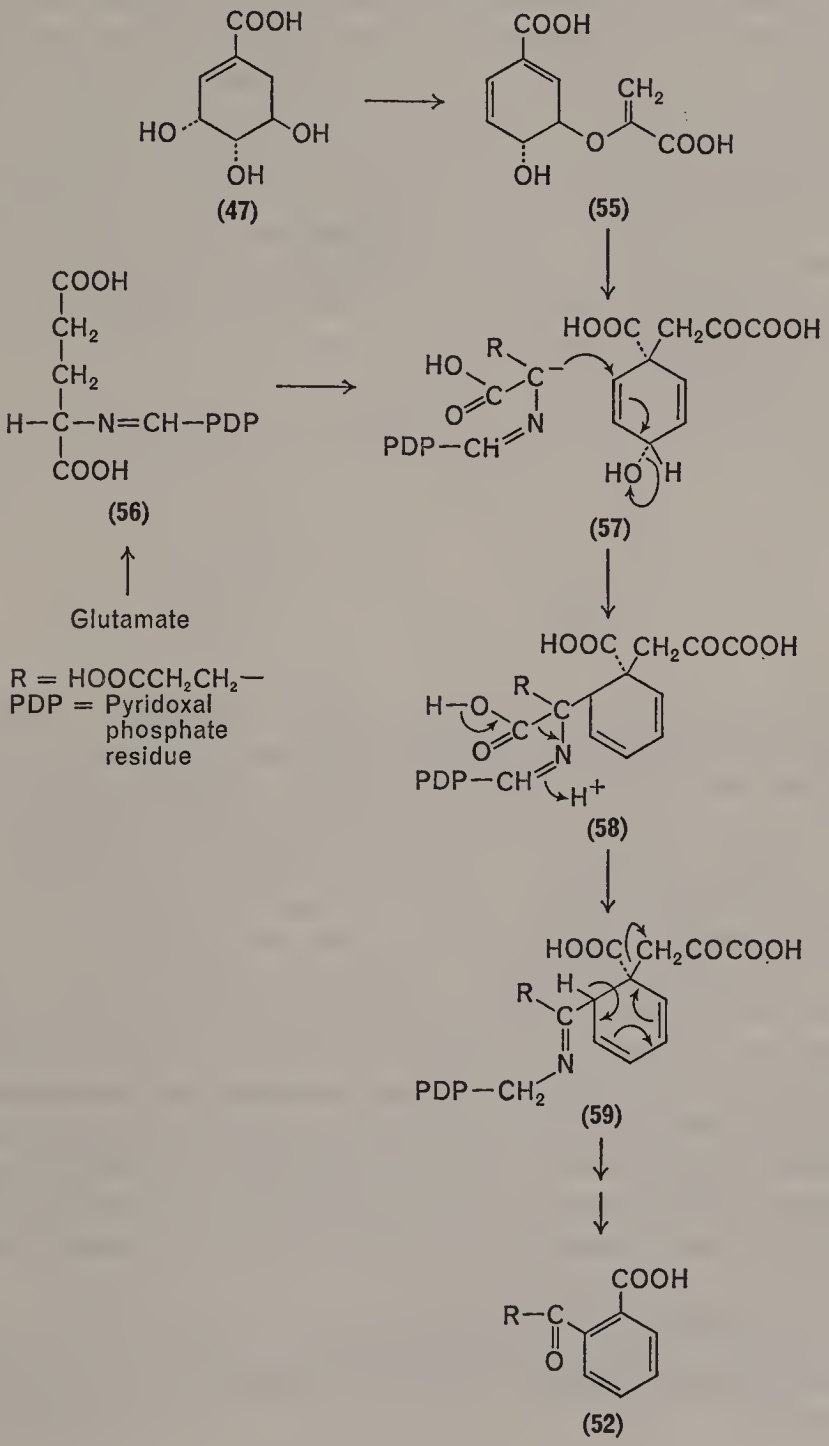
to the thiamin pyrophosphate (TPP) complex of succinic semialdehyde **54** exactly as in the initial reaction of the 2-ketoglutarate dehydrogenase system[73, 78, 79]. The addition of this material to shikimate would then be analogous to the Michael reaction. The French group, on the other hand, suggest[80] that the TPP anion is added to chorismate **55**.



An alternative coupling mechanism (**47** → **55** → **56** + **57** → **58** → **59** → **52**) wherein the anion of the pyridoxal pyrophosphate complex of *glutamate* **56** adds to prephenate **57** has recently been considered[81]. It was evoked to explain the fact that in the lawsone biosynthetic system (see later) glutamate is more efficiently incorporated than ketoglutarate.

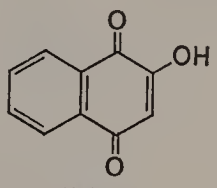
Another controversial matter concerns the possible role of 1-naphthol as a menaquinone precursor. It has been claimed that this material was incorporated into the menaquinone components of *Bacillus megaterium*[74], and *Staphylococcus aureus*[69]. We have not been able to repeat the result with *B. megaterium* and have also failed to incorporate labelled 1-naphthol into the menaquinones of *E. coli* and *M. phlei*[73]. The French group found no incorporation of [1-^{14}C]-1-naphthol in *B. megaterium*, *M. phlei* and three other bacteria, but it was incorporated by a mutant strain of *Aerobacter aerogenes*[75]. This latter strain appears anomalous since it also

incorporates 2-methyl-1,4-naphthoquinone and 1,4-naphthoquinone itself, in contrast to *M. phlei* and *E. coli*[73]. Other workers have similarly failed with a variety of microorganisms (including *B. megaterium*) and plants[82].



Mechanistically, 1-naphthol is not at the correct oxidation level to be involved in the hypothetical scheme, and in our view it is not to be regarded as a direct menaquinone precursor. Furthermore, the oxygen atoms of the quinone functions of *M. phlei* menaquinone are derived from water rather than oxygen gas[83]. If 1-naphthol were an intermediate, the introduction of the second oxygen would, of necessity, be by an aromatic hydroxylation. Since these reactions require molecular oxygen, a role for 1-naphthol is inconsistent with the origin of the oxygen atoms from water.

The shikimate pathway is involved in the biosynthesis of phylloquinone in plants[84], but evidence for the role of ketoglutarate or glutamate has not yet been reported. The simple plant naphthoquinones, lawsone **60** and juglone **61**, are also biosynthesized by this route. Indeed, as mentioned above, much of its detail has been worked out using the lawsone- and juglone-producing systems as models.



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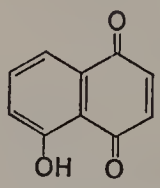
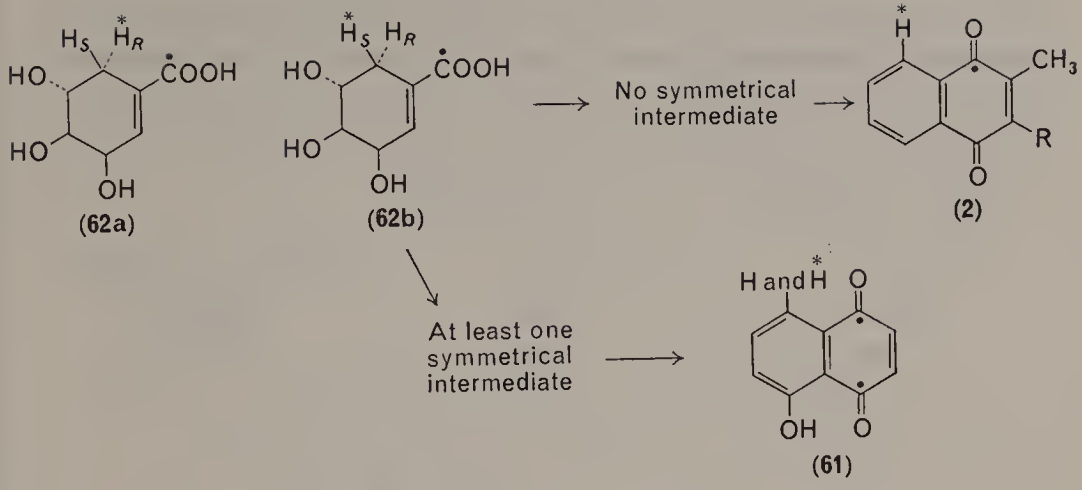


(61)

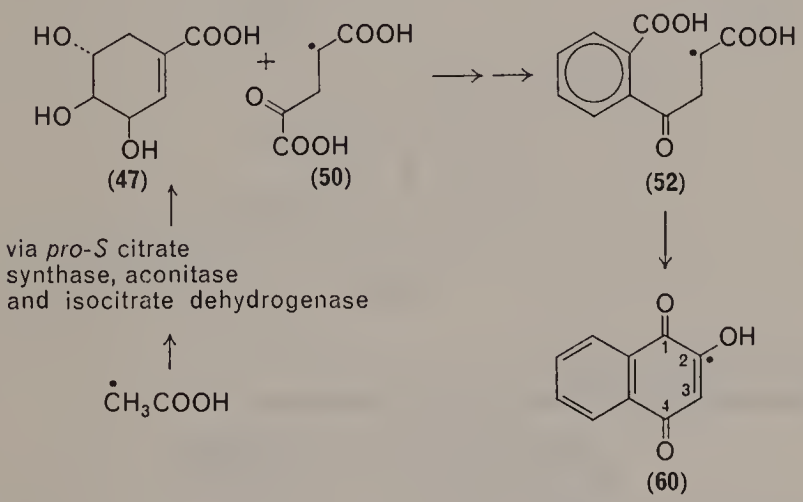
Although the precise structures of the intermediates between the succinylbenzoate **52** and the various products have not yet been determined, some information on their symmetry is available. Thus the stereochemistry of hydrogen elimination from the prochiral C-6 position of shikimate has been studied for juglone biosynthesis in *Juglans regia* and MK-7 biosynthesis in *Bacillus megaterium*[85]. In both cases, using (6*R*)-[7-^{14}C, 6-^{3}H]-shikimate (**62a**) the naphthoquinone contained no tritium. Hence, the *pro*-6*R* hydrogen is eliminated*. Using the corresponding 6*S* tritium-labelled material (**62b**) most of the isotope was retained during MK-7 biosynthesis, but only about half of the tritium in juglone biosynthesis†. From these data, it was concluded that no symmetrical intermediate was involved in menaquinone biosynthesis, but one was in juglone biosynthesis. Using a somewhat different approach, the problem has been examined in the lawsone-producing system[89]. 2-^{14}C-Acetate, fed to *Impatiens balsamina*, was found to label C-2 predominantly: a situation

* For nomenclature, see reference 86.

† It should be noted that this observation is compatible with a role for chorismate since retention of the *pro*-6*S* hydrogen also occurs in its formation[87, 88].



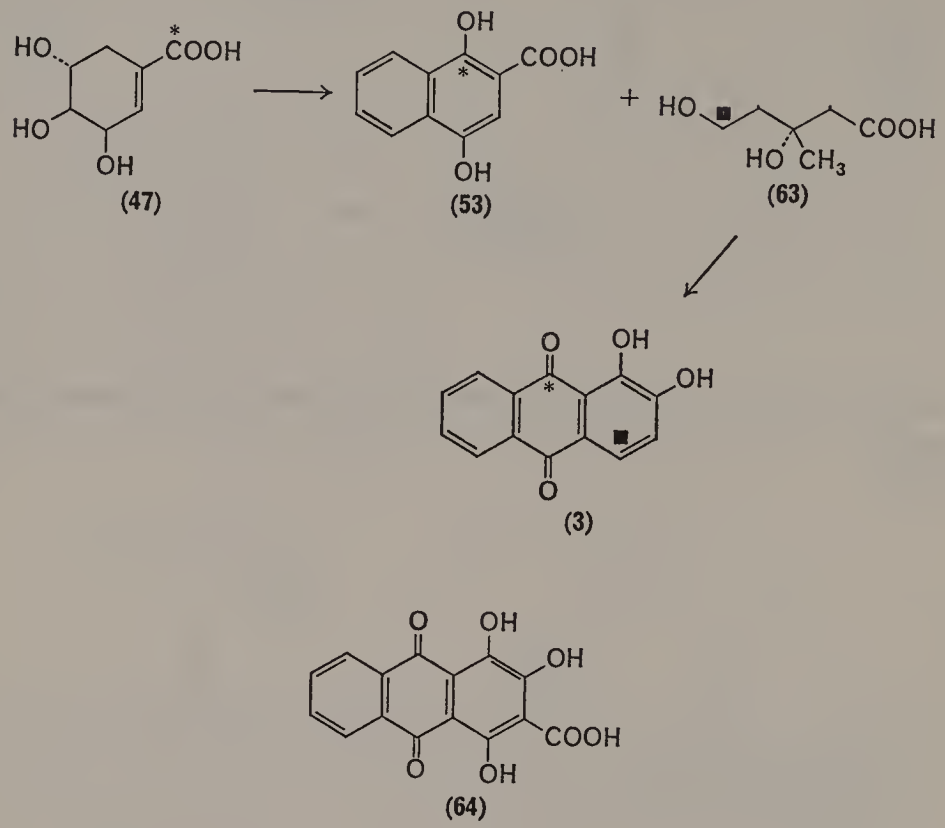
which can only occur if no symmetrical intermediates are involved. The pathway of the methyl group of acetate into C-2 of lawsone is shown below*.



A further interesting development has been the finding that some plant anthraquinones are derived by an extension of this pathway. Thus, carboxyl-labelled shikimate **47** and [5-^{14}C]-mevalonate **63** were incorporated specifically into alizarin **3** [76, 90–92]. The biosynthetic sequence shown below explains the observed labelling pattern. Label from the carboxyl group of shikimate was not randomized between the two carbonyl functions, consistent with involvement of non-symmetrical intermediates.

* This finding also indicates that C-1 of lawsone derives from the carboxyl group of shikimate.

The succinylbenzoate **52** is known to be an intermediate in the biosynthesis of pseudopurpurin **64** in plants[80]; it also yields anthraquinones in tissue cultures of *Rubria* species[93].



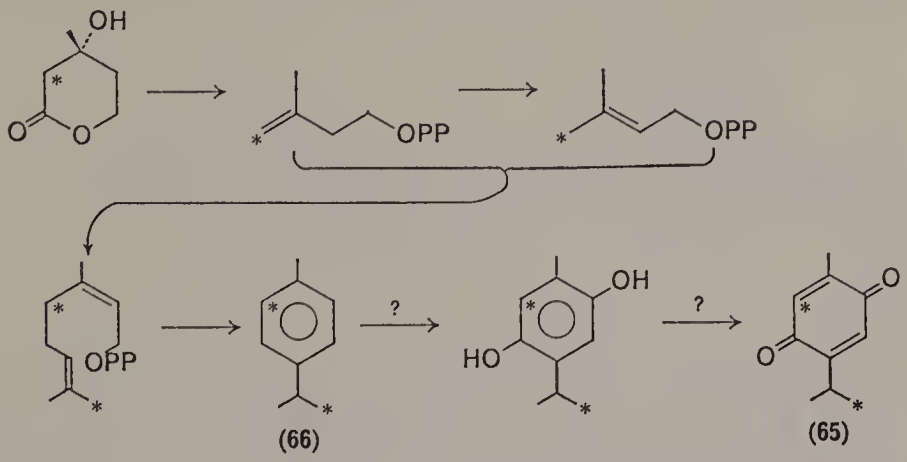
C. *Quinones Derived Wholly from Mevalonate*

Benzoquinones: fungi, plants
Naphthoquinones: plants

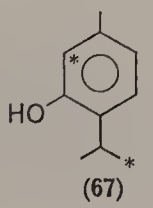
The structures of some naturally occurring quinones are in harmony with the 'Empirical Isoprene Rule'[94], and are clearly related to terpenes and hence, ultimately, to mevalonate. Thymoquinone **65** and its quinol occur in some plants and are probably derived from *p*-cymene **66**. This latter monoterpene is a likely precursor for thymol **67**, a phenol which has been shown to be labelled, with the anticipated isotope pattern, on administration of [2-^{14}C]-mevalonate to *Orthodon japonicum*[95].

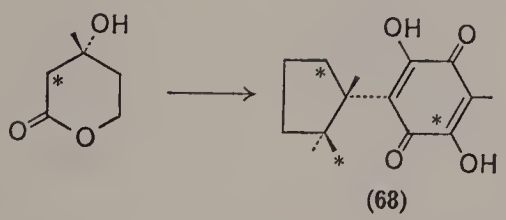
At the sesquiterpene level, the fungal benzoquinone, helicobasidin **68** (from *Helicobasidium mompa*) has been shown to be derived from labelled acetate and mevalonate with the anticipated labelling pattern[96,97]. Of

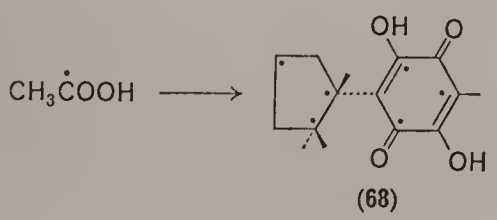
several possible hypotheses, it now appears that a direct cyclization of *trans-cis*-farnesyl pyrophosphate takes place[96]. The reaction is more complex than originally proposed since helicobasidin incorporates two of the three possible *pro-R* hydrogen atoms from C-4 of mevalonate[98]. Since the six-membered ring is fully substituted, a hydrogen transfer must



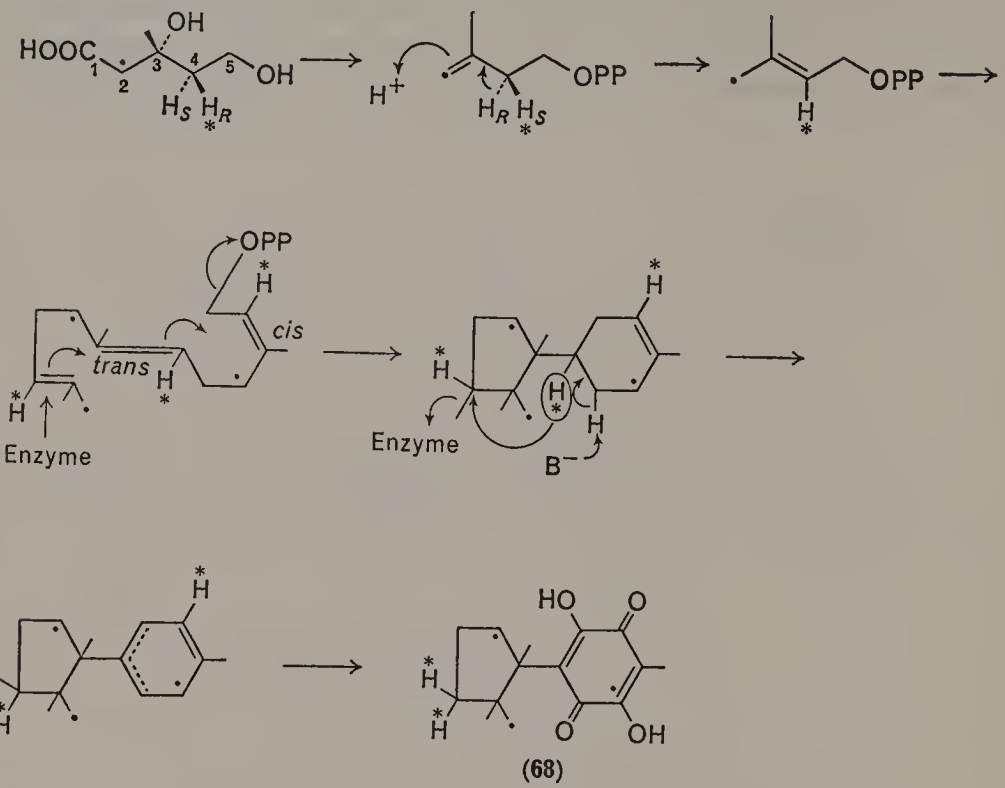
PP = Pyrophosphate





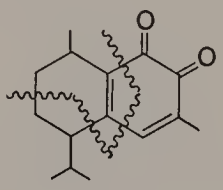


have occurred: this is postulated by Adams and Hanson to take place in an enzyme displacement step as shown below[99]:

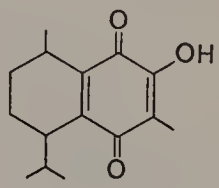


(68)

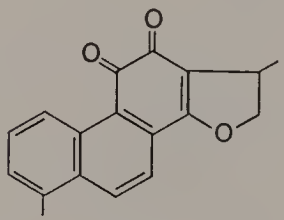
Although no feeding experiments have yet been recorded, it is clear that many other quinones, both 1,4- and 1,2- systems, derive from terpenoid precursors and hence mevalonate. Some of these are shown below, e.g. mansonones A and B (**69** and **70**), tanshinone I (**71**) and coleon A (**72**).



(69)



(70)



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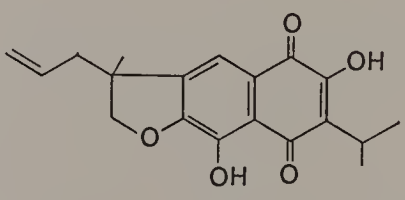
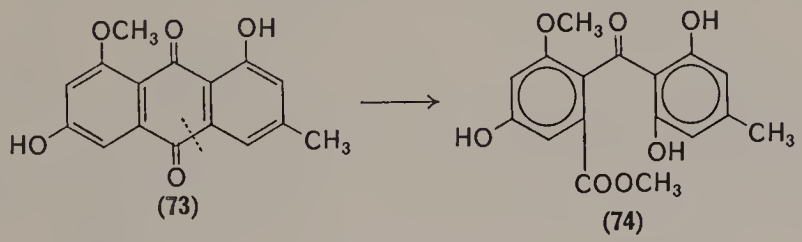


(72)

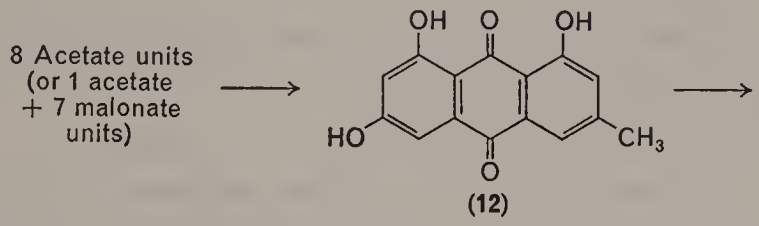
D. Quinones as Intermediates in Formation of Other Secondary Metabolites

In several cases, quinones function as intermediates in the biosynthesis of other secondary metabolites, some of which, such as the tetracyclines and aflatoxins, have considerable importance. This possibility was first considered in structural terms, namely a similarity between the anthraquinone, questin **73** and the benzophenone, sulochrin **74**. That questin in

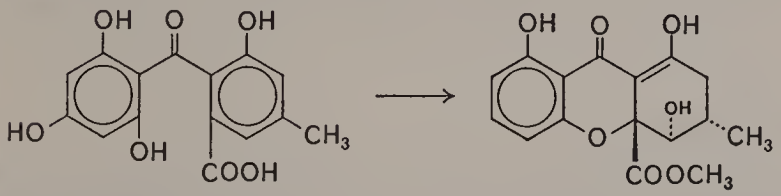


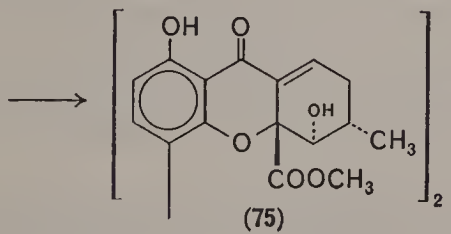
(73) (74)

fact yields sulochrin has been demonstrated directly in *Penicillium frequentans*[100] and *Aspergillus terreus*[101]. A similar type of cleavage takes place in the biosynthesis of the various ergochromes from emodin **12** in *Claviceps purpurea*. The reactions yielding ergochrome BB (**75**) are shown below[102, 103]:



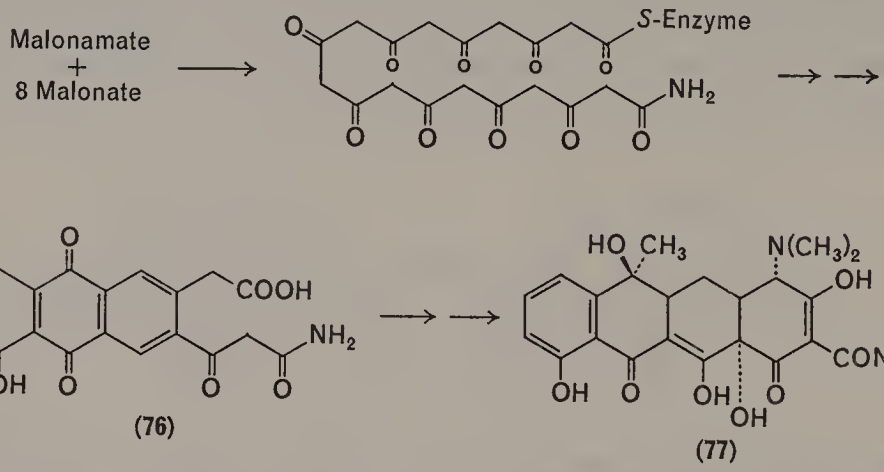
(12)





(75)

Anthraquinone derivatives are intermediates in the formation of the important antibiotics, the tetracyclines, e.g. protetrone **76**[104] in the tetracycline **77** bisynthetic sequence shown below*. Quinones are also apparently



(76) (77)

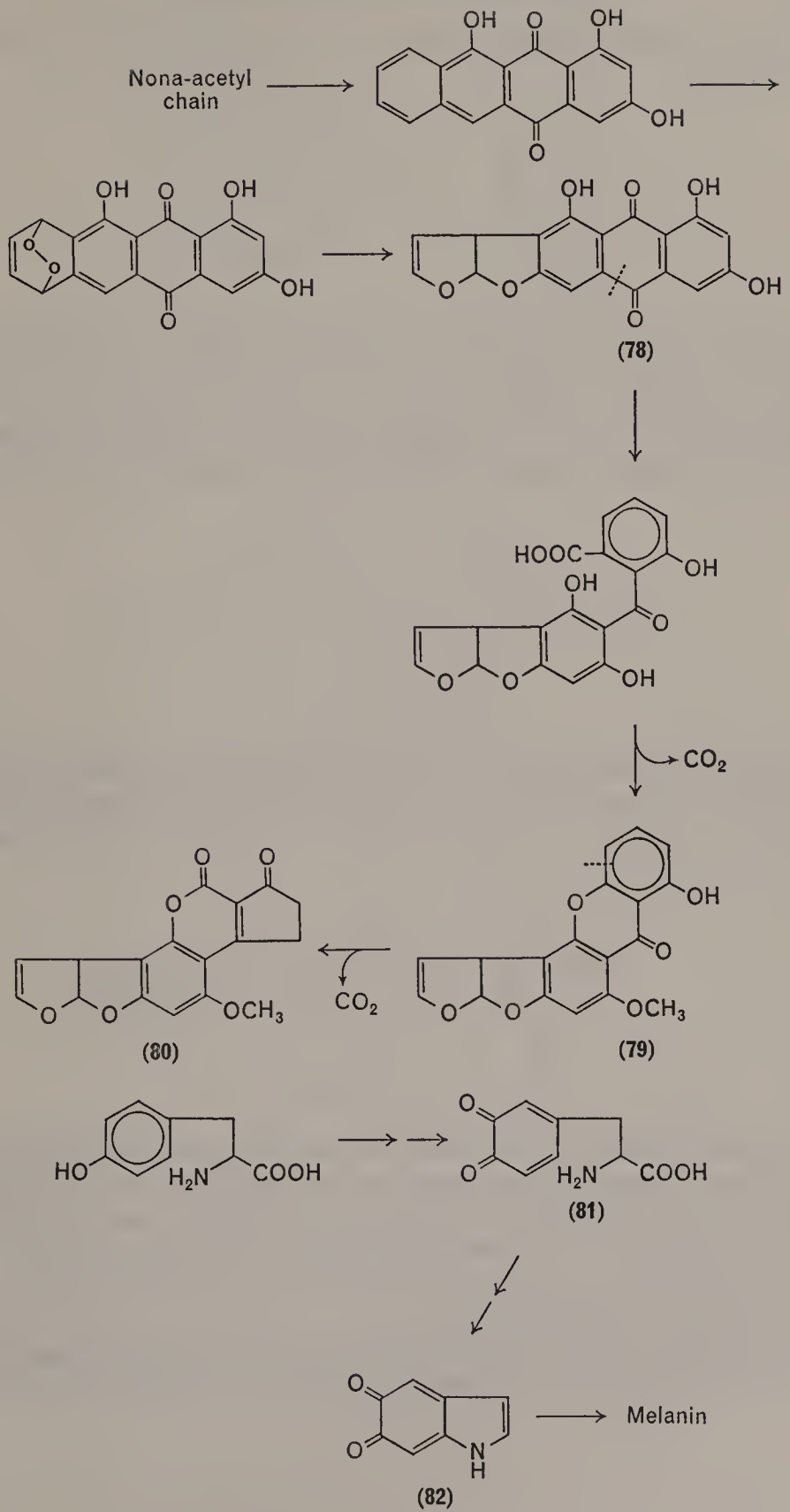
involved as intermediates in the biosynthesis of a group of interesting difurans. To account for the observed results in the biosynthesis of aflatoxins in *Aspergillus flavus*, the following pathway has been proposed[105]. The quinonoid species versicolorin A (**78**) together with its methyl ether and sterigmatocystin (**79**) has been encountered in *Aspergillus versicolor*. The final product of the sequence below is aflatoxin B_1 (**80**). Recent work on sterigmatocystin **79** in *A. versicolor* by Tanabe and coworkers[106] lends credence to this scheme of Büchi.

Although not specifically a secondary metabolite, it is convenient to note at this stage that melanin, the black polymeric pigment found in the skin, the retina and various other specialized tissues, is synthesized from tyrosine via Dopa quinone (**81**) and indole 5,6-quinone (**82**) as shown below.

E. Polymeric Quinones

Many examples of naturally occurring polymeric quinones are known; it is likely that these are produced by the 'phenolic coupling' reaction although little direct experimental evidence is available[107]. However, unpurified enzyme preparations from *Polystictus versicolor* are reported to convert 2,6-dimethylphenol (**83**, R = CH_3) or 2,6-dimethoxyphenol (**83**, R = OCH_3) to 3,5,3′,5′-tetramethyl-diphenoquinone (**84**, R = CH_3)

* The role of malonamate as a starter unit is unique. Although generally accepted as correct, the evidence on this point is not wholly definitive.


Nona-acetyl chain
OH
O
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OH
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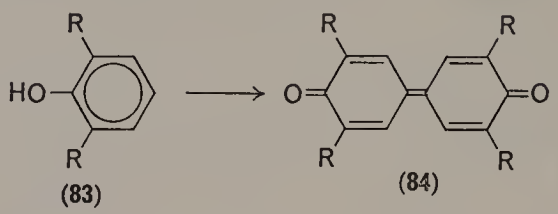
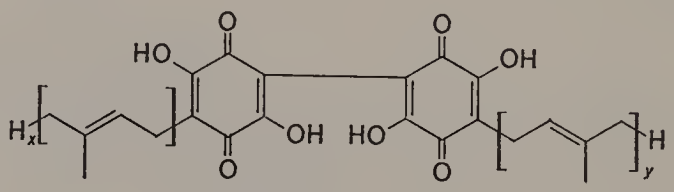
OH
O
O
OH
O
O
OH
O
(78)
HOOC
OH
OH
O
O
O
OH
CO2
O
O
OH
O
O
O
OCH3
CO2
O
O
O
OCH3
(80)
(79)
HO
H2N
COOH
O
O
H2N
COOH
(81)
O
O
N
H
Melanin
(82)

or 3,5,3′,5′-tetramethoxy-diphenoquinone (coerulignone) (**84**, R = OCH_3), respectively[108].



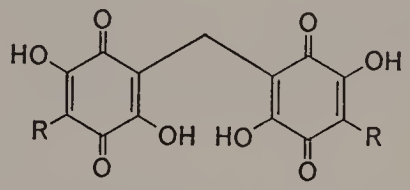
(**83**) (**84**)

Thomson's prediction[109] that the isolation of many more biquinones can be expected is being borne out. For instance, in the benzoquinone field, diboviquinones (e.g. **85** and **86**) have been isolated[110] from *Boletus* (*Suillus*) *bovinus* as well as a new member of the regular boviquinone series (boviquinone-3, nomenclature as for ubiquinone and menaquinone).



(**85**), $x = 3, y = 4$
(**86**), $x = y = 4$

Furthermore, these authors have found compounds (**87**, **88** and **89**) in which two quinone units are linked at the 6,6′-position through a methylene group; in this case, of course, more than a simple phenolic coupling is presumably involved.

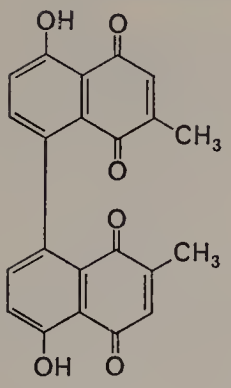


R = prenyl as in (**85**) and (**86**)

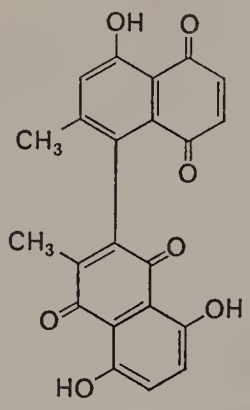
(**87**), $x = y = 3$ (**88**), $x = 3, y = 4$ (**89**), $x = y = 4$

Diospyros species are good sources of naphthoquinone derivatives and several new binaphthyls have been reported from extracts of *Diospyros kaki*, e.g. maritinone **90** and hydroxyisodiospyrin **91**[111]. Similarly, a blue pigment isolated from extracts of the sapwood of *Diospyros buxifolia* has been identified as 8,8′-dihydroxy-4,4′-dimethoxy-6,6′-dimethyl-2,2′-binaphthyl-1,1′-quinone (**92**)[112].

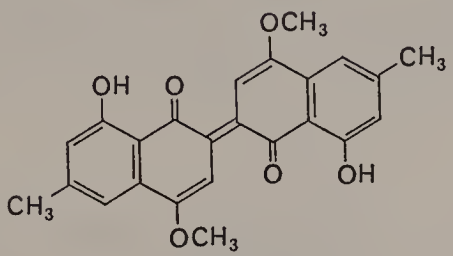
Other sources of naphthoquinones ('spinochromes') and of binaphthoquinones are various sea urchin species. From *Spatangus purpureus*,



(90)

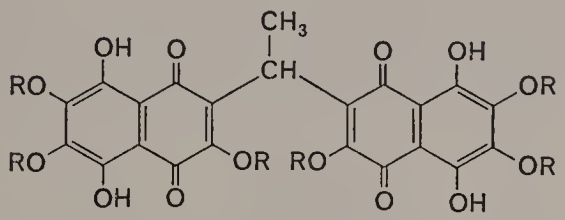


(91)



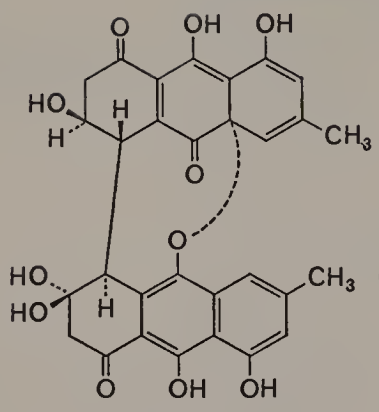
(92)

Mathieson and Thomson isolated four pigments, two of which were biquinones (**93**, **94**)[113]. The quinone units were linked by a $CH_3CH\langle$ group, reminiscent of the methylene linkage in the methylene diboviquinones.

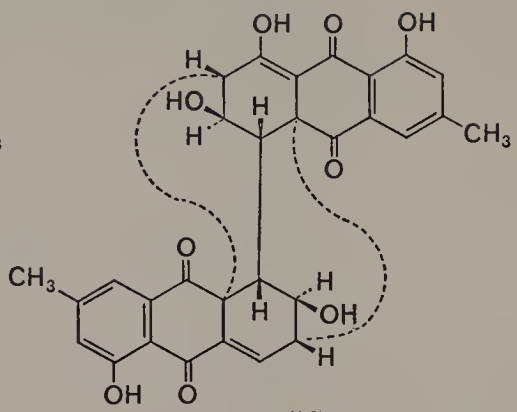


(**93**), R = H (**94**), R = CH_3

Some materials, previously reported as monomeric quinones, are now known to be polymeric. Thus, (−)-flavoskyrin, a pigment of *Penicillium islandicum*, is now formulated as **95** and is related to (−)-rugulosin **96**; it is, in fact, converted to the latter by the action of pyridine[114]. (−)-Rugulosin has been isolated from *P. islandicum* and *Myrothecium verrucaria*; the enantiomer, (+)-rugulosin, was well known as a metabolite of *Penicillium rugulosum*. The stereochemistry of these cage structures is not easily shown. In formula **96** the 'cage' is imagined to be

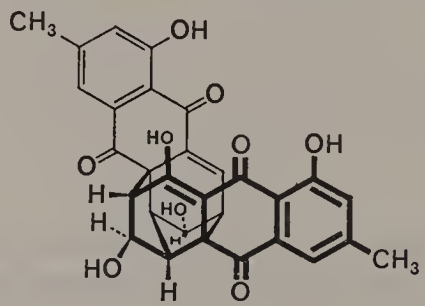


(95)



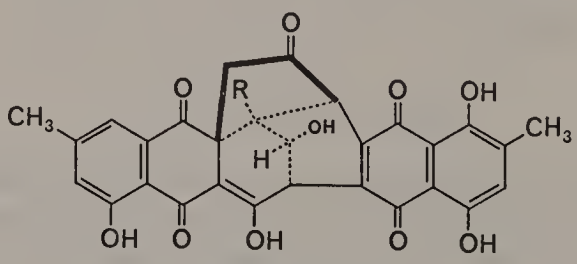
(96)

opened up by stretching two of the three bonds linking the anthraquinone units; the two anthraquinone units are then roughly coplanar. A more accurate representation of the stereochemistry of (−)-rugulosin is **97** [115].



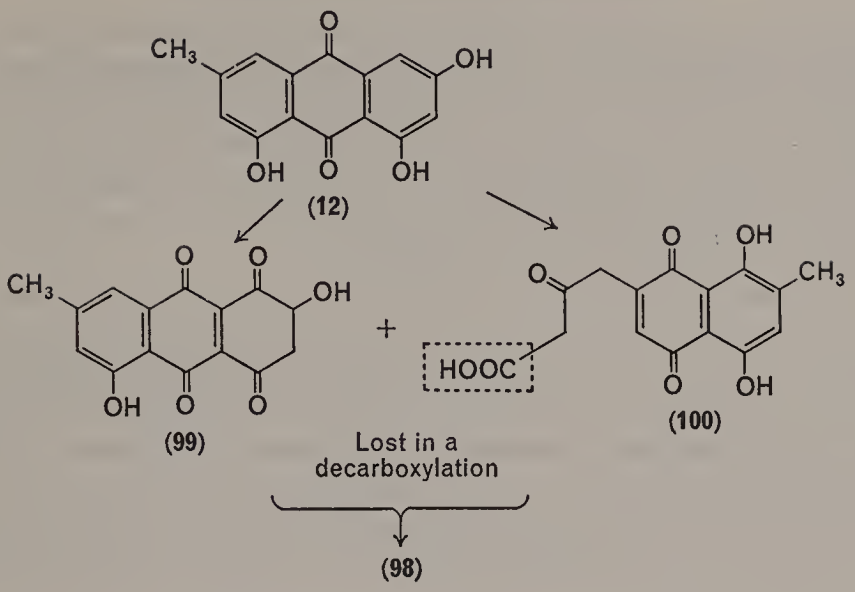
(97)

Although not strictly a dimer, the revised structure for the principal colouring matter from *Penicillium purpurogenum*, purpurogenone **98**, is of interest[116]. It has been suggested that this molecule originates from 2 molecules of emodin (**12**) (or of its carboxylic acid, endocrocin **18**) by a



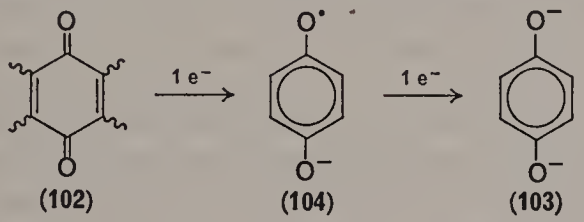
(98), R = OH
(101), R = H

complex series of reactions. A Michael addition between two systems such as **99** and **100** would be a key step. A deoxypurpurogenone, **101**, has also been isolated as a minor pigment from this fungus[117].



III. THE FUNCTIONAL SIGNIFICANCE OF QUINONES

The most important reaction of quinones as far as biology is concerned is their reversible reduction to the corresponding hydroquinone (**102–103**). This is a relatively mild chemical process, being accomplished by such gentle laboratory reagents as bisulphite and Fe^{2+}. When the reducing agent is a single electron donor, the reaction can be viewed as a two-stage process, the semiquinone, **104**, being the intermediate. Since quinones and



hydroquinones are highly conjugated species, their mutual interconversion can be followed very effectively by ultraviolet spectrometry. Moreover, since semiquinones possess an unpaired electron in their structure, their presence can be detected through the use of electron paramagnetic resonance (e.p.r.) spectrometry. Both of these techniques have been used extensively in the study of quinones in biology.

Analysis of the various quinonoid structures mentioned in the previous sections reveals compounds of two distinct classes. Firstly, there are the

biochemist's compounds, materials such as the menaquinones, the ubiquinones and the plastoquinones which even the most esoteric molecular biologist would have no trouble recognizing. Such is the case because the biological role of these substances is fairly well established, albeit sometimes not totally in molecular terms. Most of the text of this section will therefore be devoted to them (Part A). This class of material is also connoted by the term 'primary metabolite'.

On the other hand, there are in section II many examples of what the organic chemist refers to as 'natural products'. Also known as 'secondary metabolites', these materials are characterized somewhat negatively by having no firmly established role to play in the cell that makes them. True, many secondary metabolites have distinct and often profound effects on cells other than those from which they come: the inventory of any pharmaceutical company bears cogent witness to this fact. Recently, however, some wisps of insight have come into this field and these will be considered in Part B.

A. The Quinones that are Primary Metabolites

It is a well-known fact that the principal energy-yielding reactions of the biosphere are associated with the phenomena of photosynthesis and respiration. In the former, the energy radiated by the sun is trapped by green plants and by the photosynthetic bacteria and converted into the standard energy currency of cells, adenosine triphosphate (ATP), and reduced nicotinamide adenine dinucleotides (NADH/NADPH). This potential energy is subsequently used to synthesize 'energy-rich' tissue components such as carbohydrates, fatty acids and amino acids from simple, fully oxidized precursors such as carbon dioxide, nitrate, etc. These materials eventually act as foodstuffs for non-photosynthetic species. Creatures such as man degrade them oxidatively and in so doing recover, in the form of NADH, the reducing power they contained. In the process of respiration, the NADH is used to reduce molecular oxygen. Thereby ATP is generated for the use of the non-photosynthetic organism (energetically speaking therefore, the non-photosynthetic organism has vicarious communion with the sun!). In both photosynthesis and respiration, the potential energy form that is transduced into metabolically useful energy is a redox potential gradient. Discharge of this gradient by a series of coupled chemical redox reactions leads to the synthesis of ATP. Since the redox gradient discharge necessarily involves electron movements, the series of coupled reactions is frequently referred to as an electron transport chain.

As will be amplified in the following section, the redox reaction, quinone $\rightleftharpoons$ hydroquinone, constitutes one of the elements of the electron transport chain found both in photosynthesis and in respiration. For ease of discussion, procaryotes (organisms such as bacteria and the blue-green algae whose cells lack nuclei) and eucaryotes (organisms such as animals, plants, fish, fungi, green, brown and red algae, etc., whose cells possess nuclei) will be considered separately.

I. Photosynthesis in eucaryotes[118–123, 126]*

Photosynthesis in green plants and the eucaryotic algae is conducted in special, membrane-encompassed, subcellular organelles called chloroplasts. These relatively large bodies have been the subject of much electron microscopy and the details of their structure are now well known[124]. The operational unit appears to be the thylakoid disc.

Chemical analysis of whole chloroplasts indicates that several quinonoid species are present[29, 122, 125, 126]. Plastoquinones, **35**, are the major constituents and the entities believed to be obligatorily involved in photosynthesis; phylloquinone and several tocopherolquinones have also been found, but have been attributed no definite role to date. Some doubt exists as regards which specific member(s) of the plastoquinone family is (are) involved naturally. The prenylogue with nine isoprene units (PQ-9≡PQ-A)† is the member most frequently encountered and the substance most commonly used in experimental work. Different chain lengths and derivatization states have been encountered, however. Thus materials with phytyl side-chains, hydroxylated side-chains (the PQ-C/D group and PQ-Z), ester functions in the side-chain (PQ-B and PQ-Z) and monomethyl quinols have been isolated, while PQ-C and -B have all been further fractionated[29, 126–129].

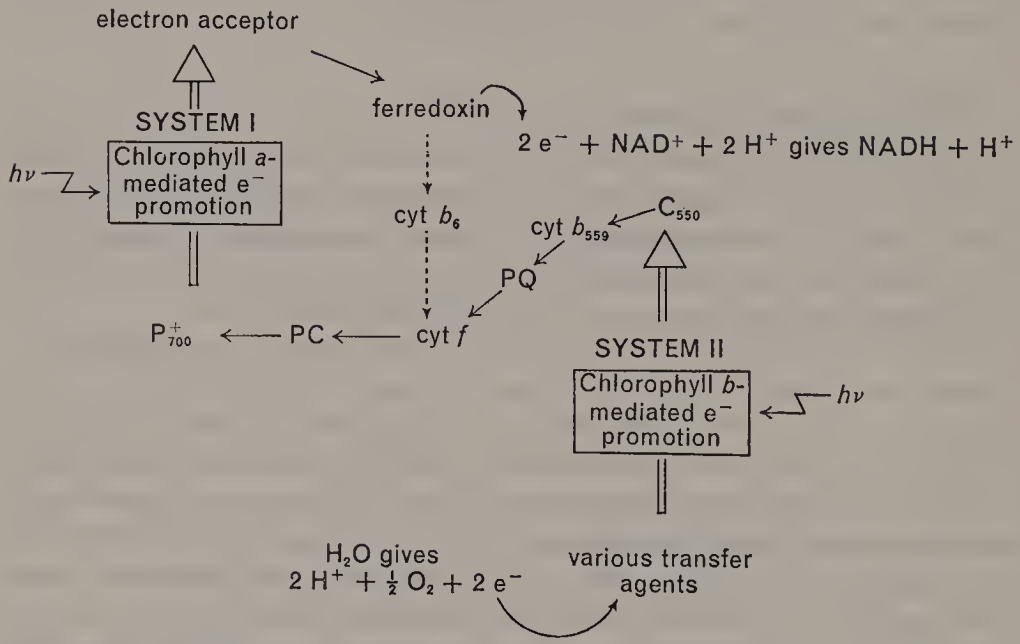
It seems clear that methods such as partition chromatography, gel filtration and mass spectrometry, which were so effective in the fields of menaquinone multiplicity, will be needed to resolve fully the question of plastoquinone composition[130, 131]. Moreover, these analytical methods will need to be applied very judiciously if their results are to have real biological function significance. Cognizance will need to be taken of the facts, established by Lichtenthaler[132], that (i) plastoquinone pools are

* Since consideration is concentrated on the role of quinones in these various processes, a series of review references is provided for those readers seeking more complete coverage of the topic.

† PQ = plastoquinone. PQ-*n* = plastoquinone with *n*-prenyl units in the side-chain.

associated with two distinct chloroplastic subfractions, the photoactive lamellae and the photoinert plastoglobuli and (ii) plastoquinone levels fluctuate widely with the age and physiological state of the chloroplast.

The general context in which the plastoquinones operate in photosynthesis is shown in Figure 1, but this scheme is far from being the final



PC = plastocyanin; PQ = plasto-quinone; cyt = cytochrome.

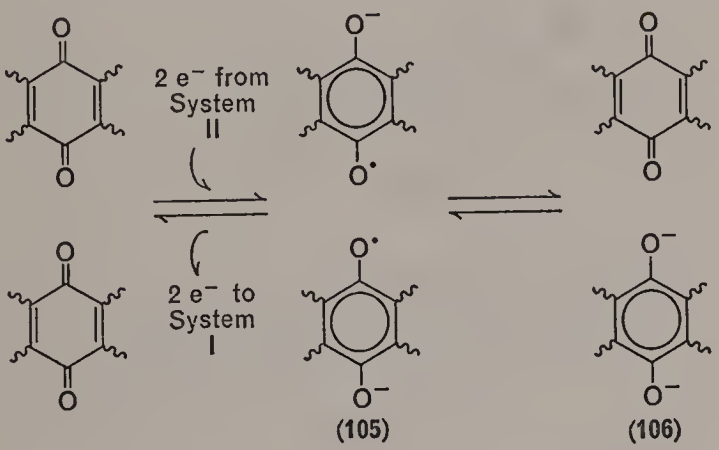
FIGURE 1. Note how the 2-electrons extracted from water are eventually made available for the reduction of NAD^+.

word. It has suffered many alterations and expansions since it was first introduced in 1963[133]; many more can be expected. Notwithstanding the general air of uncertainty, the basic principles are easily appreciated. Starting from the right-hand side, light of short wavelength (< 680 nm) activates chlorophyll *b* * molecules causing electrons to be excited and consequently transferred to an acceptor species referred to cryptically as C_{550} (this is the compound *Q* of former literature)[134]. By this simple process the necessary redox gradient is established. In response to the redox pressure it creates, electrons flow into the oxidized chlorophyll *b* via various transfer agents from water. Meanwhile, the electrons donated by chlorophyll *b* to C_{550} tumble down the redox gradient that consists in

* Chlorophyll *b* is the agent in green plants; chlorophyll *c* is the agent in the brown algae, chlorophyll *d* in the red algae.

part of a low potential form of cytochrome b_{559}[135,136], plastoquinone, cytochrome f[137] and plastocyanin. At this point, the electrons serve to discharge the oxidizing pole of another photo-established redox gradient. This second photo promotion involves chlorophyll *a* (in all species), long wavelength light (>700 nm) and the electrons are eventually donated to NAD. The electron passage from reduced C_{550} to oxidized P_{700} is coupled in a way not yet fully understood to the synthesis of ATP*.

Many of the details of the electron transport chain through the plastoquinone pool have been worked out by Witt and coworkers[123,139,140]. Firstly, they have established that the electron transport chain does not exist as a series of single, isolated 'wires' made up of a single representative of each of the constituent molecules. Chains interact with each other and it appears that one of the major sites of interaction is located at the plastoquinone level. Siggel and coworkers[139] suggest that at least ten individual chains can feed into a common plastoquinone pool. On the basis of the analysis of kinetic data, they propose that electrons enter this pool as a pair from two coupled System II centres. The first-formed product is a plastosemiquinone twin **105** which subsequently disproportionates with the formation of a plasthydroquinone anion, **106**. This latter entity migrates through the pool to the appropriate acceptor



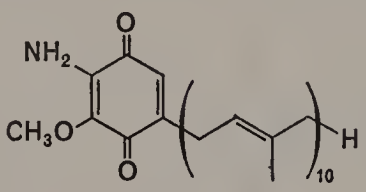
* This overall pathway can be short circuited if and when cytochrome b_6 feeds electrons from ferredoxin to cytochrome f. This pathway, leading to the direct conversion of actinic energy into ATP, is called cyclic photophosphorylation.

We also note at this time that the scheme described above has been amended somewhat by Arnon[138]. The amendation is not as yet generally accepted. It considers System I to be divided into two; one part executing cyclic photophosphorylation exclusively, the second part coupling in the manner we have described with System II.

location, reforms the plastosemiquinone twin and discharges its two-electron complement, presumably to a pair of single-electron acceptors. The scheme neatly explains how single and paired electron redox agents can operate in consort. The pool concept also helps to rationalize the observed fact that plastoquinones are found in great molar excess relative to the cytochromes, etc.

2. Photosynthesis in procaryotes[141–143]

Several species of bacteria (green and purple) and the blue-green algae can also harness the energy of sunlight to the synthesis of ATP and the generation of a reduced nicotinamide derivative. This they do, not in chloroplasts, but in specialized cell membrane locations isolable as chromatophores. Ubiquinone **1** is the main quinonoid material found in the electron transport chain of bacteria, although it is not exclusive[29, 122, 126]. Thus *Rhodospirillum rubrum* contains the substance rhodoquinone **107**, vitamins K_2 (**2b**) are found in various photosynthetic bacteria, and species of *Chlorobium* contain the compound, chlorobiumquinone **108**, unusual in that it contains a keto grouping in the side-chain. Also, the length of the polyprenyl side-chain found in the ubiquinone alters from one



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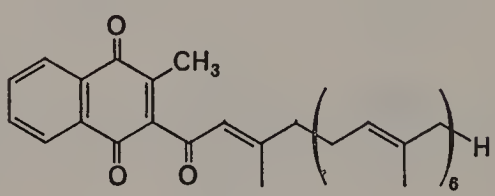


(108)

organism to another: ubiquinone-7 through ubiquinone-10 being common. Mixtures are also found within the same organism. Thus, *R. rubrum* has been shown to contain ubiquinone-1 through ubiquinone-10[144].

In some ways, the photosynthetic process is simpler in bacteria than in green plants since bacteria do not possess an analogue of Photosystem II, i.e. they do not oxidize water to molecular oxygen. In some other ways, however, they are much more complex. There is thus not the same degree of uniformity from one organism to another as is found in eucaryotes,

and multiple pathways are not uncommon. The review by Frenkel established these points effectively[142]. Moreover, the production of reduced NAD can be accomplished in at least two ways. For the present purpose, however, it is sufficient that we note the general pattern of events (Figure 2).

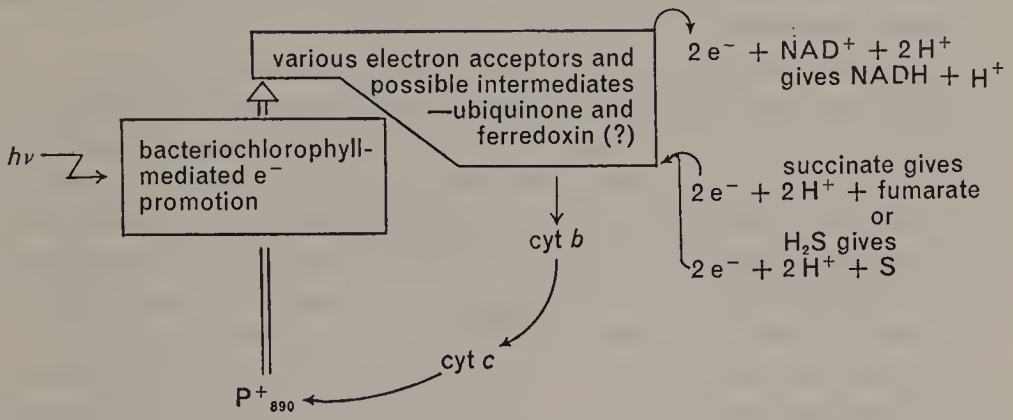


FIGURE 2. Note how the 2-electrons extracted from substrates such as succinate etc. are eventually made available for the reduction of NAD^+.

As in eucaryotic photosynthesis, a primary photo event creates an oxidizing agent and a reducing agent and thereby sets up a redox gradient. The photoactivator is a set of specially situated bacteriochlorophyll molecules: the species P_{890}. The reducing pole of the redox gradient is coupled directly to the oxidizing pole via a series of ATP-producing reactions. Ubiquinone is one of the electron carriers in this chain and it has been suggested recently that in *Rhodopseudomonas spheroides* ubiquinone is in fact one of the primary electron acceptors[145]. NADH (or NADPH) is formed either in the photoreduction manner described for eucaryotes, using electrons derived from substrates such as succinate or hydrogen sulphide, or by an ATP-catalysed reversal of oxidative phosphorylation (see later). In these organisms, it is not certain as yet whether the ubiquinone functioning in the photophosphorylation process is spatially distinct from that functioning in respiration.

3. Respiration in eucaryotes[122, 126, 146–154]

Ubiquinones are also implicated in the electron transport chain associated with eucaryotic respiration. This process is conducted in special subcellular organelles, the mitochondria. In view of what has been discussed above, it will be no surprise to learn that side-chain length

variability is found in the mitochondrial quinones. Ubiquinone-10 is the predominant form found in vertebrates, but ubiquinone-6 through ubiquinone-9 are found as major forms in yeasts and plants[29, 122, 126]. Beef heart muscle, the tissue used extensively in respiration investigation, appears to produce ubiquinone-10 exclusively. It is interesting to note that sometimes ubiquinones with shorter chain lengths markedly out-perform the natural material in *in vitro* experiments[155].

Respiration involves the overall oxidation by molecular oxygen of the reducing equivalents that have resulted from metabolic degradation of ingested foodstuff. The principal source of these equivalents is the citric acid cycle. Pyruvate, isocitrate, malate and 2-ketoglutarate dehydrogenases yield reduced NAD while succinate dehydrogenases yield reduced flavin adenine dinucleotide (FAD). Both these entities can also be formed from fatty acid degradation (hydroxy fatty acyl CoA dehydrogenase, NADH; fatty acyl CoA dehydrogenase, $FADH_2$). The $NAD^+/NADH$ system has a standard electrode potential of $-0{\cdot}32$ volts, the $FAD/FADH_2$ system has a corresponding value of $-0{\cdot}19$ volts, while the $\frac{1}{2}O_2/OH^-$ system records a value of $+0{\cdot}82$ volts. The redox gradient between the former two and the latter one is spanned by a series of reactions which involve cytochromes of the *a*, *b* and *c* type. The reader will notice that there is no immediate external energy input to the process of respiration.

Until recently, the general consensus of bioenergetic opinion was that ubiquinone fitted into the electron transport chain on the substrate side of cytochrome *b*. It was seen to act as a kind of chemical electron transport interface between the various flavoprotein dehydrogenases and the chain of cytochromes which accomplished the eventual reduction of oxygen (Figure 3). As with the pools of plastoquinone in photosynthesis, the ubiquinone molecules were considered to diffuse freely in the lipophilic medium of the membrane. In support of this role for ubiquinone in respiratory electron transport was the fact that pentane extraction of lyophilized mitochondria yielded a product which, when warmed and resuspended in buffer, was not able to conduct electron transport. Viability could, however, be restored by addition of ubiquinone-10 or a lower prenylogue[156]. Moreover, methods of mitochondrial fractionation have been developed which allow four complexes to be isolated which together are able to conduct electron transport in its entirety[157]. It was found that complex I reduced ubiquinones at the expense of NADH, complex II reduced ubiquinone at the expense of succinate, and complex III reduced cytochrome *c* at the expense of reduced ubiquinone*.

* Complex IV reduced oxygen at the expense of reduced cytochrome *c*.

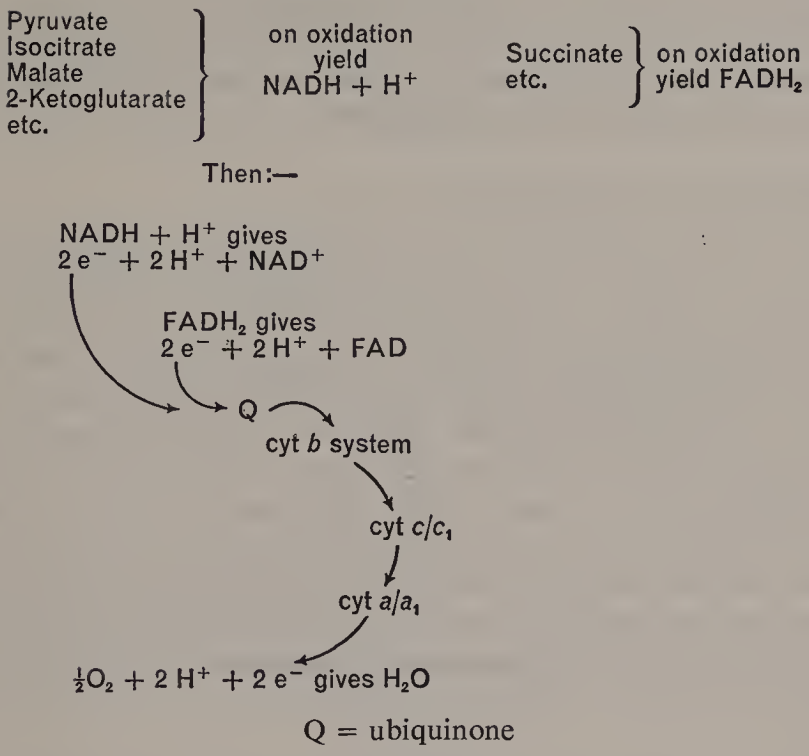


FIGURE 3.

Recent work on several fronts has demonstrated that such a simple representation is inadequate. The reviews by Slater[153] and Chance[154] indicate just how complex the situation has become. Of greatest significance to the quinonoid issue, and therefore the only topic we will consider here, is the finding in several laboratories that under certain conditions succinate dehydrogenase can be coupled to the cytochrome *b* ensemble in the absence of ubiquinone[158–161]. Further evidence that the electron path from succinate to oxygen does not actually pass through ubiquinone is the observation[162, 163] that ubihydroquinone may be a NADH-sensitive, conformational-altering activator of succinate dehydrogenase. This activator role for ubiquinone would provide a possible explanation for the fact that in restitution experiments with pentane-extracted beef heart mitochondria, the succinate dehydrogenase complex could be reconstituted equally well with ubiquinones-2 through -10, while the NADH dehydrogenase was quite specific for ubiquinones-7 through -10[164, 165]. Thus once again uncertainty rises vis-à-vis the obligatory nature of ubiquinone's involvement in electron transport[166]. This time, however, the question is not so far-reaching since there seems no doubt that ubiquinone is required to link NADH dehydrogenation with cytochrome *b* reduction[167].

Nothing comparable to the Witt–Siggel–Stiehl[123, 139, 140] analysis of the electron flow into the plastoquinone pool has yet been done for the ubiquinone pool in respiration. It is, however, known that free radicals, presumably semiquinones, are involved[168].

4. Respiration* in procaryotes[122, 147, 205]

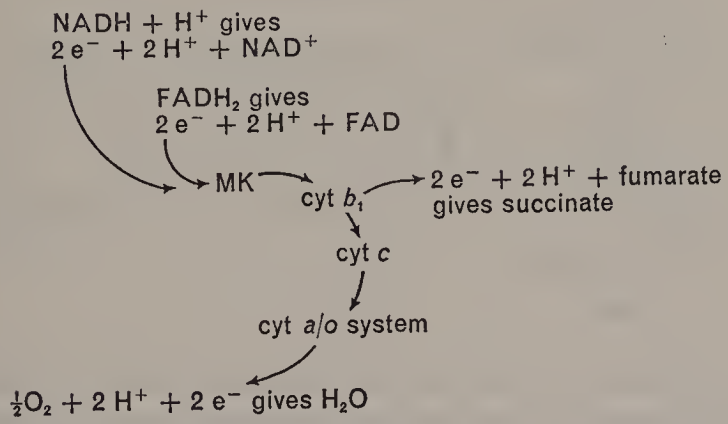
We have seen earlier that procaryotes have no chloroplasts yet some of them can conduct photosynthesis; likewise they have no mitochondria, but they can respire. The respiratory centres are found bound to the cytoplasmic membrane. Two quinone types are found in such centres, menaquinones and ubiquinones[29, 122, 126]. In general, the menaquinones are found in Gram-positive species while the ubiquinones are found in Gram-negative ones[169]. Some of the enterobacteria, e.g. *E. coli*, contain both ubiquinones and menaquinones. As in the case of the eucaryotic respiratory quinones, they exist in a high molar excess relative to the other electron transport chain components and exhibit some structure diversity. For instance, hydrogenated menaquinone side-chains have been found in *Mycobacterium phlei*[170] and species of *Streptomyces*[171, 172]. The full range of ubiquinones from ubiquinone-1 to ubiquinone-8 has been found in *E. coli*[144].

Where an organism contains only a single quinone type, the general trend of the experimental analysis to date is that the quinone participates in the electron transport chain in a manner analogous† to that described above for the eucaryotes, i.e. it acts as a collection funnel for the electrons derived from the action of the various NAD- and FAD-linked dehydrogenases of the cell. The experimental evidence has been obtained from pentane-extraction/quinone-replacement studies, reduction extent and time course examinations and work with chain inhibitors. The general pattern proposed by Kröger and Dadák[174] for *Bacillus megaterium* can be taken as typical for several bacteria (Figure 4). Note how, in the absence of molecular oxygen, after the electrons have passed from the menaquinone pool through cytochrome *b*, they can be used to reduce fumarate. All NADH-forming substrates seem to have equal access to the menaquinone pool; a measure of compartmentalization was found in a similar

* The term 'respiration' is used here a little loosely to preserve the continuity of the discussion. It must be noted, however, that many bacteria are able to use materials other than molecular oxygen as the terminal oxidant of the electron transport chain, e.g. the nitrogen-fixing bacteria, the anaerobes, etc.

† The bacterial cytochromes differ somewhat from the eucaryotic type. In particular, a cytochrome *o* acts in consort with the cytochromes of the *a* type in the final reduction of oxygen[173].

study as far as the demethylmenaquinone pool was concerned in *Hemophilus parainfluenzae*[175]. E.p.r. signals possibly emerging from menasemiquinonoid species have been detected in *Mycobacterium phlei*[176]. Whether or not this scheme is oversimplified remains to be seen.



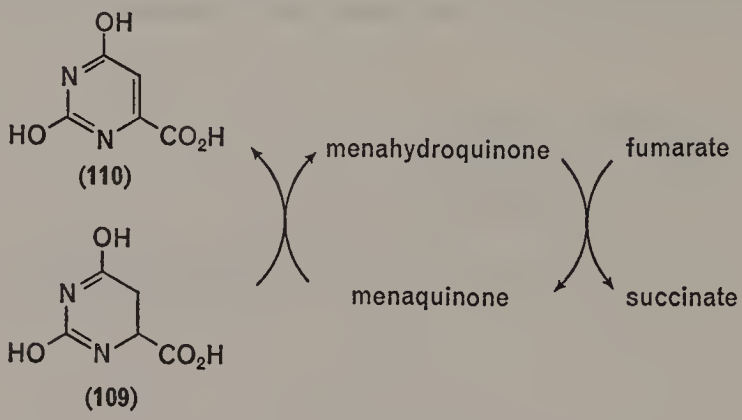
MK = menaquinone

FIGURE 4.

In organisms where ubiquinones and menaquinones co-exist, the roles of the two species seem to be divided. Some ten years ago, work by Kashket and Brodie[177] suggested that in *E. coli* menaquinones were exclusively associated with NADH oxidation, while ubiquinones took care of succinate oxidation. Recent work has revised the nature of this division of labour. In a detailed study using *E. coli* mutants lacking the power to make menaquinones and/or ubiquinones, Cox, Gibson and coworkers[178,179] showed that menaquinones were needed for anaerobic growth, while ubiquinones were needed for aerobic growth. Thus the entire responsibility for electron transport *into oxygen* was attributable to ubiquinone. Inhibitor studies, however, constrained these workers to conclude that ubiquinone was not functioning as a single, isolated component of the chain, but as an obligatory part of *two* iron–ubiquinone complexes. One of these was situated before cytochrome *b*, the other on the oxygen site of that cytochrome. E.p.r. studies suggest that ubisemiquinones participated[180]. Thus the low seven-eighths of the iceberg of complexity are beginning to show in procaryotic respiration!

The function of menaquinone in *E. coli* was more conclusively defined by the same study. Its principal role was not as a component of the respiratory chain, but as a cofactor in that step of pyrimidine biosynthesis leading

from dihydroorotate **109** to orotate **110**. This oxidation is conducted at the expense of fumarate, thus:

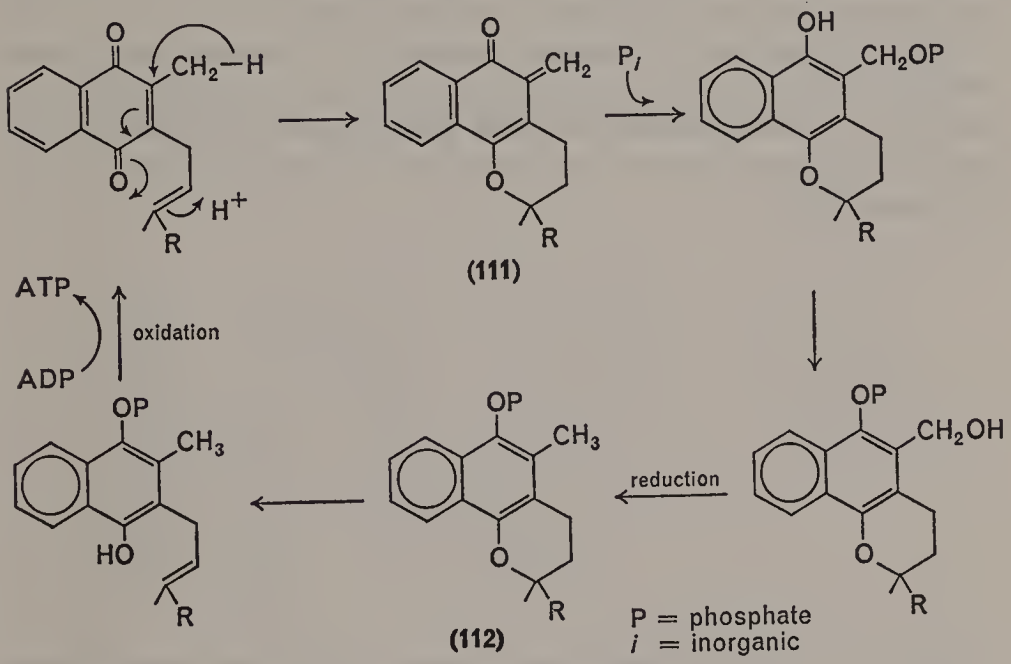


A similar pattern of menaquinone/ubiquinone function was found by Kröger and coworkers[181] to pertain in another enterobacterium, *Proteus rettgeri*. Thus, ubiquinone was shown to be on the *direct* path for electron transport from succinate, formate and NADH to oxygen and was situated at a point on the substrate side of cytochrome *b*. The menaquinone component was shown to be involved in the anaerobic discharge of reduced NAD (and formate) into fumarate through the action of the enzyme fumarate reductase. Further metabolism of the succinate so formed presumably required the succinate dehydrogenase/ubiquinone/cytochrome chain.

The involvement of menaquinones in anaerobic growth, demonstrated by Cox and Gibson and coworkers and by Kröger and coworkers is in harmony with the known fact that facultative anaerobes which contain both ubiquinone and menaquinone form higher relative proportions of menaquinone when grown anaerobically[182].

There is a tradition in the discipline of physics that if an hypothesis is simple and theoretically beautiful, the chances are that it is based on reality. Some years ago, such an hypothesis was proposed in relation to quinones and oxidative phosphorylation[183], the process in respiration whereby the energy derived from the redox gradient is actually converted into ATP (see reference 184 and 185 for the early history of this hypothesis). It was applicable to procaryotes and eucaryotes, but since most investigative work was performed with *M. phlei*, it will be considered here. The scheme involved the formation of a quinone methide **111** which picked up inorganic phosphate (P_i) and eventually transferred this unit to ADP as shown. The scheme was supported by the finding that 6-chromanyl

phosphates such as **112** could reduce cytochrome *c* and convert ADP to ATP when incubated anaerobically with appropriate extracts of *M. phlei*[186]. Despite its inherent plausibility and beauty, the weight of experimental evidence[187] is now against this scheme. Current thoughts on the mechanism of oxidative phosphorylation are contained in references 152–154.



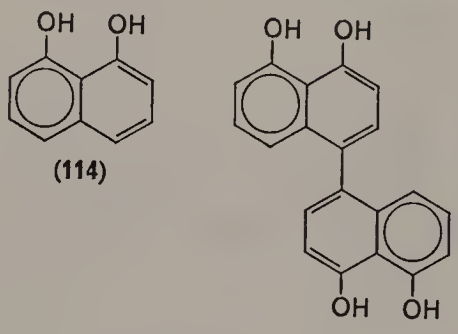
B. The Quinones that are Secondary Metabolites

Two observations emerge from Part A of this section which are particularly striking. Firstly, the structures of plastoquinones, ubiquinones and menaquinones are markedly alike. They all possess polyprenyl side-chains and can be deemed formally substituted benzoquinones. Secondly, and with the exception of chlorobiumquinone and rhodoquinone, there is little species specificity. The same ubiquinone which powered the muscles of a Caesar's conquering hand provides the lowly alga with its energy needs. This latter feature is a characteristic of all primary metabolites. In contrast thereto, secondary metabolites exhibit great species specificity sometimes even being strain-specific. It is this fact, maybe more than any other, that has made the problem of determining their function so difficult.

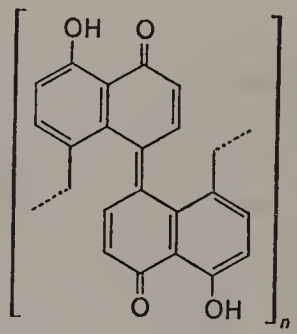
An interesting avenue of exploration has opened up with the demonstration that quinones are found in the defensive secretions of several arthropods[188a, b]. By far the most spectacular defence mechanism is that

of the bombardier beetles[189]. When threatened, these creatures jet onto their assailant a concoction of benzoquinones in hydrogen peroxide! Several substitution patterns are found in the benzoquinone armoury of the arthropods, viz. ethyl; 2,3-dimethyl; 2,5-dimethyl; 2,3,5-trimethyl; methoxy; 2-methoxy-3-methyl[188b]. Recently 6-methyl, 6-ethyl, 6-propyl and 6-butyl-1,4-naphthoquinones have been identified in the defensive secretions of the tenebrionid beetle, *Argoporis alutacae*[190].

Along similar lines of function should be considered the 'fungal melanins'[191]. The sporophores of species of *Daldinia* are darkly coloured due to the investment of their cell walls with quinonoid polymers such as **113**[192]. This polymer can be formed by phenol coupling of 1,8-dihydroxynaphthalene (**114**).



(114)



(113)

Not all the secondary metabolites, however, can be considered to have a defensive or structural role. In an attempt to rationalize the existence of the phenomenon itself, Bu'Lock[193] proposed that secondary metabolism is the organism's response to exhaustion of a specific nutrient from the environment. This nutritional deficiency causes a 'dislocation' in the organism's primary metabolic process, a 'dislocation' which takes the form of momentarily elevated levels of a few primary metabolites such as acetate, mevalonate, shikimate, etc. These elevated pool sizes trigger the production of secondary metabolite synthases and secondary metabolism is under way. In this manner, the organism protects itself from undue over-accumulation of any primary metabolite. Bu'Lock's ideas have been amplified in two recent reviews by Weinberg[194, 195]. While this concept of secondary metabolite function has much to commend it, and may, in fact, be correct in many situations, it is not the complete answer. Many secondary metabolites, both quinonoid and otherwise, are formed before any nutritional deficiency can possibly be felt, e.g. lawsone production in developing cultured root tips of *Impatiens balsamina*[196]. For such materials, our search for functional significance must continue.

IV. EPILOGUE

It is apparent that quinones play a variety of roles in our overall life cycle and that interest in their biological function has stimulated basic chemical research in several areas. The use of quinones, in fact, dates to antiquity and the recorded and verifiable history of these compounds is perhaps longer than that of any other group of naturally occurring compounds. Quinones came to man's attention in two ways—as pigments and as drugs.

As drugs, the use of crude preparations of various plants as purgatives has been recorded for well over 4000 years. Rhubarb, which contains various anthraquinones, is described in the Chinese herbal, *Pen-king*, believed to date from 2700 B.C.[197]. The use of senna was introduced by the Arabs who described its properties as early as the 9th century[198]. Its use survives today even in Europe and the United States and many other plant extracts have been used for the same purpose.

As pigments, two materials stand out, henna and madder. Henna is a paste of powdered leaves of *Lawsonia inermis* and has been used since antiquity as a cosmetic. It was considered indecent in ancient Egypt not to dye the fingernails with the orange-red colour of this preparation and many mummies have been found so decorated. It has also been used to dye parts of the hands, feet, hair and beard, as well as the manes of horses. Henna is believed to be the 'camphire' of *The Song of Solomon*[199] and was also used in the preparation of Moroccan leather[200]. The active principle is 2-hydroxynaphthoquinone (lawsone). Even in 1972, henna preparations are still used to dye hair (in the United States)[201]; to the younger hairdressers who are 'into ecology', it has the advantage of being a natural substance unassisted by chemistry!

Madder, a preparation of the root of *Rubia tinctorum* and other plants, contains the anthraquinone, alizarin. Cloth dyed with madder (which has not faded) has been found on Egyptian mummies, and it is also said to have been used to dye the cloaks of Libyan women in the days of Herodotus[202]. Madder was also used as a drug (to treat amenorrhea) by the ancients and in the Middle Ages.

A recent investigation of human bones from the cemetery at Qumran has provided evidence that the diet of this Dead Sea community included the madder plant. Alizarin has long been known to have a selective affinity for bone-forming areas of the skeleton and when growing animals are fed on madder, or subject to alizarin injection, the extremities of the long bones are particularly stained. Seven of ten skeletons from Qumran were likewise stained and a definite identification of alizarin was possible by infrared spectometry. It is known that madder root was made into

garlands by Jews from the second century B.C. to the second century A.D. as a preventive against witchcraft. Arabs still make a sherbet drink of madder which protects against the 'evil eye'. The concrete evidence for the dietary use of madder by the Essenes identifies a cultural custom persisting for at least 2000 years[203].

Madder was a major commercial dyestuff of considerable importance until the present century. The chemical synthesis of alizarin from anthracene by Graebe and Liebermann in 1868 and the development of a viable commercial process by Sir William Perkins (1869) are, of course, milestones in the history of organic chemistry. Synthetic alizarin was placed on the market in 1871 (for historical review, see Fieser[204]).

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CHAPTER 14

Electrochemistry of quinones

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I. INTRODUCTION

Simple quinone–hydroquinone couples are perhaps the most thoroughly studied organic redox couples. Discussions of the quinhydrone electrode are included in most instrumental analysis and elementary physical chemistry textbooks and can be found in some freshman chemistry books. The half-reaction (1) is presented as a typical reversible couple whose

$$Q + 2\,H^+ + 2\,e^- \rightleftharpoons QH_2 \qquad (1)$$

potential is rapidly established at an electrode surface and obeys the Nernst equation.

$$E = E^0 + \frac{RT}{2F}\ln\frac{a_Q}{a_{QH_2}} + \frac{RT}{2F}\ln a_{H+}^2 \qquad (2)$$

In these equations and throughout this chapter, Q represents the oxidized, or quinoidal form, QH_2 represents the hydroquinone form, and a_i is the activity of the ith species. The remaining terms in equation (2) have their usual significance. Under ordinary polarographic or potentiometric conditions equilibrium behaviour is observed for equation (1) and potentials of quinhydrone couples readily give solution pH values. But when the electrode kinetics of quinhydrone couples are examined closely, non-textbook complexities are evident.

Since quinone couples are easily studied and often readily available, they have been used as test cases for experimental verification of various theoretical models. Thus a wide range of ideas and methodologies have been applied to the interpretation of the electrochemical behaviour of quinone couples. Approaches to the study of quinone electrochemistry range from classical Tafel plots to pure voltammetry to synthetic organic chemistry. The outline chosen for this review is primarily mechanistic in nature. Contributions to the understanding of the kinetics and mechanisms of quinone and hydroquinone electrode reactions are reviewed. Both homogeneous and heterogeneous reactions are included. Electrode reactions of *ortho* and *para* quinones are emphasized; the isoelectronic quinonediimines, the phenylenediamines and their derivatives are mentioned only in passing. Purely analytical applications are not included.

The literature coverage is not intended to be complete, the emphasis being on the last fifteen years although an attempt has been made to include the important early polarographic papers. The pioneering potentiometric studies of Michaelis, Fieser and others are not dealt with as this work is well covered in the monograph by Clark[1]. Literature coverage for this chapter extends into early 1972.

The electrochemistry of quinones has been reviewed previously. The relevant chapters in the books by Kolthoff and Lingane[2] and by Brezina and Zuman[3] are excellent introductions to the older polarographic literature. The latter is especially strong on the analytical applications to physiological and biological samples. Quinones are also covered in the comprehensive text by Heyrovsky and Kuta[4], in the book on non-aqueous electrochemistry by Mann and Barnes[5] and in the monograph by Adams[6]. The chapter by Peover[7], who has made major contributions to modern quinone electrochemistry in non-aqueous solvents, is quite useful in this area. The biennial reviews in *Analytical Chemistry* by Wawzonek and more recently by Pietrzyk[8–13] contain sections on quinones and are an extremely useful and complete source of references.

None of these reviews contains an extensive survey of the kinetic and mechanistic aspects of the quinone electrode reactions and it is hoped that this chapter will fill that void.

II. HALF-WAVE POTENTIALS

A. Aqueous Solutions

Quinone reductions at the dropping mercury electrode (d.m.e.) are often electrochemically reversible and consequently polarographic half-wave potentials ($E_{\frac{1}{2}}$) of quinones are good approximations to potentiometric formal standard potentials, $E^{0\prime}$ values. These terms are related by the familiar equation (3) at 25°C where the potentials are given in volts.

$$E_{\frac{1}{2}} = E^{0\prime} - \frac{0{\cdot}06}{n} \log \sqrt{\frac{D_{ox}}{D_{red}}} \tag{3}$$

If the ratio of the diffusion coefficients of the oxidized and reduced forms of a couple is within 10% of unity, as is usually the situation for quinone couples, we have equation (4).

$$E_{\frac{1}{2}} = E^{0\prime} \pm 0{\cdot}001 \text{ V} \tag{4}$$

The polarographic experiment is less tedious than the potentiometric one and $E_{\frac{1}{2}}$s for a great variety of quinones in various mixed solvents are scattered throughout the chemical literature. The variety of experimental conditions (solvent, pH, supporting electrolyte, buffer components, etc.) makes a summary of $E_{\frac{1}{2}}$ data in aqueous solutions impracticable here. The monograph by Zuman[14] contains an outstanding compilation of the older $E^{0\prime}$ and $E_{\frac{1}{2}}$ data in the chapter on quinoidal compounds. Recent reports which contain extensive $E_{\frac{1}{2}}$ data on quinones in aqueous solution include the following series: 121 pyrocatechols[15], 27 pyrocatechols[16],

104 substituted 1,4-naphthoquinones[17], 35 sulphonyl derivatives of benzohydroquinone[18], 43 benzoquinones[19], 15 thio- and phenylsulphonyl benzoquinones[20], 25 benzohydroquinones[21], 12 halogenated and sulphonated 9,10-dihydroxyanthracenes[22], 23 substituted amino derivatives of benzoquinone[23] and 26 aminoquinones and quinone thioethers[24].

B. Non-aqueous Solutions

Table 1 in the Appendix to this chapter lists half-wave potentials for quinones in non-aqueous solvents. The first value listed usually corresponds to the reduction potential for the simple one-electron process (5),

$$Q + e^- \rightleftharpoons Q^{\bullet -} \tag{5}$$

to form the semiquinone anion. A second electron can be added to most quinones at more negative potentials and other waves may be present as well. The potentials for these waves are given in Table 1 when they are available.

Many of these $E_{\frac{1}{2}}$ values are referenced against an aqueous saturated calomel electrode (s.c.e.). Unfortunately, due to the variable liquid junction potentials which are encountered with this electrode in non-aqueous solvents, the aqueous s.c.e. is recognized as a poor choice for a non-aqueous reference electrode. The Ag/Ag^+ couple is often used as a basis for a non-aqueous reference electrode and is a superior choice to the s.c.e. However, when $E_{\frac{1}{2}}$ values are measured in non-aqueous solvents, some attempt should be made to relate the potential of the reference electrode used to the aqueous s.c.e. so that a comparison with the literature is possible. Best values for the half-wave potentials in Table 1 are difficult to determine because the reference electrode and liquid junction potentials cannot be compared in many cases. The half-wave potentials in this table have been rounded off to the nearest 0·01 V. Different experimenters working on the same system have obtained no better agreement than this. However, internal precision for a given series of quinones may well be better than 0·01 V and this information is not contained in Table 1. Also, in some cases the $E_{\frac{1}{2}}$s of simple derivatives of heterocyclic quinones are not given even though the data are available in the literature. The reader is referred to the literature on the parent compound in these cases.

Table 1 is organized in the following general manner. Simple quinones and their derivatives are given first, followed by the more complex hydrocarbons and then some heterocycles. The table is not meant to be an exhaustive listing (especially for the heterocycles), but does represent a

thorough literature search through 1971 and is a good entry into the literature for systems not discussed explicitly in this chapter.

C. Substituent Effects

Substituent effects on reversible half-wave potentials of quinone/hydroquinone couples have been elegantly treated by Zuman in a 1962 paper[14,25]. Half-wave potentials and $E^{0\prime}$ values for several series of benzo-, naphtho- and polycyclic quinones were shown to correlate with substituent constants using a modified Hammett equation:

$$\Delta E_{\frac{1}{2}} = \rho_{\pi,Q}\,\sigma_{P-X} \tag{6}$$

In this equation $\Delta E_{\frac{1}{2}}$ is the shift in half-wave potential relative to the unsubstituted quinone, $\rho_{\pi,Q}$ is the proportionality or reaction constant in volts and σ_{P-X} is the total polar substituent constant. The latter term is based on the acid dissociation constants of a series of substituted benzoic acids,

$$\sigma_{P-X} = \log(K_{XC_6H_4CO_2H}/K_{C_6H_5CO_2H}) \tag{7}$$

and contains contributions from both polar and resonance effects. For a quinone/hydroquinone couple polar effects would be predominantly operative in the quinone form, while resonance effects would be more important in the aromatic hydroquinone or semiquinone forms. Perhaps the most spectacular success of equation (6) is afforded by the correlation of the one-electron $E_{\frac{1}{2}}$s of quinones in acetonitrile solutions[26] shown in Figure 1[14]. The reaction constant, $\rho_{\pi,Q}$, for these data is 0·53 V and a range of almost 1·4 V is covered. Because the electrode process in this solvent is a simple one-electron step, this reaction constant can be viewed as an intrinsic parameter of the electron transfer process. In aqueous solutions much lower proportionality constants are obtained (ca. 0·2–0·3 V) and substituent effects are not always additive in a series of poly-substituted quinones. As Zuman has pointed out[14], care must be taken in interpretation of $\Delta E_{\frac{1}{2}}$ values in aqueous solutions because acid–base dissociation constants of substituted quinones and hydroquinones will be influenced by the substituents. In order to apply equation (6), the experimenter must establish that the $E_{\frac{1}{2}}$ versus pH dependence is identical for each member of the series under the experimental conditions of the study. For further details the reader is referred to Zuman's monograph[14].

D. Molecular Orbital Correlations

Simple molecular orbital theory was used to interpret potentiometric E^0 values of quinones several years ago with some success[27–30]. Following

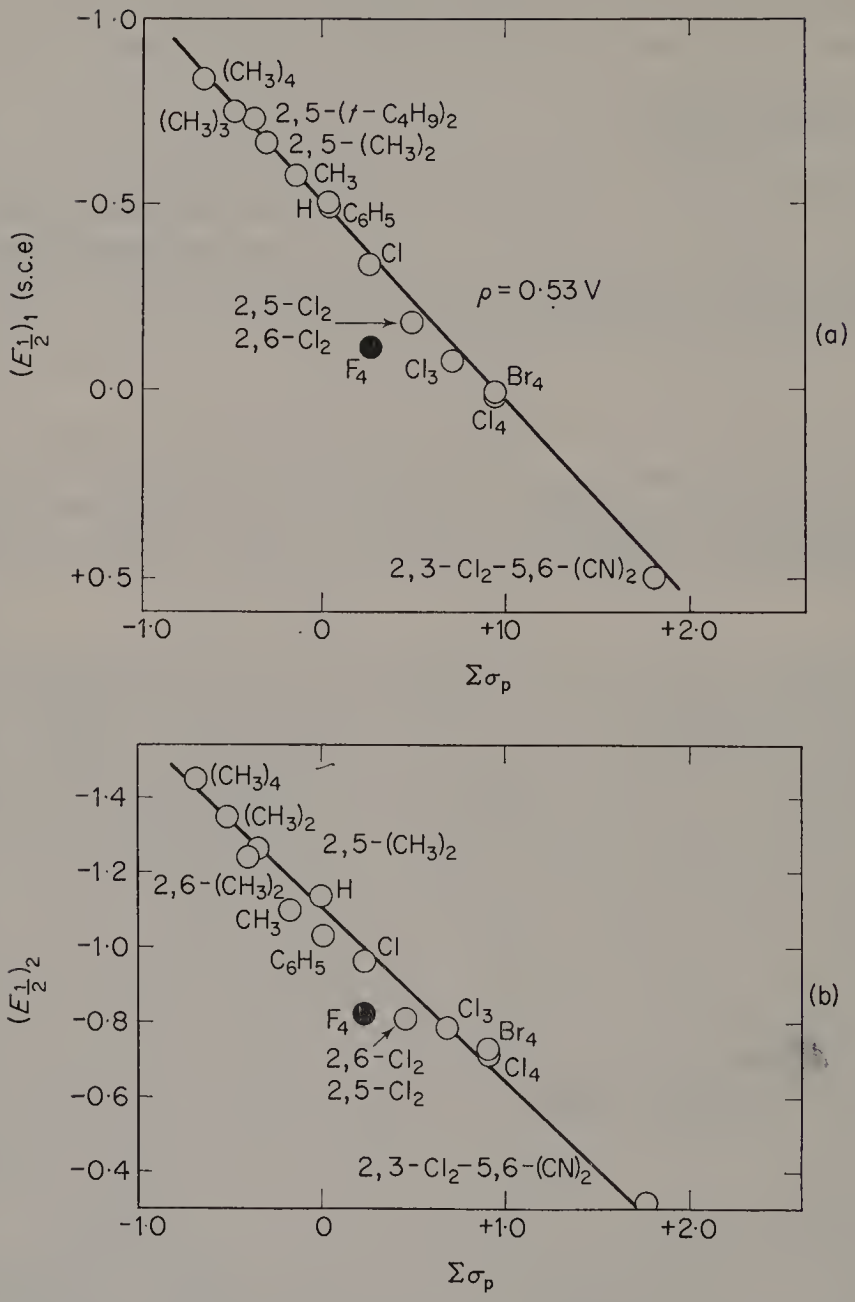


FIGURE 1. Relation of half-wave potentials for the reduction of substituted *p*-benzoquinones in acetonitrile solution to the sum of the Hammett substituent constants $\Sigma\sigma_{P-X}$. Half-wave potentials from reference 26; supporting electrolyte 0·1M $N(C_2H_5)_4ClO_4$. Value for tetrafluoroderivative (full point) deviates. (a) first wave; (b) second wave. (Reproduced with permission from P. Zuman, *Substituent Effects in Organic Polarography*, Plenum Press, 1967, Figure VIII-6, p. 287.)

Maccoll[31], who first demonstrated the relationship between electron affinities and polarographic $E_{\frac{1}{2}}$ values, equation (8) is readily derived[32].

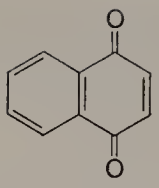
$$E_{\frac{1}{2}} = -E_{m+1} + C \tag{8}$$

Here the half-wave potential is equal to $-E_{m+1}$, the negative of the energy of the lowest unoccupied molecular orbital (l.u.m.o.), plus a constant which includes the difference in solvation energies of the neutral molecule and its radical anion. If this last term is constant, $\Delta E_{\frac{1}{2}}$ for a series of quinones should be given by $-\Delta E_{m+1}$. This relation has been demonstrated experimentally by Peover[33,34] for a limited series of unsubstituted quinones in acetonitrile. The half-wave potential of the second one-electron wave correlates with E_{m+1} as well, thus indicating that both the first and second electrons are added to the l.u.m.o. in the electrode processes.

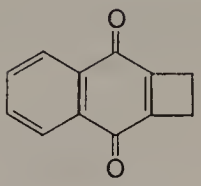
Dewar's semi-empirical molecular orbital procedure has been applied to the calculation of redox potentials for 25 quinone/hydroquinone couples[35]. The calculated values show good correlation with potentiometric $E^{0\prime}$ values in 95% ethanol, 0·1M LiCl, 0·1M HCl solutions.

Correlation of $E_{\frac{1}{2}}$s for substituted quinones with molecular orbital calculations has not been as successful. Hydroxyl derivatives in particular exhibit half-wave potentials more positive than those predicted by theory[36]. In some of these cases there is evidence that the electrode processes involve inter- and intramolecular hydrogen bond formation, thus invalidating a simple application of m.o. theory. The half-wave potentials for the first and second one-electron waves of a series of mono- and disubstituted chloroanthraquinones correlate with the energies of the l.u.m.o., but with different slopes[37]. In this series it appears that interactions of the chloro substituents with the reducible group are weaker in the semiquinone than in the quinone.

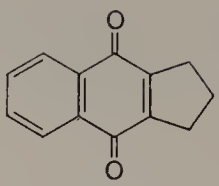
Ring-strain effects on half-wave potentials are nicely illustrated in a series of substituted 1,4-naphthoquinones[38]. Strain in the cyclobutane derivative induces more *p* character and less *s* character in the bonding of the carbons in the 2,3-positions and decreases the ability of the α-carbons to donate electron density to the quinone framework. Thus the half-wave potential of the cyclobutane derivative is almost the same as that of the parent naphthoquinone where there are no α-carbons to donate electron density. The strain-free cyclohexane derivative, on the other hand, has a half-wave potential almost identical with that of 2,3-dimethyl-1,4-naphthoquinone.



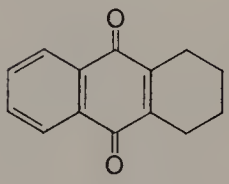
$E_{\frac{1}{2}} = -0.685$ V



-0.695 V



-0.748 V



-0.854 V

E. Spectroscopic Correlations

The most thoroughly interpreted correlation of quinone half-wave potentials is that between the maximum frequency of donor→quinone charge-transfer absorption bands (ν_{CT}) and polarographic $E_{\frac{1}{2}}$ values due to Peover and coworkers[26, 39, 40]. Quinones readily serve as acceptors in charge-transfer complexes with aromatic hydrocarbon donors such as anthracene, pyrene, hexamethylbenzene and others. The energy of the long wavelength absorption of the resulting complex can be approximated by the Mulliken equation,

$$h\nu_{CT} = I_D - E_A + \text{constant} \tag{9}$$

where I_D is the ionization energy of the donor molecule and E_A is the electron affinity of the acceptor. Using this equation, Peover and coworkers showed that ν_{CT} and $E_{\frac{1}{2}}$ values for equation (5) in non-aqueous solvents permitted estimates of relative electron affinities of quinones. Since the electron affinity of *p*-benzoquinone was known from gas-phase measurements, absolute values of E_A were determined for 13 mono-substituted quinones[26]. The principal assumption underlying the measurement is that solvation energies are similar throughout the series under study. For simple quinones in which a large fraction of the charge is localized on the oxygen atoms the approximation should be a good one. This assumption is usually necessary when spectroscopic $E_{\frac{1}{2}}$ correlations are made and has been discussed by Peover[41]. Other correlations of this type have been demonstrated for a series of high-potential quinones[42].

Various additional spectroscopic correlations have been proposed. A sampling of these involves the correlations of quinone half-wave potentials with the following parameters: the energy of the long wavelength $n \rightarrow \pi^*$ transition of 12 *para* and 3 *ortho* quinones[43], the shift ($\overline{\Delta\nu}$) of the O—H

stretching mode in some methyl-substituted benzohydroquinones[44], the p.m.r. chemical shifts of H_7 and H_3 in 2- and 2,3-disubstituted naphthoquinones[45], the energies of the absorption bands of the radical anions[46], the e.s.r. hyperfine splitting constant of the amine nitrogen in a series of aminosemiquinones[24] and the activation energies for the decay of a photoexcited state[47].

III. ELECTROCHEMISTRY IN NON-AQUEOUS SOLVENTS

In aprotic non-aqueous solvents quinones are reduced in two successive one-electron steps which are electrochemically reversible under usual polarographic conditions:

$$Q \underset{}{\overset{e^-}{\rightleftharpoons}} Q^{\bar{\cdot}} \overset{e^-}{\rightleftharpoons} Q^{2-} \qquad (10)$$

The first clear demonstration of semiquinone formation in the first polarographic wave was given by Wawzonek and coworkers[48]. In this early work, benzoquinone, duroquinone, 2-methylnaphthoquinone and anthraquinone were studied in acetonitrile (MeCN) and *N*,*N*-dimethylformamide (DMF) and the effect of proton sources on the positions and heights of the two waves noted. Several years later the first observation of an e.s.r. signal from an electrochemically generated radical ion was made by Austen and coworkers[49] who observed the spectrum of the radical anion of anthraquinone after freezing an electrolysis solution. These simple experiments have been refined and repeated for many quinone systems under a variety of experimental conditions in the last fifteen years.

The straightforward polarographic behaviour of quinones in aprotic solvents can be altered by any perturbation on the diffusion layer concentrations of Q, $Q^{\bar{\cdot}}$ or Q^{2-}. Acid–base, ion-pairing and complex formation equilibria are the principal perturbations on those concentrations which have been studied. These effects can simply shift the first or second quinone reduction waves in a Nernstian manner or can completely eliminate waves and replace them with new diffusion or kinetically controlled processes. For the most part the electrochemistry of quinones and hydroquinones in non-aqueous solvents involves these diffusion layer chemical reactions. The electron transfer reactions appear to be very fast, and when attempts have been made to measure them, diffusion-controlled reactions have been indicated[34]. Furthermore, adsorption seems to be minimal in these solvents for most simple quinones and does not come into play unless biologically important quinones with large molecular weights are examined.

A. Proton Donor Effects

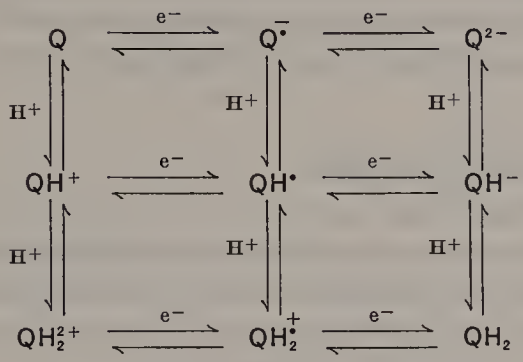
I. General considerations

As electrons are added to the quinone structure (equation 10), the electron density on the oxygen atoms and the basicity of the molecule increases dramatically. Each of the species in equation (10) is capable of accepting one or two protons. For *p*-benzoquinone, the fully reduced dianion is a relatively strong base, the pK_as of *p*-benzohydroquinone being 10·35 and 11·4. The pK_as of the semiquinone oxidation state are much smaller. For $QH^{\bullet}$ a pK_a of ca. 4·0 has been determined by pulse radiolysis and e.s.r. measurements in aqueous solutions[50–52]. The pK_a of $QH_2^{+\bullet}$ has not been reported, but this species is stable in strongly acid media such as $AlCl_3$–$MeNO_2$ mixtures[53] and concentrated sulphuric acid[54]. The quinoidal structure is more difficult to protonate and few reports of K_as for QH^+ species are in the literature. Biedermann has estimated $pK \approx -1$ for protonated *p*-benzoquinone from shifts of less than 1 mV in the potentiometric $E^{0\prime}$ value in concentrated acid solutions[55]. However, there is some dispute over this value since quinone species which are stable in concentrated acid solutions give pK values considerably lower on a Hammett acidity function scale[56, 57]. Badoz-Lambling and Demange-Guérin report that *p*-benzoquinone is not protonated in DMF by perchloric acid on the basis of spectrophotometric studies[58].

In non-aqueous solvents, in which a wide range of hydrogen ion activity is possible, the role of proton donors and proton availability in quinone redox processes becomes clearly evident. Potential shifts of almost 1 V can occur for a reduction of a given quinone by variation of the type and amount of proton donor present in non-aqueous solvents. Incidentally, these results were anticipated, in part, by Müller who studied the quinhydrone couple in weakly buffered aqueous solutions[59–61]. He found that both the amounts of buffer components present and the rates at which they act as proton donors or acceptors would effect the position of the Q and QH_2 waves. In a novel experiment, the addition of the enzyme carbonic anhydrase, which catalyses the acid–base proton transfer reactions in carbonate buffers, converts an irreversible Q/QH_2 polarographic wave (pH 7·5, carbonate buffer) into a reversible one[61].

If each possible protonated form is considered, a nine species array of electrochemical pathways is possible (equation 11). The Q/QH_2 couple has been analysed in terms of this array previously by Jacq[62] and by Jeftic and Manning[63]. If we ignore the unlikely intermediacy of the QH_2^{2+} species, there are five possible pathways from Q to QH_2. By the addition of proton donors of varying acid strength, each of

these routes can be demonstrated in the electrode reactions of most quinones.



(11)

2. Protonation of $Q^{\bar{\cdot}}$ and Q^{2-}

In their early experiments Wawzonek and coworkers[48] observed that addition of water to DMF solutions shifted the second one-electron wave of several quinones to more positive potentials and did not markedly alter the first one-electron wave. These results indicate that rapid protonation of Q^{2-} is taking place in the diffusion layer. If stronger proton donors than water are employed, it is possible to protonate $Q^{\bar{\cdot}}$ at potentials of the first wave. This was first demonstrated by Given and Peover[64], who studied anthraquinone reduction in the presence of phenol and benzoic acid. With the latter proton donor, the first wave is increased at the expense of the second until a single two-electron wave is observed at a 5 : 1 ratio of acid to quinone. This behaviour is interpreted by postulating protonation of $Q^{\bar{\cdot}}$ to form $QH^{\cdot}$, which is reduced at the potential of the first wave (equation 12). This is the mechanism originally suggested by

$$
\begin{aligned}
&Q + e^- \rightleftharpoons {}^{\bar{}}Q^{\cdot} \\
&Q^{\bar{\cdot}} + HA \rightleftharpoons QH^{\cdot} + A^- \\
&QH^{\cdot} + e^- \xrightarrow{\text{fast}} QH^- \\
&Q^{\bar{\cdot}} + QH^{\cdot} \longrightarrow Q + QH^-
\end{aligned}
\qquad (12)
$$

Hoijtink and coworkers for the reduction of aromatic hydrocarbons in the presence of HI[65]. The fourth reaction represents a solution electron transfer step which will be thermodynamically favoured if $QH^{\cdot}$ is readily reduced at the potential of the first wave. This reaction was initially suggested by Austen and coworkers[49]. The calculations of Hoijtink for hydrocarbons show that the electron affinity of the protonated radical

anion is greater than that of the parent hydrocarbon and thus one two-electron reduction occurs. This pathway has been shown to be operative in several quinone reductions including stilbene quinones[66], α-tocopheryl-quinone[67], ubiquinone-1[68] and 2-methylnaphthoquinone[69] in addition to the simple ones[64].

3. Disproportionation reactions

Reactions other than those contained in equation (11) are possible in the presence of proton donors, e.g. disproportionation and dimerization. Umemoto has found that the Hoijtink mechanism (equation 12) does not describe the reduction of anthraquinone (AQ) in the presence of a large excess of water[70]. In 50% water–DMF mixtures, the anthraquinone reduction wave has almost reached a two-electron height, although the semiquinone species has an appreciable lifetime in solution. A kinetic analysis of the decay of the e.s.r. signal indicated that the radical species decays via a disproportionation reaction:

$$\begin{aligned} AQ^{\bar{\bullet}} + AQ^{\bar{\bullet}} &\rightleftharpoons AQ + AQ^{2-} \\ AQ^{2-} + 2\,H_2O &\rightleftharpoons AQH_2 + 2\,OH^- \end{aligned} \qquad (13)$$

Disproportionation reactions for $AQ^{\bar{\bullet}}$ and AQH have also been discussed by Kuwana and coworkers[71,72] who report absorption spectra of anthraquinone reduction products in LiOH solutions using optically transparent electrodes[71].

Solvent effects on the $E_{\frac{1}{2}}$s of AQ in DMF/H_2O mixtures have been correlated with the $\Delta\lambda_{max}$ of the absorption bands of $AQ^{\bar{\bullet}}$ and AQ^{2-} in the visible region[73]. Marked blue-shifts are observed, which are consistent with strong hydrogen bonding between the anions and water.

4. Preprotonation reactions

If the proton donor is a sufficiently strong acid, quinone reduction occurs via the protonated species, QH^+. For simple benzoquinones, addition of acids such as perchloric acid, *p*-toluenesulphonic acid and chloroacetic acids results in the appearance of a 'prewave' which is proportional to the concentration of the acid. These prewaves occur at potentials as much as 0·6 V more positive than the simple one-electron reduction of the corresponding quinone. This potential shift is too large to be explained by a rapid follow-up protonation of $Q^{\bar{\bullet}}$ in the diffusion layer and suggests prior protonation of the quinone (equation 14).

$$Q + H^+ \underset{k}{\overset{k_1}{\rightleftharpoons}} QH^+ \xrightarrow{2e^-,H^+} QH_2 \qquad (14)$$

Although the inequality, $k_1[H^+] \ll k_{-1}$, obtains under most polarographic conditions, reduction may proceed via QH^+ if $k_1[H^+]_{x_2}$ is large, where $[H^+]_{x_2}$ is the concentration of hydrogen ions in the diffuse double layer. These 'QH^+ waves' in non-aqueous media have been reported for simple quinones[63,74–77], benzopyrenequinones[78], biologically important quinones[67–69] and others. Reduction via QH^+ is similar to the mechanism proposed by Vetter[79] for quinone reduction in acidic aqueous solutions which is discussed below. Significantly, the non-aqueous QH^+ waves have roughly the same appearance and position for mercury, platinum and carbon electrodes[75]. The involvement of adsorbed hydrogen atoms in the electrode process is therefore unlikely. However, in the presence of excess acid on electrodes such as platinum the reduction process can be complicated by the simultaneous evolution of hydrogen[67,75].

The QH^+ wave is dependent on both the pK_a of the proton donor and the basicity of the quinone. By introducing electron-donating substituent groups on the quinone ring, Cauquis and coworkers have clearly demonstrated the intermediacy of the QH^+ species[77]. For 2,6-dimethoxybenzoquinone and 3,3′,5,5′-tetramethoxybiphenylquinone, the QH^+ species are readily prepared in acetic acid–acetonitrile solutions and their u.v. and visible absorption spectra obtained. For these quinones the two-electron QH^+ waves have a log slope of 30 mV and shift by 30 mV per decade increase in acid concentration. These results are consistent with a reversible two-electron reduction of QH^+ to QH_2.

The value of $-E_{\frac{1}{2}}$ for the QH^+ wave in methyl cellosolve solutions is directly proportional to the pK_a of the proton donor. For a series of proton donors including chloracetic acids and chlorophenols, the $E_{\frac{1}{2}}$ for QH^+ was found to shift by ca. -50 mV per unit increase in pK_a[80,81]. Similar dependences have been reported in DMF solutions by Demange-Guérin[82] and by Kheifets and coworkers[83,84].

While the intermediacy of the QH^+ species is well established, the kinetics of the reduction process (equation 14) have not been worked out. In general the QH^+ wave is somewhat drawn-out and exhibits kinetic character. (The term 'kinetic character' is used in the sense that the flux of an electroactive species at the electrode surface, and hence the current, is limited by the rate of a chemical reaction which is slow on the time scale of the electrochemical measurement.) Even the well-behaved systems studied by Bessard, Cauquis and Serve[77] (see above) exhibit kinetic character when the time scale of the electrochemical experiment is decreased. Thus the experimental current function of 3,3′,5,5′-tetramethoxybiphenylquinone in $HClO_4$ solutions decreases at fast sweep rates[77]. Similar behaviour was observed for the duroquinone QH^+ wave

in acetonitrile[75]. On the other hand, the current function of the unsubstituted benzoquinone on both mercury and platinum electrodes was found to be constant at sweep rates up to 500 V/s[75]. Slow heterogeneous steps, both electron transfer and adsorption, as well as slow protonation reactions, are possible kinetic complications in these QH^+ electrode reactions.

The QH^+ wave has been exploited by several workers for the analytical determination of acids. For example, Takamura and Hayakawa[80, 81, 85] have been able to analyse mixtures of acids, e.g. acetic and perchloric acids, which give separate QH^+ polarographic waves. In the presence of excess quinone these waves are proportional to the acid concentrations. This procedure has also been used in unbuffered aqueous solutions for the determination of trace acidic components[86].

5. Reduction of hydroxylquinones

Hydroxy derivatives of quinones fall into a somewhat special category since mechanistic complications not encompassed by equation (11) are possible. These molecules can function as proton donors themselves, and if the hydroxyl substituent is α to the carbonyl group, intramolecular hydrogen-bond formation can stabilize the intermediate semiquinone species. This latter behaviour is well documented in the e.s.r. literature[87]. Thus half-wave potentials for α-hydroxylquinones are more positive than those of the parent compounds by up to 0·4 V and do not correlate with Hammett substituent constants or simple molecular orbital calculations[33, 34, 36, 88].

By far the most thoroughly studied α-hydroxylquinone is 1-hydroxy-9,10-anthraquinone, HOAQ. Piljac and Murray[89] studied the effect of proton donors on the electrochemistry of HOAQ and its conjugate base (OAQ^-) in several non-aqueous solvents and came to some interesting conclusions. Reduction of OAQ^- in the absence of added proton donors occurs in a two-electron, one-proton step in which protons are supplied by the media:

$$OAQ^- + HS + 2\,e^- \rightleftharpoons HOAQ^{2-} + S^- \qquad (15)$$

Addition of the weak proton donor, phenol, results in the appearance of two new diffusion-controlled waves at potentials more negative than the reversible one-electron reduction of HOAQ and more positive than the two-electron reduction of OAQ^- (equation 15). The first of these waves

is assigned to the reduction of a heteroconjugate acid–base dimer via the following reactions:

$$C_6H_5OH + OAQ^- \rightleftharpoons [C_6H_5OH \cdots OAQ]^-$$

$$[C_6H_5OH \cdots OAQ]^- + e^- \longrightarrow HOAQ^{\bullet -} + C_6H_5O^- \qquad (16)$$

$$[C_6H_5OH \cdots OAQ]^- + C_6H_5O^- \longrightarrow [C_6H_5OH \cdots OC_6H_5]^- + OAQ^-$$

The overall reaction is

$$OAQ^- + 2\,C_6H_5OH + e^- \longrightarrow [C_6H_5OH \cdots OC_6H_5]^- + HOAQ^{\bullet -} \qquad (17)$$

The second wave is due to reduction of unreacted OAQ^-; i.e.

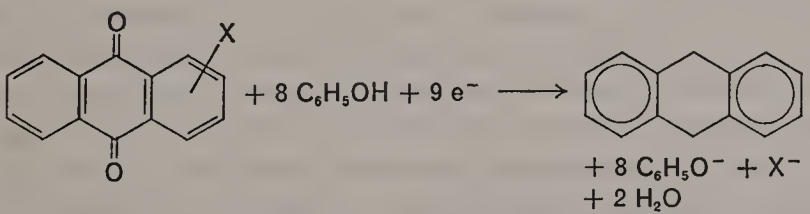
$$OAQ^- + e^- \longrightarrow OAQ^{2-}$$

$$OAQ^{2-} + [C_6H_5OH \cdots OC_6H_5]^- \longrightarrow HOAQ^{\bullet -} + 2\,C_6H_5O^- \qquad (18)$$

In equations (16)–(18), the homoconjugate acid–base dimer, $[C_6H_5OH \cdots OC_6H_5]^-$, is a product of the reductions. This species can also act as a proton donor, e.g. equation (18), but is a weaker acid than phenol. Splitting of the second wave in the reduction of HOAQ in the presence of phenol is attributed to follow-up protonation reactions by both C_6H_5OH and $[C_6H_5OH \cdots OC_6H_5]^-$. These results of Piljac and Murray[89], which are supported by spectroscopic in addition to polarographic data, represent one of the most detailed analyses of proton donor effects in non-aqueous electroorganic chemistry.

6. Carbon–oxygen bond scission

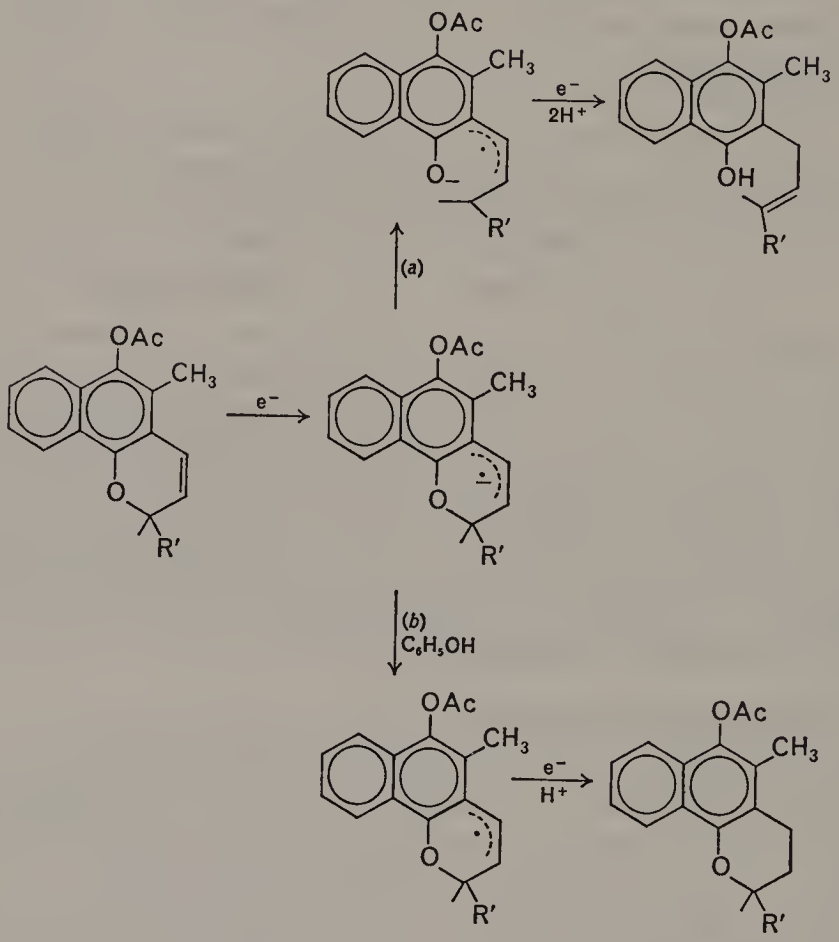
Finally, scission of carbon–oxygen bonds has been reported for some quinones by reduction at very negative potentials in the presence of an excess of proton donor. For example, electrolysis of anthraquinone–phenol solutions in DMF–tetraethylammonium iodide at −2·15 V versus s.c.e. gives a 60% yield of 9,10-dihydroanthracene[90]. Similar products were obtained for some halogen derivatives of anthraquinone by Bezuglyi and coworkers[91] who report the following stoicheiometry in DMF solutions.



(19)

Phyllochromanol acetates are reduced via two routes (equation 20) in DMF[92]. In the absence of added proton donor, C—O bond fission occurs

(route *a*) to yield the hydroquinone form, while in the presence of a hundredfold excess of phenol the chromanol ring remains intact during the reaction. In the absence of added proton donors (route *a*) protons are presumably supplied by residual water and/or the supporting electrolyte.



(20)

B. Oxidation of Hydroquinones

All of the oxidative pathways from QH_2 to Q contained in equation (11) have been postulated for various hydroquinone oxidations in non-aqueous solvents. In the presence of excess tetrabutylammonium hydroxide both protons are removed from simple hydroquinones and separate one-electron waves are observed for oxidation of the Q^{2-} and $Q^{\dot{-}}$ species[75, 82]. In these strongly basic solutions, this apparently simple behaviour is complicated considerably by autooxidation of the quinone[69] and by precipitation of a QH^- salt[82, 93]. The solubility product

$K_{sp} = [NBu_4^+][QH^-]$, is $10^{-4.5}$ for the tetrabutylammonium salt of the monoanion of *p*-benzohydroquinone in DMF[82,93]. Thus, as QH_2 is titrated with NBu_4OH in acetonitrile, all voltammetric waves decrease until the end-point is reached. Past the end-point the precipitate dissolves according to equation (21).

$$NBu_4QH + OH^- \longrightarrow NBu_4^+ + Q^{2-} + H_2O \qquad (21)$$

1. Oxidation of QH^-

Oxidation of QH^- can be observed by the use of a non-hydroxylic base such as pyrrolidine[75], 2,6-lutidine[76] or pyridine[69]. In these solutions a new wave appears at potentials ca. 0·7 V more positive than the corresponding QH_2 oxidation wave. This wave has been assigned to oxidation of a QH^- species (equation 22). The analysis is similar to that for the QH^+ wave

$$\begin{aligned} QH_2 + B &\underset{k_1}{\overset{k_1}{\rightleftharpoons}} BH^+ + QH^- \\ QH^- &\rightleftharpoons QH^{\bullet} + e^- \\ QH^{\bullet} &\rightleftharpoons Q^{\bar{\bullet}} + H^+ \\ Q^{\bar{\bullet}} &\xrightarrow{\text{fast}} Q + e^- \end{aligned} \qquad (22)$$

discussed above; i.e. if $k_1[B]_{x_2}$ is large, oxidation can proceed via QH^-.

2. Oxidation of QH_2

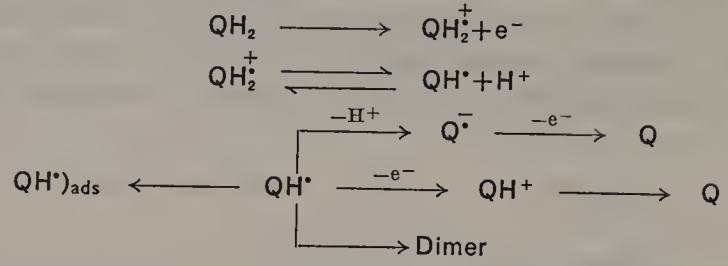
Oxidation of the fully protonated hydroquinone occurs via an irreversible two-electron process (equation 23). The products of the

$$QH_2 \longrightarrow Q + 2H^+ + 2e^- \qquad (23)$$

oxidation are the corresponding quinone and protons, which are readily detected in the cyclic voltammetric experiment by the appearance of a QH^+ wave on the reverse potential sweep. This behaviour was originally reported by Turner and Elving[94] for pyridine solutions and is general for aprotic solvents[74,75].

Kinetic character has been reported for QH_2 oxidation waves although this point has been disputed. The linear sweep voltammetry current functions for some simple hydroquinones have been reported to decrease at fast sweep rates and give apparent *n*-values less than two[75]. Similar behaviour has been observed for 2-methylnaphthohydroquinone[69]. These results suggest the existence of a kinetically significant one-electron intermediate in the QH_2 oxidation process, i.e. $QH^{\bullet}$ or its equivalent in

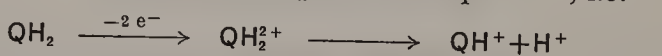
the following oxidation scheme:



(24)

Several possible routes are available to a one-electron intermediate as indicated by equation (24). A reduction wave which has been observed in the cyclic voltammograms of simple hydroquinones has been tentatively assigned to an intermediate dimeric species[75]. This interpretation has been challenged by Parker and Eberson[75] who found that the limiting current constant for QH_2 oxidation at a platinum rotating disk electrode was constant at angular velocities up to 500 rad/s and indicated a two-electron process. Furthermore, the limiting current was not decreased by the addition of a tenfold excess of 2,6-lutidine. Eggins[96] has recently re-interpreted the data of Parker and Eberson in terms of a one-electron transfer. More experimental work over a wider concentration range appears to be necessary to settle this issue.

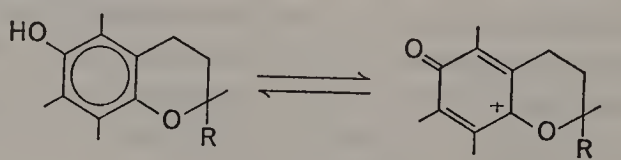
The role of protons in QH_2 oxidations is clearly indicated by the effect of acids on the oxidation of 3,3′,5,5′-tetramethoxybiphenylhydroquinone[77]. The addition of 10^{-2}M $HClO_4$ results in the increase of the linear sweep voltammetry current function by ca. 40%, although the limiting current at a rotating disk electrode remains constant. This suggests an increase in reversibility and implicates protons in a rate-determining step in the oxidation process. Cauquis and coworkers[77] suggest that the oxidation proceeds via the QH_2^{2+} species in the presence of protons; i.e.



(25)

3. Oxidation of tocopherols

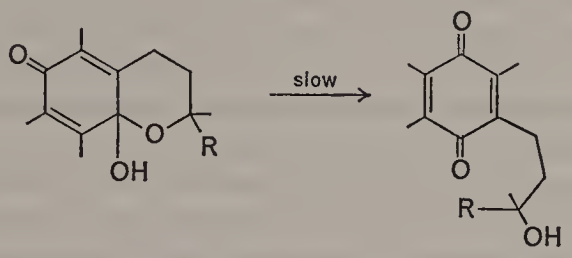
In some cases the two-electron hydroquinone oxidation process becomes electrochemically reversible. This is nicely demonstrated by α-tocopherol and the model compound, 2,2,5,7,8-pentamethyl-6-hydroxychroman, which produce reversible two-electron cyclic voltammograms in acetonitrile solutions[97–99].



$+ H^+ + 2e^-$ (26)

R = $C_{16}H_{33}$ or CH_3

The resulting carbonium ion is rapidly attacked by water to give an electroinactive species which opens to give an electroactive quinone[98] (equation 27). This latter reaction has been studied in detail and has been shown to involve both general acid and base catalysis[99].



(27)

C. Metal Ion Effects

Small amounts of metal ions can have striking effects on the current-potential curves of quinones in non-aqueous solvents. Both the semiquinone and the quinol dianion species can complex and/or form ion pairs with metal ions. The usual result is to shift the first or second one-electron wave to more positive potentials, but in some cases the behaviour becomes more complicated.

Peover and Davies have studied the effect of metal perchlorates on the reduction of anthraquinone in DMF solutions[100]. The radical anion, $AQ^{\bullet-}$, forms a 1 : 1 complex with Li^+ but not with Na^+ K^+, NEt_4^+ or NBu_4^+. The dianion AQ^{2-} is complexed by all these cations, which shifts the second reduction wave to considerably more positive potentials. The order of complexing strength is $Li^+ > Na^+ > K^+ > NEt_4^+ > NBu_4^+$. Similar results were indicated for *p*-benzoquinone and chloranil. Ion-pair formation is more prevalent in acetonitrile solutions, but the tetraalkylammonium salts, $NR_4^+Q^{\bullet-}$, were also found to be completely dissociated in this solvent.

Metal ions have similar effects on the reduction of 1,2-naphthoquinone and 1,4-naphthoquinone in DMF, DMSO, CH_3CN, propylene carbonate and acetone[101]. The effect of complex formation is more pronounced with the *ortho* quinone and increases in the order,

$$K^+ < Na^+ < Li^+ < Mg^{2+} < Zn^{2+}$$

With the divalent cations the two one-electron waves are merged into one drawn-out two-electron process. The solvent effect operative in these systems has been recently interpreted in terms of solvent donicity[102].

In the above systems the $NR_4^+Q^{\bullet-}$ salts were found to be completely dissociated at polarographic concentration levels. This is not always the

case; for example, the tetrabutylammonium salt of a pyracylene semiquinone appears to be associated in DMSO[103].

Cyclic voltammograms and reverse current chronopotentiograms of *p*-benzoquinone at hanging mercury drop and platinum electrodes in the presence of lithium ions present features more complex than suggested by the above polarographic results. In DMSO, chronopotentiometric results indicate that addition of LiCl causes the second one-electron wave to disappear, although the first wave retains its one-electron character[104]. In addition, a small wave appears at potentials between the original one-electron waves. Controlled potential electrolysis indicates that severe electrode filming occurs at potentials corresponding to the first wave. Similar results were obtained by Eggins[105] who reported deposition of a yellowish-blue film on a platinum electrode in acetonitrile solutions containing 0·1M $LiClO_4$. A large anodic stripping wave was observed which was attributed to oxidation of adsorbed LiQH.

D. Change–transfer Complexes

Polarographic half-wave potentials of quinones have been combined with spectral absorption maxima of charge-transfer complexes to estimate electron affinities of electron acceptors (see section II.E above). In addition, Peover[106] has developed the theory for determination of charge-transfer complex formation constants from shifts in the polarographic half-wave potentials. The theory was applied to several strong charge-transfer complexes, including those of chloranil and dicyanodichlorobenzoquinone with the donor molecules, hexamethylbenzene and pyrene. Comparison of spectroscopic and polarographic methods revealed that the latter technique can provide a direct method of obtaining formation constants when one of the components is electroactive.

IV. ELECTROCHEMISTRY IN AQUEOUS SOLUTIONS

A. Electrochemical Kinetics

The quinone/hydroquinone couple presents a 'non-textbook' complexity when the electrochemical kinetics are examined in detail in aqueous solutions. The 3×3 array of reactants, intermediates and products which are interrelated by electron and proton transfer steps (equation 11) must again be taken into consideration. Indeed all nine of these species (and one more) have been proposed by different authors in electrode schemes in aqueous solutions, sometimes within relatively narrow pH regions. In addition, the likelihood of adsorbed species in aqueous solutions should be considered, thus adding a third dimension to the above scheme (equation

11). Finally, the concept of partial charge-transfer at electrode surfaces has been applied to the Q/QH_2 couple, further refining the above scheme[107].

For aqueous solutions, the literature on the Q/QH_2 kinetics divides between work on mercury and work on platinum and other solid electrodes. The solid electrode results will be discussed first.

I. Kinetics at solid electrodes

The electrochemical reduction of benzoquinone was first studied by Haber and Russ[108] at the turn of the century. In spite of the incorrect conclusion that quinone reduction proceeds via hydrogen ion reduction, this paper was well ahead of its time. Thirty-three years later Rosenthal, Lorch and Hammett[109] published a careful study of Tafel plots* for quinhydrone solutions in the pH region 1–8. These workers measured reaction orders at low overvoltages and found first-order dependence on both Q and QH_2. However, the Tafel slopes were not constant and definitive mechanistics conclusions were not reached.

In an important paper in the early fifties, Vetter presented Tafel plots at platinum electrodes that extended into the limiting current regions for quinhydrone solutions between pH 0·2 and 7·2[79,110]. The limiting currents were shown to be purely diffusion controlled. Vetter's conclusion that two different consecutive charge-transfer reactions occur over a wide pH region has gained wide acceptance in the modern literature. The electrochemical reaction orders which were established for Q, QH_2 and H^+ indicated a change of mechanism between pH 5 and 6. Below pH 5 the order of electron and proton transfer for Q reduction is H^+, e^-, H^+, e^- (HeHe); while for pH greater than 6, the order is e^-, H^+, e^-, H^+ (eHeH) Thus the two mechanisms are:

$$\begin{aligned}
Q + H^+ &\rightleftharpoons QH^+ \\
QH^+ + e^- &\longrightarrow QH^\bullet \\
QH^\bullet + H^+ &\rightleftharpoons QH_2^{+\bullet} \\
QH_2^{+\bullet} + e^- &\longrightarrow QH_2
\end{aligned} \qquad pH < 5 \qquad (28)$$

$$\begin{aligned}
Q + e^- &\longrightarrow Q^{-\bullet} \\
Q^{-\bullet} + H^+ &\rightleftharpoons Q^{-\bullet} \\
QH^\bullet + e^- &\longrightarrow QH^- \\
QH^- + H^+ &\rightleftharpoons QH_2
\end{aligned} \qquad pH > 6 \qquad (29)$$

* Tafel plots represent the familiar linear dependence of overvoltage on the logarithm of the current.

Similar mechanisms have been advanced for quinone reduction on mercury electrodes (see section IV.A.2 below) and in non-aqueous solvents (see sections III.A.2 and II.A.4). In a recent paper Dohrmann and Vetter[111] have reached nearly identical conclusions for the duroquinone/durohydroquinone couple in aqueous–methanol buffers at gold electrodes. For this system the transition between the HeHe and eHeH mechanisms occurs between pH 3·1 and 6·6.

Vetter's mechanism has been disputed by Loshkarev and Tomilov[112] who found a zero-order dependence on hydrogen ion in the benzoquinone reduction on platinum. A direct rate-determining two-electron transfer over a wide pH range was proposed (equation 30). Similar results were

$$Q + 2\,e^- \longrightarrow Q^{2-} \xrightarrow{H^+} QH_2 \qquad (30)$$

obtained for 9,10-anthraquinone-2-sulphonate. Under controlled conditions a minimum in the exchange currents occurred at approximately pH 3, although the exchange currents measured by these workers tended to decrease with time due to adsorption of quinhydrone decomposition products and other impurities from solution.

The exchange current was also found to be markedly dependent on electrode material and the electrode pretreatment[113]. The following order of decreasing electrochemical activity was found although the order could be altered by differing electrode pretreatment: graphite > platinized graphite $\gg$ Au > Rh > Pd > Ir > Pt. For graphite nearly Nernstian behaviour was observed for the complete current-potential curve, while oxidized platinum gave the most irreversible behaviour. In general, cathodic polarization in H_2SO_4 increased the observed exchange current density for a particular electrode material. Surface platinum oxide formation has also been implicated as the cause of anomalous behaviour in the oxidation of QH_2 in weakly basic solutions[114].

Exchange current densities for the Q/QH couple which were constant with time and considerably higher than those reported by previous workers were found in carefully purified solutions by a second group of Russian workers[115]. The low exchange currents of previous workers[79, 112, 113] were attributed to adsorption of impurities, the supporting electrolyte or oxygen after anodic electrode pretreatment. A minimum in the exchange current pH profile was again found at approximately pH 4. The results support Vetter's mechanisms, equations (28) and (29), although the exact order of proton and electron transfer steps is not clearly stated in their papers. Adsorption of Q and QH_2 is indicated by the non-integral dependence of the exchange currents on the Q and QH_2 concentrations.

These workers extended their studies and quantitatively determined the dependence of the exchange current on the concentration of species which are adsorbed on the platinum electrode surface[116]. The decrease of the exchange current was linearly related to the logarithm of the concentration of the additive for a series of anions ($F^- < Cl^- < Br^-$), cations ($K^+ < NH_4^+ < Rb^+ < Cs^+ < NMe_4^+$) and neutral organic molecules (hexyl alcohol < isoamyl alcohol < phenylacetic acid). In these series the species least strongly specifically adsorbed (i.e. KF) was the least effective in lowering the observed exchange current. Double-layer corrections were discussed but not taken explicitly into account. It was further demonstrated by radioisotope measurements that the exchange current decreases linearly with the amount of adsorbed bromide ion on the electrode. These results readily rationalize the lack of agreement between exchange currents reported in the presence of different 'inert' supporting electrolytes. Unfortunately, double-layer parameters are not generally available for platinum electrodes so that true exchange current densities could not be determined.

Adsorption effects have also been noted by Gileadi in the current-potential curves of hydroquinones at platinum electrodes[117,118]. At QH_2 concentrations greater than approximately 0·1M 'self-inhibition' of the electrode process occurs and limiting currents are not observed. Adsorbed intermediates and products were invoked to rationalize these results. A similar phenomenon has been observed in acetonitrile solutions at high concentrations of quinhydrone; see Figure 7 in reference 75.

Finally, a novel experiment due to Peover[119] will be mentioned here, although it was carried out in a non-aqueous solvent. He applied a triangular wave to a platinum electrode directly in the cavity of an e.s.r. spectrometer and measured the resulting e.s.r. signal which was in phase with the electrode potential. The system was chloranil in acetonitrile and the resulting spectrum was ascribed to the semiquinone species in the vicinity of the electrode surface. Radical species in the bulk of the solution were not detected since they were not being modulated at the frequency of the triangular wave. The resulting spectrum was broadened and shifted downfield in accord with expectations for a semiquinone species specifically adsorbed on the electrode surface.

2. Kinetics at mercury electrodes

Although many polarographic studies on quinone systems exist in the literature, surprisingly few papers are devoted to the electrochemical kinetics of the quinone/hydroquinone couple. The intermediacy of the semiquinone species was apparent to polarographic workers[120–122], but

early studies were carried out under diffusion-controlled conditions and no meaningful kinetic information was obtained.

Quinone/hydroquinone couples present electrochemically more reversible behaviour on mercury than on most solid electrodes because the heterogeneous electron exchange rates are greater and adsorption forces tend to be weaker on mercury. Hale and Parsons[123] analysed polarographic waves for several quinhydrone solutions (benzoquinone, naphthoquinone, anthraquinone, 9,10-phenanthraquinone and 1,2-benzoanthraquinone) in aqueous and alcoholic acetate buffer solutions ($pH \approx 4$). Apparent heterogeneous rate constants of the order of 10^{-3} cm/s were measured under these conditions using Koutecky's analysis[124] and assuming a two-electron form for the waves. Free-energy differences between the various species in equation (11) were estimated from data in the literature and free energies of activation were obtained from the experimental rate constants using Marcus' theory[125] in order to obtain a free-energy profile for the Q/QH_2 reaction pathway under the experimental conditions. In agreement with Vetter's mechanism[79], they concluded that at pH 4 the reaction proceeds via successive electron transfers with nearly equal free energies of activation.

These results were questioned in a later paper by Galli and Parsons[126] who were not able to obtain agreement between the kinetic analysis of the polarographic waves and the results of a Sluyter's impedance plane analysis[127]. This small-amplitude relaxation technique indicated diffusion control at rates up to 10^3 greater than those reported previously[123]. The double-layer capacity was found to be dependent on the presence of quinhydrone and the couple behaved in a manner typical for the case of weak adsorption of reactants. Galli and Parsons attribute the irreversible behaviour in the polarographic case to adsorption effects[126].

Adsorption of quinone and hydroquinone species at the mercury electrode interface has been firmly established by several studies. Benzoquinone and benzohydroquinone have been shown to adsorb simultaneously by a chronopotentiometric[128] and a quasi-thermodynamic method[129]. In the latter the surface tension of a d.m.e. in a Q/QH_2 solution was determined by means of the drop-weight method at open circuit. By neglecting the surface excess of hydrogen ions adsorbed from the phosphate buffer solutions ($pH = 6{\cdot}4$–$7{\cdot}6$), relative surface excesses were estimated for total quinone, oxidized components and reduced components. (See Frumkin and coworkers[130] for comments on this paper.) The sum of the quinone, semiquinone and hydroquinone surface concentrations was constant for various ratios of Q to QH_2:

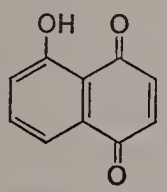
$$\Gamma_{QH_2}+\Gamma_{QH}+\Gamma_{Q} \approx 1{\cdot}2\times10^{-10} \text{ mole/cm}^2 \qquad (31)$$

where Γ_i is the relative surface excess of the ith species. The sums $\Gamma_Q + \frac{1}{2}\Gamma_{QH}$ and $\Gamma_{QH_2} + \frac{1}{2}\Gamma_{QH}$ were found to vary linearly with the potential, i.e. with the Nernstian ratio, $\log([Q]/[QH_2])$.

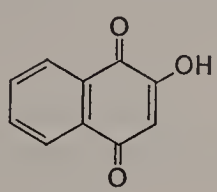
A definitive study of the electrode kinetics of a quinone couple at mercury in aqueous solutions has not appeared in the literature. The effects of pH, buffer components and temperature on the reversibility of voltammetric quinone waves have not been reported. It appears to this author that the intermediacy of the semiquinone species and its associated acid–base reactions must be taken into consideration in the analysis along with adsorption of the quinone, semiquinone and hydroquinone species.

In addition to the results of Mollers and Janenicke[128] and Plieth[129], there is more evidence for adsorption of complex quinone species at the mercury/solution interface. A careful double-step chronocoulometric study of the adsorption of anthraquinone-2-sulphonate (AQS) on Hg from fluoride, nitrate and thiocyanate electrolytes has been reported by Anson and Epstein[131]. The amount of specifically adsorbed AQS was decreased by co-adsorption of nitrate and thiocyanate ions, although neither nitrate nor thiocyanate was desorbed by co-adsorption of AQS. Changes in the ϕ_2 potential due to the presence of the negatively charged adsorbed AQS ion were detected by monitoring the half-wave potentials of the irreversible $Co(NH_3)_6^{3+}$ and CrO_4^{2-} reductions.

Adsorption phenomena of three hydroxynaphthoquinones at mercury electrodes in neutral phosphate buffers have been analysed in some detail[132–134]. The quinones studied were juglone (**1**), lawsone (**2**) and naphthazine (**3**). Only juglone, of these three quinones, gives polarographic adsorption prewaves. This is one of the smallest molecules whose



(1)



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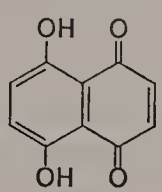


(3)

polarographic behaviour is well described by the Brdicka theory, which ascribes the presence of a prewave to strong equilibrium adsorption of the hydroquinone form in preference to the oxidized or quinone form[135, 136]. However, chronopotentiometric measurement of surface concentrations revealed that both the quinone and hydroquinone forms are strongly adsorbed at prewave potentials for the juglone/hydrojuglone couple[133]. Furthermore, the adsorption isotherms are almost identical for the juglone and lawsone couples. The variation of surface concentrations with

electrode potential (Γ versus E_{Hg}) for both these systems is quite similar to the behaviour of the benzoquinone system discussed above[128, 129]. However, the rate of adsorption of juglone is slow on the polarographic time scale (less than ca. 4 s), thus formally creating a situation analogous to the requirements of the Brdicka theory. This is not the case for lawsone adsorption. The appearance of a prewave, therefore, is associated with the slow rate of quinone adsorption and not with a large difference in free energy of adsorption in these systems[133]. To complicate matters further, the total surface coverages were found to be somewhat greater than unity for the juglone/hydrojuglone couple in the vicinity of the prewave. This suggests bilayer adsorption and was tentatively ascribed to charge-transfer complex formation between the protonated semiquinone species and adsorbed quinone (equation 32)[133].

$$Q + H^+ + Q)_{ads} \xrightarrow{e^-} Q \leftarrow QH^\bullet)_{ads} \qquad (32)$$

Bimolecular complexes have also been postulated as intermediates in the reduction of 1,4- and 2,7-dihydroxyanthraquinone in weakly basic solution[137].

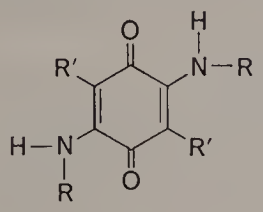
Adsorbed charge-transfer complexes have also been invoked to explain the unusual enhancing effect of anthracene and other hydrocarbons on the polarographic maximum of methylbenzoquinone[138, 139]. Charge-transfer complexes are seen to form between adsorbed aromatic hydrocarbon and the quinone substrate. As the π-system of the adsorbed hydrocarbon is increased, the height of the polarographic maximum increases.

Extensive adsorption of the biologically important quinone, ubiquinone-6, occurs in aqueous methanol solutions at the hanging mercury drop electrode[140]. Surface concentrations are almost independent of solution concentration between 7×10^{-6} and 9×10^{-5}M and are close to the saturation limit, $4{\cdot}3 \times 10^{11}$ mole/cm^2. At higher concentrations reversible polarographic behaviour is observed[141]. Adsorption of monohalogen-substituted 9,10-anthraquinones has been reported[142].

A more detailed description of the hydroquinone adsorption process has been sought by Lorenz and coworkers who have applied Lorenz's theory[107] of partial charge-transfer reactions at electrode surfaces to the Hg–QH_2 interaction[143]. For pH > 5, the amount of adsorption was found to be pH and potential dependent and QH_2 was found to be partially dissociated in the adsorbed state. Dissociation of adsorbed QH_2 was increased by an increase in the electrode potential. For example at pH ≈ 6, the average adsorbed species is $QH_2)_{ads}$ at $-0{\cdot}7$ V versus s.c.e. and $QH_{1{\cdot}7})_{ads}$ at $-0{\cdot}2$ V versus s.c.e. Thus the charge on the electrode induces a predissociation of QH_2 on the electrode surface. In another paper,

Gaunitz and Lorenz have determined that the desorption process for hydroquinone at negative potentials is diffusion-controlled at frequencies up to more than 10^5 s^{-1} [144].

A complete kinetic description of the interactions between the electron transfer, proton transfer and adsorption steps in quinone/hydroquinone couples remains to be presented. A brute-force approach would be to examine many quinone couples in the light of the details now understood about simple quinones. One such attempt has been made by Huntington and Davis[24] who measured apparent heterogeneous rate constants (k_s) for a series of aminoquinones and sought correlations with the hyperfine splitting constant of the corresponding semiquinones. The compounds studied were derivatives of **4**. The apparent $\log k_s$ values were found to



R′ = H; R = Me, Et, Pr, *i*-Pr, *t*-Bu, $-CH_2CH{=}CH_2$
R′ = Me; R = *t*-Bu

(4)

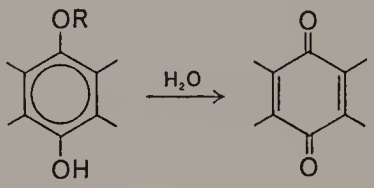
increase monotonically with the splitting constant of the nitrogen proton. However, the heterogeneous rate constants were determined at one pH value and include possible variations in proton transfer rates, adsorption isotherms and the stabilities of semiquinone intermediates. Refinements in the kinetic measurements in studies of this type should lead to a more detailed picture of the heterogeneous kinetics and electron-transfer transition states at electrode surfaces.

B. Coupled Chemical Reactions

Since the heterogeneous kinetic steps in Q/QH couples are often diffusion-controlled, chemical reactions coupled to the electron-transfer steps have readily observable effects on the electrochemical behaviour. Modern electroanalytical methods such as cyclic voltammetry[145] provide techniques for producing unstable species in solution where their kinetic behaviour can be followed. Examples of chemical reactions which are coupled to the Q/QH_2 system on the time scale of electrochemical experiments are briefly summarized in the following paragraphs.

The oxidation of ether and ester derivatives of hydroquinones, i.e. **5**, at solid electrodes presents features similar to the Q/QH_2 couples discussed above. A significant difference is that the oxidations are usually highly

irreversible and take place at more positive potentials than the corresponding hydroquinones. The overall electrode process involves two-electrons to yield the quinone (equation 33), which is readily detected in



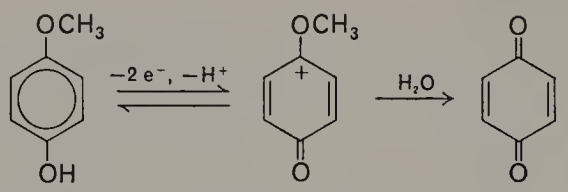
$$+ \text{ ROH} + 2\text{H}^+ + 2\text{e}^- \qquad (33)$$

(5)

cyclic experiments. It should be mentioned here that many examples of reactions of this general type exist in the older electroorganic literature[146]. Constant current electrolysis of phenols often leads to substituted quinones as intermediates or products of the electrode reaction.

Chambers and coworkers have studied several phosphate ($R = PO_3H_2$) and sulphate ($R = SO_3H$) ester derivatives of various hydroquinones at carbon paste electrodes over a wide pH range[147–150]. These workers stressed the intermediacy of one-electron intermediates and proposed mechanisms similar to Vetter's[79] in terms of the order of proton- and electron-transfer steps. However, diffusion-controlled electron-transfer rates were postulated with irreversible chemical reactions following the first and second electron-transfer steps. In strongly acidic solutions, these esters undergo reversible two-electron, one-proton transfers followed by rapid hydrolysis reactions. In these solutions the behaviour is further complicated by specific adsorption of the reduced form[148,150].

Similar electrode reactions have been described for 4,4′-dihydroxydiphenyl ether, *p*-methoxy- and *p*-ethoxyphenol in sulphuric acid solutions[6,151,152]. The monograph by Adams[6] should be consulted for

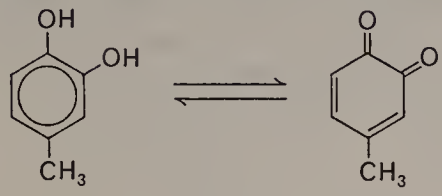


$$+ \text{ CH}_3\text{OH} + \text{H}^+ \qquad (34)$$

more details on these oxidations as well as the analogous reactions for aminophenols and phenylenediamines.

Electrochemical techniques have proved to be versatile and convenient for the measurement of rates of addition of nucleophiles to quinones[6]. The procedure is to generate the appropriate quinone substrate from the hydroquinone and measure the apparent electrochemical *n*-value as a

function of electrolysis time. The following reaction scheme has been shown to apply to several benzoquinones[153,154].



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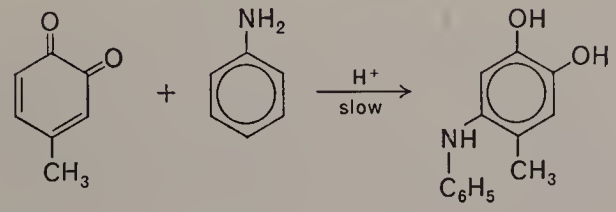

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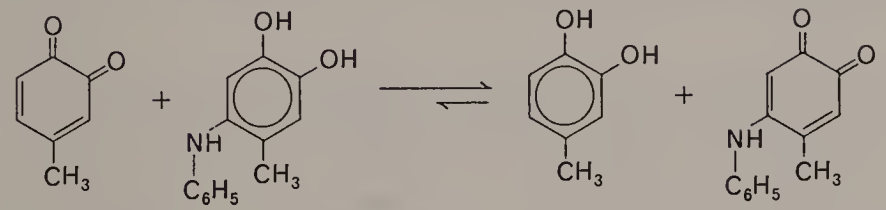
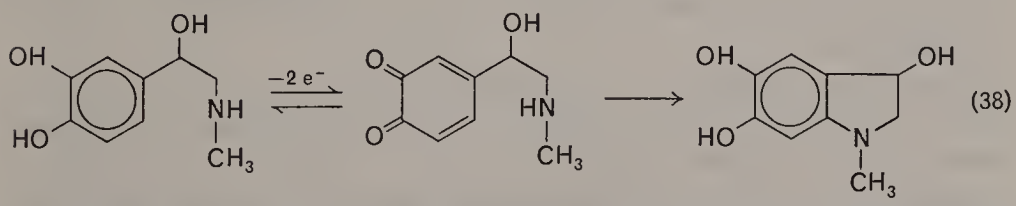


(37)

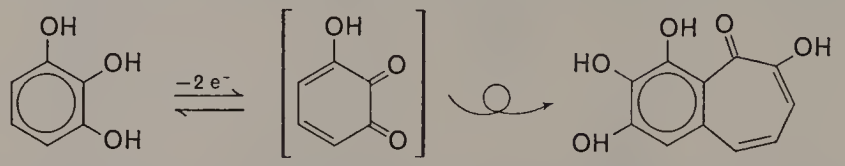
At short times (compared to the lifetime of the initial electrode product) a two-electron oxidation is observed which undergoes a transition into a four-electron process as the equilibrium (equation 37) is established in the diffusion layer. (This is the nuance of the e.c.e. mechanism or the e.c.c. mechanism[153]. In electrochemical parlance, an e.c.e. mechanism refers to a sequence in which a chemical reaction occurs between two heterogeneous electron-transfer steps. The same overall reaction can be realized in the e.c.c. mechanism if an homogeneous electron-transfer reaction follows the first two steps of the e.c.e. mechanism.) Similar reactions occur for a series of catechloamines, whose quinoidal forms undergo intramolecular 1,4 Michael additions[155]. This reaction is given below (equation 38) for



(38)

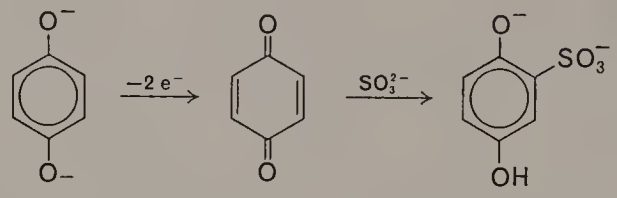
the cyclization of adrenalinequinone to leucoadrenochrome. The catecholamines studied in addition to adrenaline were noradrenaline, α-methyladrenalines, dopamine and isoproterenol.

The electrochemical oxidation of pyrogallol involves an initial two-electron step followed by rapid, complex reactions to form purpurogallin[156]. Kalousek polarography indicated that the initial electron-transfer step was reversible. Chemical oxidation of pyrogallol is believed to involve a dipolar dimerization of the intermediate *ortho* quinone[157].

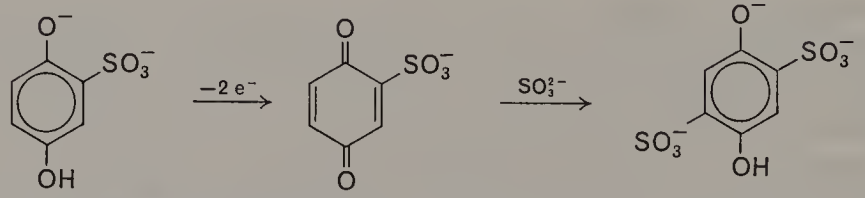


(39)

The electrochemical oxidation of *p*-benzohydroquinone in neutral sodium sulphite solutions appears to involve 1,4-addition reactions. Two two-electron waves are observed at carbon paste electrodes corresponding to formation of the monosulphonate and disulphonate derivatives, equations (40) and (41)[158].



(40)

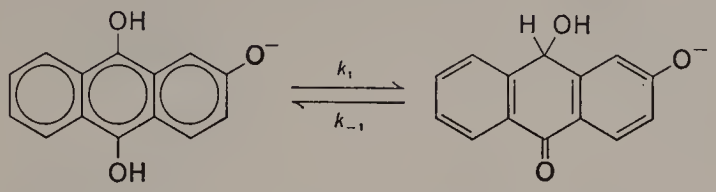


(41)

In this case the initial addition product is not more easily oxidized than the simple hydroquinone and the e.c.e. or e.c.c. pathway is not followed. Sulphonated benzohydroquinones are also formed in concentrated sulphuric acid solutions[159]. Up to ca. 10M H_2SO_4, oxidation occurs via oxygen protonated hydroquinone, QH_3^+. At higher acid strengths sulphonation of the benzene ring occurs and the behaviour becomes complex[159].

Several papers have dealt with the tautomerism of 2-substituted anthrohydroquinones since the original report of this equilibrium by Gill and Stonehill[160–164]. Freshly prepared aqueous solutions of anthrohydroquinones exhibit diffusion-controlled oxidation waves which are time-dependent due to a slow tautomerism of the ionized form (equation 42). The equilibrium constant for this reaction is pH-dependent and obtains a maximum value in the neighbourhood of pH 9. The tautomeric oxanthrol

form is itself polarographically reducible at a potential ca. 0·5 V more negative than reduction of the corresponding quinone. Thus polarograms of the quinone exhibit a diffusion-controlled wave followed by a

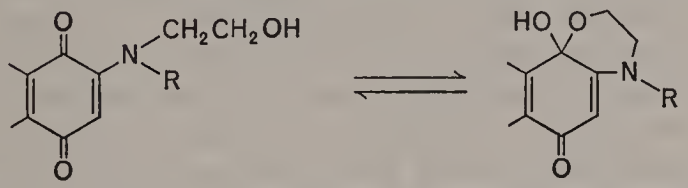


(42)

kinetically controlled wave[161]. Equilibrium rate constants for this process have been determined for several anthrahydroquinones substituted in the 2-position[164].

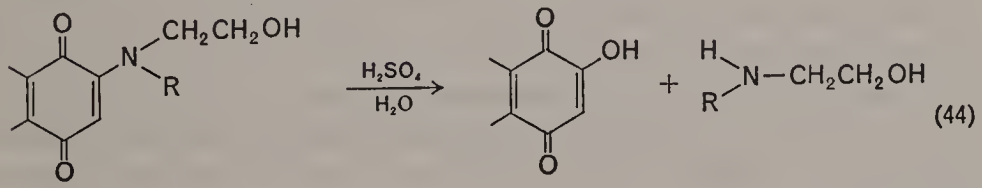
The use of borate buffers alters these reactions by complex formation with the hydroxy groups[163]. This is a well-known property of borate buffer solutions; for a good example of this effect see the work of Hofmann and Jaenicke on the oxidation of 1,2,4-trihydroxybenzene in basic borate buffers[165].

The polarographic behaviour of a series of amino-substituted quinones has been reported by Berg and coworkers[166–168]. β-Hydroxyalkylamino-benzoquinones give two polarographic waves over a wide pH range. The normal quinone, which is reduced at the more positive potential, is in equilibrium with a quinol formed by an intramolecular addition reaction (equation 43). The structure of this cyclization product has been recently



(43)

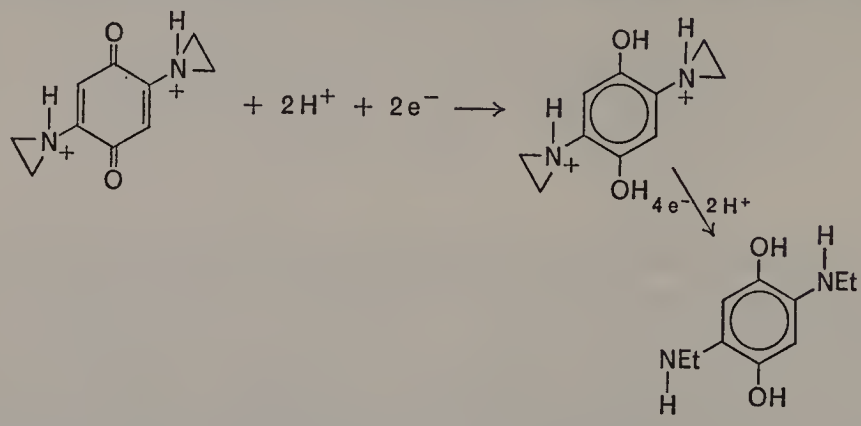
confirmed[169]. In sulphuric acid solutions the quinone form is hydrolysed to 2-hydroxybenzoquinone via equation (44)[168].



(44)

Berg and Wayner[170] have also studied the reduction of some ethylene-iminobenzoquinones. These quinones are reduced in two steps, initially to the hydroquinones followed by catalytic hydrogen waves at very negative potentials.

Photochemical reactions of quinones are also easily coupled to their electrode reactions[171–174], sometimes inadvertently. Quinones exhibit



(45)

strong $n \rightarrow \pi^*$ bands in the ultraviolet or visible region of the spectrum. Irradiation of quinones with light of this wavelength causes reactions of the following type to occur:

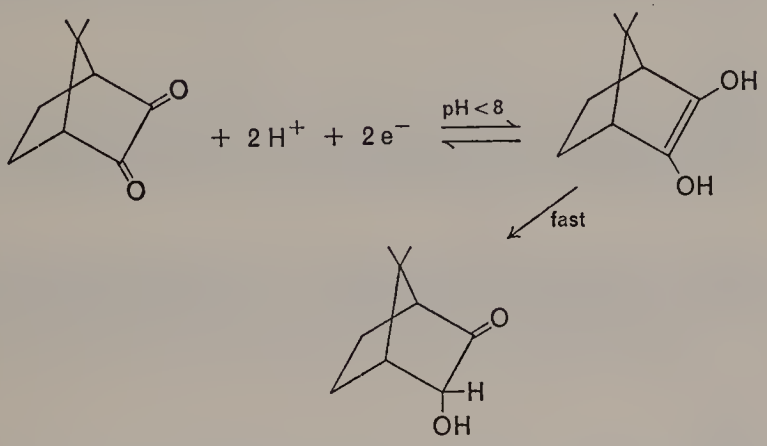
$$\begin{aligned} Q + h\nu &\longrightarrow Q^* \\ Q^* + H_2O &\rightleftharpoons QH^\bullet + HO^\bullet \\ 2\,QH^\bullet &\rightleftharpoons QH_2 + Q \end{aligned} \qquad (46)$$

Quinone solutions are accordingly sometimes unstable in the presence of ordinary laboratory light. Also 'photocatalytic' currents are readily observed in the presence of the proper radiation. These latter techniques have been coined 'Photopolarography' and were initially employed by Berg and coworkers[171]. Hydroxylation of the parent quinone is sometimes observed, presumably arising from reactions of the $HO^\bullet$ radical[175]. Electrochemical observation of this latter species has been recently claimed[176].

Hydroxyl radicals have also been invoked in the reactions of quinones in basic aqueous and aprotic solutions[177]. The reactions of quinones in these solutions have been followed by polarography, cyclic chronopotentiometry and e.s.r. spectroscopy. Reaction is initiated by an electron transfer between Q and OH^- followed by disproportionation reactions (equation 47). Further reactions occur, including formation of electroinactive polymers[177].

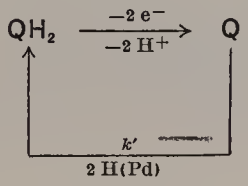
$$\begin{aligned} Q + OH^- &\rightleftharpoons Q^{\bullet-} + {}^\bullet OH \\ 2\,Q^{\bullet-} + 2\,H^+ &\longrightarrow Q + QH_2 \end{aligned} \qquad (47)$$

The polarographic reduction of camphorquinone has been studied in aqueous solutions[178]. This compound represents an interesting comparison for typical quinone reductions since its behaviour corresponds to that of an α,β-diketone (equation 48). Above pH 12 one-electron reduction and dimer formation is observed[178].



(48)

Rates of rapid microheterogeneous catalytic hydrogenation reactions of quinones have been measured polarographically. Oxidation of hydroquinone in the presence of palladium catalyts yields electrochemical currents according to the following scheme and rates of hydrogenation can be conveniently determined under a wide variety of conditions[179].



(49)

V. APPENDIX: HALF-WAVE POTENTIALS OF QUINONES IN NON-AQUEOUS SOLVENTS

TABLE 1

Name	$-E_{\frac{1}{2}}$ (V)	Reference electrode[a]	Solvent[b]	Supporting electrolyte[c, d]	T[e] (°C)	Reference
p-Benzoquinone	0·48	S.c.e.	DMF	TEAP	25	180
p-Benzoquinone	0·54, 1·23	S.c.e.	DMF	TEAP	25	34
p-Benzoquinone	0·15, 0·81	Ag/AgCl	DMF	TEAP	19	36
p-Benzoquinone	0·54[f], 1·33[f]	S.c.e.	MeCN	TEAP	—	77
p-Benzoquinone	0·51, 1·17	S.c.e.	MeCN	TEAP	25	26
p-Benzoquinone	0·51, 1·14	S.c.e.	MeCN	TEAP	25	34
p-Benzoquinone	0·10, 0·84	HgPool	MeCN	TEAP	—	48
p-Benzoquinone	0·60, 1·32	S.c.e.	MeCN	TBAP	—	181
p-Benzoquinone	−0·04, 0·47	HgPool	MeCN	TBAI	—	182
p-Benzoquinone	0·15, 0·89	S.c.e.	MeCN	$LiClO_4$	—	42
p-Benzoquinone	0·35, 1·2	S.c.e.	DMSO	TEAP	—	104
p-Benzoquinone	0·40, 1·24	S.c.e.	DMSO	TEAP	25	183
p-Benzoquinone	0·38, 1·17	S.c.e.	DMSO	TEAI	25	103
p-Benzoquinone	0·52[f], 1·04[f]	S.c.e.	PC	TEAP	—	63
p-Benzoquinone	0·51[f]	S.c.e.	NB	TEAP	—	63
p-Benzoquinone	0·4	S.c.e.	$MeNO_2$	TMACl	26	184
p-Benzoquinone	0·18[f]	Ag/Ag+	Py	$LiClO_4$ (0·5M)	25	94
p-Benzoquinone, fluoro-	0·374, 1·05	S.c.e.	MeCN	TEAP	25	26
p-Benzoquinone, chloro-	0·34, 0·97	S.c.e.	MeCN	TEAP	25	26
p-Benzoquinone, chloro-	0·34, 0·92	S.c.e.	MeCN	TEAP	25	34
p-Benzoquinone, bromo-	0·325, 0·95	S.c.e.	MeCN	TEAP	25	26
p-Benzoquinone, iodo-	0·33, 1·05	S.c.e.	MeCN	TEAP	25	26
p-Benzoquinone, 2,5-dichloro-	0·18, 0·81	S.c.e.	MeCN	TEAP	25	34
p-Benzoquinone, 2,6-dichloro-	0·18, 0·81	S.c.e.	MeCN	TEAP	25	34
p-Benzoquinone, trichloro-	0·08, 0·78	S.c.e.	MeCN	TEAP	25	34
p-Benzoquinone, tetrafluoro-	0·04, 0·82	S.c.e.	MeCN	TEAP	25	34
p-Benzoquinone, tetrachloro-	−0·01, 0·71	S.c.e.	MeCN	TEAP	25	34

p-Benzoquinone, tetrachloro-	−0·20, −0·04	S.c.e.	MeCN	$LiClO_4$	—	42
p-Benzoquinone, tetrachloro-	0·02, 0·90	S.c.e.	DMF	TEAP	25	34
p-Benzoquinone, tetrachloro-	−0·33	Ag/AgI	$CHCl_3$	TBAP (0·5M)	25	106
p-Benzoquinone, tetrachloro-	−0·35, 0·43	Ag/AgI	CH_2Cl_2	TBAP (0·5M)	25	106
p-Benzoquinone, tetrachloro-	−0·08, 0·73	S.c.e.	DMSO	TEAP	25	183
p-Benzoquinone, tetrabromo-	0·00, 0·72	S.c.e.	MeCN	TEAP	25	34
p-Benzoquinone, cyano-	0·120, 0·83	S.c.e.	MeCN	TEAP	25	26
p-Benzoquinone, 2,3-dicyano-	−0·31, −0·05	S.c.e.	MeCN	$LiClO_4$	—	42
p-Benzoquinone, 2,3-dicyano-5-chloro-	−0·41, −0·08	S.c.e.	MeCN	$LiClO_4$	—	42
p-Benzoquinone, 2,3-dichloro-5,6-dicyano-	−0·51, 0·30	S.c.e.	MeCN	TEAP	25	34
p-Benzoquinone, 2,3-dichloro-5,6-dicyano-	−0·50, −0·12	S.c.e.	MeCN	$LiClO_4$	—	42
p-Benzoquinone, 2,3-dichloro-5,6-dicyano-	−0·81, −0·02	Ag/AgI	$CHCl_3$	TBAP (0·5M)	25	106
p-Benzoquinone, 2,3-dichloro-5,6-dicyano-	−0·78, 0·02	Ag/AgI	CH_2Cl_2	TBAP (0·5M)	25	106
p-Benzoquinone, 2,3-dicyano-5-phenylsulphonyl-	−0·52, −0·20	S.c.e.	MeCN	$LiClO_4$	—	42
p-Benzoquinone, 2,3-dicyano-5-chloro-6-phenylsulphonyl-	−0·62[g], −0·20	S.c.e.	MeCN	$LiClO_4$	—	42
p-Benzoquinone, nitro-	−0·405, 0·32	S.c.e.	MeCN	TEAP	25	26
p-Benzoquinone, methyl-	0·58, 1·12	S.c.e.	MeCN	TEAP	25	26
p-Benzoquinone, methyl-	0·58, 1·10	S.c.e.	MeCN	TEAP	25	34
p-Benzoquinone, methyl-	0·580	S.c.e.	MeCN	TBAP	25	185
p-Benzoquinone, methyl-	0·17	HgPool	MeOEtOH	LiCl(0·25M)	25	186
p-Benzoquinone, 2,5-dimethyl-	0·67, 1·27	S.c.e.	MeCN	TEAP	25	34
p-Benzoquinone, 2,5-dimethyl-	0·68, 1·34	S.c.e.	DMF	TEAP	25	34
p-Benzoquinone, 2,6-dimethyl-	0·665	S.c.e.	MeCN	TBAP	25	185
p-Benzoquinone, 2,6-dimethyl-	0·660	S.c.e.	MeCN	TBAP	25	187
p-Benzoquinone, trimethyl-	0·75, 1·35	S.c.e.	MeCN	TEAP	25	34
p-Benzoquinone, trimethyl-(3′-methyl-3′-hydroxybutyl)-	0·8, 1·4	S.c.e.	MeCN	TEAP	22·5	67
p-Benzoquinone, tetramethyl-	0·84, 1·45	S.c.e.	MeCN	TEAP	25	34
p-Benzoquinone, tetramethyl-	0·84	S.c.e.	MeCN	TBAP	25	185
p-Benzoquinone, tetramethyl-	0·76	S.c.e.	DMF	TEAP	25	180
p-Benzoquinone, tetramethyl-	0·33, 1·05	HgPool	MeCN	TBABr	—	48

TABLE 1 (*cont.*)

Name	$-E_{\frac{1}{2}}$ (V)	Reference electrode[a]	Solvent[b]	Supporting electrolyte[c, d]	T[e] (°C)	Reference
p-Benzoquinone, tetramethyl-	0·73, 1·53	S.c.e.	DMSO	TEAP	25	183
p-Benzoquinone, trifluoromethyl-	0·306, 0·98	S.c.e.	MeCN	TEAP	25	26
p-Benzoquinone, 2-methyl-5-isopropyl-	0·665	S.c.e.	MeCN	TBAP	25	185
p-Benzoquinone, 2-methyl-6-*t*-butyl-	0·685	S.c.e.	MeCN	TBAP	25	185
p-Benzoquinone, *i*-propyl-	0·590	S.c.e.	MeCN	TBAP	25	187
p-Benzoquinone, 2,6-di-*i*-propyl-	0·675	S.c.e.	MeCN	TBAP	25	187
p-Benzoquinone, 2-*i*-propyl-6-*t*-butyl-	0·700	S.c.e.	MeCN	TBAP	25	187
p-Benzoquinone, *t*-butyl-	0·610	S.c.e.	MeCN	TBAP	25	185
p-Benzoquinone, 2,6-di-*t*-butyl-	0·730	S.c.e.	MeCN	TBAP	25	187
p-Benzoquinone, 2,5-di-*t*-butyl-	0·715	S.c.e.	MeCN	TBAP	25	185
p-Benzoquinone, 2,5-di-*t*-butyl-	0·73, 1·24	S.c.e.	MeCN	TEAP	25	34
p-Benzoquinone, 2,5-di-*t*-butyl-	0·15, 0·71	HgPool	MeCN	TBAI	—	182
p-Benzoquinone, 2,5-di-*t*-amyl-	0·725	S.c.e.	MeCN	TBAP	25	185
p-Benzoquinone, phenyl-	0·49, 1·11	S.c.e.	MeCN	TEAP	25	26
p-Benzoquinone, phenyl-	0·50, 1·03	S.c.e.	MeCN	TEAP	25	34
p-Benzoquinone, 2,5-dihydroxy	0·01	Ag/AgCl	DMF	TEAP	19	36
p-Benzoquinone, tetrahydroxy-	0·32	Ag/AgCl	DMF	TEAP	19	36
p-Benzoquinone, methoxy-	0·615	S.c.e.	MeCN	TEAP	25	26
p-Benzoquinone, 2,6-dimethoxy	0·74[f], 1·48[f]	S.c.e.	MeCN	TEAP	—	77
p-Benzoquinone, 2,5-dimethoxy	0·43, 0·97	Ag/AgCl	DMF	TEAP	19	36
p-Benzoquinone, carbomethoxy-	0·315, 0·91	S.c.e.	MeCN	TEAP	25	26
p-Benzoquinone, acetyl-	0·306, 0·98	S.c.e.	MeCN	TEAP	25	26
p-Benzoquinone, *N*,*N*-dimethylamino-	0·745, 1·28	S.c.e.	MeCN	TEAP	25	26
p-Benzoquinone, 2,5-bis(trimethylsilyl)-	−0·04, 0·51	HgPool	MeCN	TBAI	—	182
p-Benzoquinone, 2,6-bis(trifluoromethylthio)-	0·01, 0·43	S.c.e.	MeCN	$LiClO_4$	—	42
p-Benzoquinone, tris(trifluoromethylthio)-	−0·15, 0·09	S.c.e.	MeCN	$LiClO_4$	—	42
p-Benzoquinone, tetrakis(trifluoromethylthio)-	−0·23	S.c.e.	MeCN	$LiClO_4$	—	42

p-Benzoquinone, trifluoromethylsulphonyl-	−0·15, 0·12, 0·38	S.c.e.	MeCN	$LiClO_4$	—	42
o-Benzoquinone	0·31, 0·90	S.c.e.	MeCN	TEAP	25	34
o-Benzoquinone	0·220	S.c.e.	DMSO	TBAI	25	102
o-Benzoquinone, 4-*t*-butyl-	0·455	S.c.e.	MeCN	TBAP	25	185
o-Benzoquinone, 3,5-di-*t*-butyl-	0·560	S.c.e.	MeCN	TBAP	25	185
1,4-Naphthoquinone	0·71, 1·25	S.c.e.	MeCN	TEAP	25	34
1,4-Naphthoquinone	0·70, 1·33	S.c.e.[h]	MeCN	TEAP (0·05M)	25	101
1,4-Naphthoquinone	0·85, 1·55	S.c.e.	MeCN	TBAP	—	181
1,4-Naphthoquinone	0·685	S.c.e.	MeCN	TEAP	—	38
1,4-Naphthoquinone	0·60	S.c.e.	DMF	TEAP	25	180
1,4-Naphthoquinone	0·63, 1·35	S.c.e.[i]	DMF	TEAP (0·05M)	25	101
1,4-Naphthoquinone	0·63, 1·35	S.c.e.	DMF	TBAP	—	188
1,4-Naphthoquinone	0·31, 0·96	Ag/AgCl	DMF	TEAP	19	36
1,4-Naphthoquinone	0·72, 1·63	S.c.e.	DMF	TEAP	25	34
1,4-Naphthoquinone	0·69, 1·18	S.c.e.[j]	Me_2CO	TEAP (0·05M)	25	101
1,4-Naphthoquinone	0·58, 1·29	S.c.e.[k]	DMSO	TEAP (0·05M)	25	101
1,4-Naphthoquinone	0·55, 1·29	S.c.e.	DMSO	TBAI	25	103
1,4-Naphthoquinone	0·67, 1·05	S.c.e.[l]	PC	TEAP (0·05M)	25	101
1,4-Naphthoquinone, 2-methyl-	0·78	S.c.e.	MeCN	TEAP	25	48
1,4-Naphthoquinone, 2-methyl-	0·77, 1·28	S.c.e.	MeCN	TEAP	25	34
1,4-Naphthoquinone, 2-methyl-	0·27, 0·94	HgPool	MeCN	TBABr	—	48
1,4-Naphthoquinone, 2-methyl-	1·10	Ag/Ag^+ (0·01M)	MeCN	TEAP	—	69
1,4-Naphthoquinone, 2-methyl-	0·69	S.c.e.	DMF	TEAP	25	180
1,4-Naphthoquinone, 2-methyl-	0·20, 1·02	HgPool	DMF	TBABr	—	48
1,4-Naphthoquinone, 2-methyl-	0·34, 1·05	HgPool	DMF	$NaNO_3$	—	48
1,4-Naphthoquinone, 2,3-dimethyl-	0·846	S.c.e.	MeCN	TEAP	—	38
1,4-Naphthoquinone, 2,3-cyclobutano-	0·695	S.c.e.	MeCN	TEAP	—	38
1,4-Naphthoquinone, 2,3-cyclopentano-	0·748	S.c.e.	MeCN	TEAP	—	38
1,4-Naphthoquinone, 2,3-cyclohexano-	0·854	S.c.e.	MeCN	TEAP	—	38
1,4-Naphthoquinone, 2,3-(3,4-diphenylcyclobutano)-	0·40, 0·86	S.c.e.	DMF	TBAP	—	188
1,4-Naphthoquinone, 2-amino-	0·92, 1·40	S.c.e.	MeCN	TEAP	25	34
1,4-Naphthoquinone, 2-hydroxy-	0·64, 1·20	S.c.e.	DMF	TEAP	25	34

TABLE 1 (*cont.*)

Name	$-E_{\frac{1}{2}}$ (V)	Reference electrode[a]	Solvent[b]	Supporting electrolyte[c, d]	T[e] (°C)	Reference
1,4-Naphthoquinone, 5-hydroxy-	0·51, 1·17	S.c.e.	DMF	TEAP	25	34
1,4-Naphthoquinone, 5-hydroxy-	0·13, 0·70	Ag/AgCl	DMF	TEAP	19	36
1,4-Naphthoquinone, 5-hydroxy-	0·52, 0·99	S.c.e.	MeCN	TEAP	25	34
1,4-Naphthoquinone, 5,8-dihydroxy-	0·05, 0·67	Ag/AgCl	DMF	TEAP	19	36
1,2-Naphthoquinone	0·20, 0·67	Ag/AgCl	DMF	TEAP	19	36
1,2-Naphthoquinone	0·51, 1·12	S.c.e.[i]	DMF	TEAP (0·05M)	25	101
1,2-Naphthoquinone	0·56, 1·02	S.c.e.	MeCN	TEAP	25	34
1,2-Naphthoquinone	0·58, 1·18	S.c.e.[h]	MeCN	TEAP (0·05M)	25	34
1,2-Naphthoquinone	0·46	S.c.e.	DMSO	TBAI	25	103
1,2-Naphthoquinone	0·49, 1·18	S.c.e.[k]	DMSO	TEAP (0·05M)	25	101
1,2-Naphthoquinone	0·57, 1·01	S.c.e.[j]	Me_2CO	TEAP (0·05M)	25	101
1,2-Naphthoquinone	0·55, 0·92	S.c.e.[l]	PC	TEAP (0·05M)	25	101
9,10-Anthraquinone	0·43, 1·05	HgPool	MeCN	TBABr	—	48
9,10-Anthraquinone	0·94	S.c.e.	MeCN	—	—	39
9,10-Anthraquinone	0·98[f], 1·50[f]	S.c.e.	MeCN	TEAP	—	63
9,10-Anthraquinone	1·04, 1·69	S.c.e.	MeCN	TBAP	—	181
9,10-Anthraquinone	0·94, 1·45	S.c.e.	MeCN	TEAP	25	34
9,10-Anthraquinone	0·34, 1·10	HgPool	DMF	TBABr	—	48
9,10-Anthraquinone	0·32, 0·92	HgPool	DMF	TEAI	—	189
9,10-Anthraquinone	0·32, 0·99	HgPool	DMF	TEAI	—	64
9,10-Anthraquinone	0·38, 1·04	HgPool[m]	DMF	TEAI	25	190
9,10-Anthraquinone	0·33, 0·9	HgPool[n]	DMF	TEAI	—	191
9,10-Anthraquinone	0·33, 0·95	HgPool	DMF	TEAI	—	192
9,10-Anthraquinone	0·30, 0·57	HgPool	DMF	LiCl (1M)	—	191
9,10-Anthraquinone	0·85, 1·43	S.c.e.	DMF	TEAP	20	70
9,10-Anthraquinone	0·93[f], 1·63[f]	S.c.e.	DMF	TEAP	—	63
9,10-Anthraquinone	0·90, 1·54	S.c.e.	DMF	TEAP	25	193

9,10-Anthraquinone	0·82, 1·44	S.c.e.	DMF	TEAP	—	194
9,10-Anthraquinone	0·98, 1·74	S.c.e.	DMF	TEAP	25	34
9,10-Anthraquinone	0·98, 1·69	S.c.e.	DMF	TEAI	25	34
9,10-Anthraquinone	0·86, 1·48	S.c.e.	DMF	TEAI (0·05M)	25	196, 197
9,10-Anthraquinone	0·97	S.c.e.	DMF	TEABr	—	198, 199
9,10-Anthraquinone	0·94	N.c.e.	DMF	TEAP	—	200
9,10-Anthraquinone	0·55, 1·17	Ag/AgCl	DMF	TEAP	19	36
9,10-Anthraquinone	0·97, 1·43	S.c.e.	PC	TEAP	—	63
9,10-Anthraquinone	0·78, 1·45	S.c.e.	DMSO	TBAI	25	103
9,10-Anthraquinone, 1-amino-	0·46, 1·04	HgPool^m	DMF	TEAI	25	190
9,10-Anthraquinone, 1-amino-	0·44, 0·96	HgPool	DMF	TEAI	—	192
9,10-Anthraquinone, 1-amino-	0·42, 0·98	HgPool	DMF	TEAI	—	189
9,10-Anthraquinone, 1-amino-	0·49, 0·80	HgPool	DMF	LiCl	—	189
9,10-Anthraquinone, 1-amino-	1·06	S.c.e.	DMF	TEABr	—	198, 199
9,10-Anthraquinone, 2-amino-	0·54, 1·09	HgPool^m	DMF	TEAI	25	190
9,10-Anthraquinone, 2-amino-	1·13	S.c.e.	DMF	TEABr	—	198, 199
9,10-Anthraquinone, 1,2-diamino-	0·63, 1·13	HgPool^m	DMF	TEAI	25	190
9,10-Anthraquinone, 1,4-diamino-	1·16	N.c.e.	DMF	TEAP	—	200
9,10-Anthraquinone, 1-bromo-	0·83, 1·45	S.c.e.	DMF	TEAI (0·05M)	25	197
9,10-Anthraquinone, 2-bromo-	0·78, 1·44, 2·31	S.c.e.	DMF	TEAI (0·05M)	25	197
9,10-Anthraquinone, 2-bromo-	0·90	S.c.e.	DMF	TEABr	—	198, 199
9,10-Anthraquinone, 1-carbamoyl	0·94	S.c.e.	DMF	TEABr	—	198, 199
9,10-Anthraquinone, 2-carbamoyl	0·90	S.c.e.	DMF	TEABr	—	198, 199
9,10-Anthraquinone, 1-chloro-	0·29, 0·88	HgPool	DMF	TEAI	—	189
9,10-Anthraquinone, 1-chloro-	0·83, 1·46, 2·23	S.c.e.	DMF	TEAI (0·05M)	25	196, 197
9,10-Anthraquinone, 1-chloro-	0·90	S.c.e.	DMF	TEABr	—	198, 199
9,10-Anthraquinone, 2-chloro-	0·78, 1·43, 2·50	S.c.e.	DMF	TEAI (0·05M)	25	196, 197
9,10-Anthraquinone, 2-chloro-	0·90	S.c.e.	DMF	TEABr	—	198, 199
9,10-Anthraquinone, 2-chloro-	0·24, 0·81	HgPool	DMF	TEAI	—	198, 199
9,10-Anthraquinone, 1,2-dichloro-	0·76, 1·43, 2·26	S.c.e.	DMF	TEAI (0·05M)	25	196
9,10-Anthraquinone, 1,3-dichloro-	0·75, 1·42, 2·21	S.c.e.	DMF	TEAI (0·05M)	25	196
9,10-Anthraquinone, 1,4-dichloro-	0·79, 1·46, 2·32	S.c.e.	DMF	TEAI (0·05M)	25	196
9,10-Anthraquinone, 1,5-dichloro-	0·79, 1·46, 2·35	S.c.e.	DMF	TEAI (0·05M)	25	196

TABLE 1 (*cont.*)

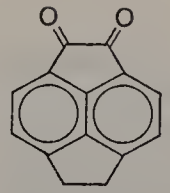
Name	$-E_{\frac{1}{2}}$ (V)	Reference electrode[a]	Solvent[b]	Supporting electrolyte[c, d]	T[e] (°C)	Reference
9,10-Anthraquinone, 1,5-dichloro-	0·25, 0·85	HgPool	DMF	TEAI	—	189
9,10-Anthraquinone, 1,6-dichloro-	0·74, 1·43, 2·30	S.c.e.	DMF	TEAI (0·05M)	25	196
9,10-Anthraquinone, 1,7-dichloro-	0·74, 1·43, 2·28	S.c.e.	DMF	TEAI (0·05M)	25	196
9,10-Anthraquinone, 1,8-dichloro	0·79, 1·46, 2·23	S.c.e.	DMF	TEAI (0·05M)	25	196
9,10-Anthraquinone, 1,8-dichloro-	0·25, 0·86	HgPool	DMF	TEAI	—	189
9,10-Anthraquinone, 2,3-dichloro-	0·71, 1·35, 2·45	S.c.e.	DMF	TEAI (0·05M)	25	196
9,10-Anthraquinone, 2,6-dichloro-	0·70, 1·32, 2·53	S.c.e.	DMF	TEAI (0·05M)	25	196
9,10-Anthraquinone, 2,7-dichloro-	0·72, 1·36, 2·64	S.c.e.	DMF	TEAI (0·05M)	25	196
9,10-Anthraquinone, 1,4-diacetoxy-	0·46, 0·85	Ag/AgCl	DMF	TEAP	19	36
9,10-Anthraquinone, 2-ethyl-	1·12, 1·69	S.c.e.	DMF	TEAI	25	34
9,10-Anthraquinone, 2-ethyl-	0·41, 0·70	HgPool	DMF	LiCl	—	201
9,10-Anthraquinone, 2-ethyl-	1·00	S.c.e.	DMF	TEABr	—	198, 199
9,10-Anthraquinone, 1,2-diethyl-	0·82	S.c.e.	DMF	TEABr	—	199
9,10-Anthraquinone, 1-fluoro-	0·83, 1·47	S.c.e.	DMF	TEAI (0·05M)	25	197
9,10-Anthraquinone, 1-fluoro-	0·92	S.c.e.	DMF	TEABr	—	198, 199
9,10-Anthraquinone, 2-fluoro-	0·77, 1·46	S.c.e.	DMF	TEAI (0·05M)	25	197
9,10-Anthraquinone, 2-fluoro-	0·93	S.c.e.	DMF	TEABr	—	198, 199
9,10-Anthraquinone, 1-hydroxy-	0·20, 0·80	HgPool[m]	DMF	TEAI	25	190
9,10-Anthraquinone, 1-hydroxy-	0·16, 0·73	HgPool[n]	DMF	TEAI	—	191
9,10-Anthraquinone, 1-hydroxy-	0·10, 0·54	HgPool	DMF	LiCl (1M)	—	191
9,10-Anthraquinone, 1-hydroxy-	0·77, 1·39	S.c.e.	DMF	TEAP	25	34
9,10-Anthraquinone, 2-hydroxy-	0·39, 0·64, 0·82, 1·10	HgPool[m]	DMF	TEAI	25	190
9,10-Anthraquinone, 2-hydroxy	0·54, 0·81	Ag/AgCl	DMF	TEAP	19	36
9,10-Anthraquinone, 2-hydroxy-	0·64, 1·26	S.c.e.(Na)	DMF	TEAP	—	89
9,10-Anthraquinone, 2-hydroxy-	0·77, 1·20	S.c.e.(Na)	MeCN	TEAP	—	89
9,10-Anthraquinone, 2-hydroxy-	0·74, 1·20	S.c.e.(Na)	PC	TEAP	—	89

9,10-Anthraquinone, 1,2-dihydroxy-	0·43	Ag/AgCl	DMF	TEAP	19	36
9,10-Anthraquinone, 1,4-dihydroxy-	0·06, 0·72	HgPool[m]	DMF	TEAI	25	190
9,10-Anthraquinone, 1,4-dihydroxy-	0·07, 0·58	HgPool[n]	DMF	TEAI	—	191
9,10-Anthraquinone, 1,4-dihydroxy-	0·42, 0·55, 0·90	HgPool	DMF	LiCl (1M)	—	191
9,10-Anthraquinone, 1,4-dihydroxy-	0·29, 0·88	Ag/AgCl	DMF	TEAP	19	36
9,10-Anthraquinone, 1,4-dihydroxy-	0·56	N.c.e.	DMF	TEAP	—	200
9,10-Anthraquinone, 1,5-dihydroxy-	0·03, 0·54	HgPool[m]	DMF	TEAI	25	190
9,10-Anthraquinone, 1,5-dihydroxy-	0·24, 0·72	Ag/AgCl	DMF	TEAP	19	36
9,10-Anthraquinone, 1,8-dihydroxy-	0·04, 0·74	HgPool[m]	DMF	TEAI	25	190
9,10-Anthraquinone, 1,8-dihydroxy-	0·27, 0·93	Ag/AgCl	DMF	TEAP	19	36
9,10-Anthraquinone, 1,8-dihydroxy-	0·64, 1·42	S.c.e.	DMF	TEAP	25	34
9,10-Anthraquinone, 1,2,4-trihydroxy-	0·18, 0·73	HgPool[m]	DMF	TEAI	19	36
9,10-Anthraquinone, 1,2,5,8-tetrahydroxy-	0·30	Ag/AgCl	DMF	TEAP	19	36
9,10-Anthraquinone, 1,4,5,8-tetrahydroxy-	0·12	Ag/AgCl	DMF	TEAP	19	36
9,10-Anthraquinone, 1-iodo-	0·84, 1·34, 1·44	S.c.e.	DMF	TEAI (0·5M)	25	197
9,10-Anthraquinone, 1-iodo-	0·93	S.c.e.	DMF	TEABr	—	198, 199
9,10-Anthraquinone, 2-iodo-	0·78, 1·37, 1·48	S.c.e.	DMF	TEAI (0·05M)	25	197
9,10-Anthraquinone, 1-methoxy-	0·43, 0·89	HgPool[m]	DMF	TEAI	25	190
9,10-Anthraquinone, 1-methoxy-	1·01	S.c.e.	DMF	TEABr	—	198, 199
9,10-Anthraquinone, 2-methoxy-	0·39, 0·93	HgPool[m]	DMF	TEAI	25	190
9,10-Anthraquinone, 1,4-dimethoxy-	0·50, 1·04	HgPool[m]	DMF	TEAI	25	190
9,10-Anthraquinone, 1,4-dimethoxy-	0·71, 1·04	Ag/AgCl	DMF	TEAP	19	36
9,10-Anthraquinone, 1,5-dimethoxy-	0·54, 1·04	HgPool[m]	DMF	TEAI	25	190
9,10-Anthraquinone, 1,5-dimethoxy-	0·71, 1·05	Ag/AgCl	DMF	TEAP	19	36
9,10-Anthraquinone, 1,8-dimethoxy-	0·50, 1·06	HgPool[m]	DMF	TEAI	25	190
9,10-Anthraquinone, 2-methyl-	1·00	S.c.e.	DMF	TEABr	—	198, 199
9,10-Anthraquinone, 1,4-dimethyl-	1·08, 1·57	S.c.e.	MeCN	TEAP	—	202
9,10-Anthraquinone, 1,4,5,8-tetramethyl-	1·27, 1·73	S.c.e.	MeCN	TEAP	—	192
9,10-Anthraquinone, 1-nitro-	0·07, 0·70, 0·98	HgPool	DMF	TEAI	—	192
9,10-Anthraquinone, 1-nitro-	0·76	S.c.e.	DMF	TEABr	—	198, 199
9,10-Anthraquinone, 1-nitro-2-carboxy-	0·86	S.c.e.	DMF	TEABr	—	199
9,10-Anthraquinone, 1,2-diphenyl-	0·32	HgPool	DMF	TEABr	—	198
9,10-Anthraquinone, 2-sulphonate (Na)	0·91, 1·40	S.c.e.	MeCN	TEAP	25	34

TABLE 1 (*cont.*)

Name	$-E_{\frac{1}{2}}$ (V)	Reference electrode[a]	Solvent[b]	Supporting electrolyte[c, d]	T[e] (°C)	Reference
9,10-Anthraquinone, 2-sulphonate (Na)	0·98, 1·64	S.c.e.	DMF	TEAI	25	34
9,10-Anthraquinone, 2-sulphonate (Na)	0·33, 0·97	HgPool	DMF	TEAI	—	189
1,4-Anthraquinone	0·75, 1·25	S.c.e.	MeCN	TEAP	25	34
9,10-Phenanthraquinone	0·12, 0·69	HgPool	DMF	TEAI	—	64
9,10-Phenanthraquinone	0·30, 0·76	Ag/AgCl	DMF	TEAP	19	36
9,10-Phenanthraquinone	0·70	S.c.e.	DMF	TEAP	25	203
9,10-Phenanthraquinone	0·66, 1·22	S.c.e.	MeCN	TEAP	25	34
9,10-Phenanthraquinone	0·66	S.c.e.	MeCN	TBAP	RT	46
9,10-Phenanthraquinone	0·24	S.c.e.	MeCN	$LiClO_4$	RT	46
9,10-Phenanthraquinone	0·54, 1·28	S.c.e.	DMSO	TBAI	25	103
9,10-Phenanthraquinone, 2,4,7-trinitro-	0·10	S.c.e.	MeCN	TBAP	RT	46
9,10-Phenanthraquinone, 2,4,7-trinitro-	−0·08	S.c.e.	MeCN	$LiClO_4$	RT	46
9,10-Phenanthraquinone, 3,6-dinitro-	0·15	S.c.e.	MeCN	TBAP	RT	46
9,10-Phenanthraquinone, 3,6-dinitro-	−0·06	S.c.e.	MeCN	$LiClO_4$	RT	46
9,10-Phenanthraquinone, 2,7-dinitro-	0·20	S.c.e.	MeCN	TBAP	RT	46
9,10-Phenanthraquinone, 2,7-dinitro-	−0·04	S.c.e.	MeCN	$LiClO_4$	RT	46
9,10-Phenanthraquinone, 2,5-dinitro-	0·26	S.c.e.	MeCN	TBAP	RT	46
9,10-Phenanthraquinone, 2,5-dinitro-	−0·01	S.c.e.	MeCN	$LiClO_4$	RT	46
5,12-Naphthacenequinone	1·13, 1·65	S.c.e.	MeCN	TBAP	—	181
1,2-Benz-9,10-anthraquinone	0·66, 1·19	S.c.e.	DMF	TEAP	—	194
6,13-Pentacenequinone	1·23, 1·55	S.c.e.	MeCN	TBAP	—	181
1,6-Benzopyrenequinone	0·57[f], 0·77[f]	S.c.e	MeCN	TEAP	—	63
3,6-Benzopyrenequinone	0·60[f], 0·86[f]	S.c.e.	MeCN	TEAP	—	63
6,12-Benzopyrenequinone	0·58[f], 0·90[f]	S.c.e.	MeCN	TEAP	—	63
Benzocyclobutadienequinone	1·20	S.c.e.	MeCN	TEAP	25	204
1,2-Acenaphthaquinone	0·81, 1·66	S.c.e.	DMSO	TBAI	25	103
Diketopyracene (**1**)	0·91, 1·73	S.c.e.	DMSO	TBAI	25	103

Pyracycloquinone (**2**)	0·74, 1·30	S.c.e.	DMSO	TBAI	25	103
4,8-Dibenzopentalenoquinone (**3**)	0·90, 1·63	S.c.e.	DMSO	TBAP	—	205
Triptycenequinone (**4**)	0·64, 1·25	HgPool	DMF	KNO_3	—	206
12,15-Dihydro-12,15-dioxo-2,3:6,7-dibenzo-triptycene (**5**)	0·67, 1·28	HgPool	DMF	KNO_3	—	206
9,10-Dihydroanthrylenenaphthoquinone (**6**)	0·09, 0·47	HgPool	DMF	LiCl	—	206
Naphthotriptycenequinone (**7**)	0·94, 1·40	HgPool	DMF	KNO_3	—	206
12,15-Dihydro-12,15-dioxo(2,3-6,7-13,14)-tribenzotrypticene (**8**)	0·81, 1·35	HgPool	DMF	KNO_3	—	206
12,15-Dihydro-12,15-dioxo-2,3:6,7-dibenzo-13,14-naphthotriptycene (**9**)	0·82, 135	HgPool	DMF	KNO_3	—	206
(**10**)	0·66, 1·34	HgPool	DMF	KNO_3	—	206
(**11**)	0·63, 1·26	HgPool	DMF	KNO_3	—	206
Biphenylquinone	0·23, 0·52	S.c.e.	MeCN	TBAP	—	207
Biphenylquinone	0·24, 0·41	S.c.e.	MeCN	TEAP	25	34
Biphenylquinone, 3-methyl-	0·28, 0·62	S.c.e.	MeCN	TBAP	—	207
Biphenylquinone, 3-*t*-butyl	0·30, 0·64	S.c.e.	MeCN	TBAP	—	207
Biphenylquinone, 3,3′-dimethyl-	0·34, 0·64	S.c.e.	MeCN	TBAP	—	207
Biphenylquinone, 3,3′-di-*t*-butyl-	0·36, 0·72	S.c.e.	MeCN	TBAP	—	207
Biphenylquinone, 3,3′,5,5′-tetramethyl-	0·44, 0·77	S.c.e.	MeCN	TBAP	—	207
Biphenylquinone, 3,3′,5,5′-tetraisopropyl-	0·45, 0·80	S.c.e.	MeCN	TBAP	—	207
Biphenylquinone, 3,3′,5,5′-tetra-*t*-butyl-	0·50, 0·90	S.c.e.	MeCN	TBAP	—	207
Biphenylquinone, 3,3′-dimethyl-5,5′-di-*t*-butyl-	0·47, 0·83	S.c.e.	MeCN	TBAP	—	207
Biphenylquinone, 3,3′-diisopropyl-5,5′-di-*t*-butyl-	0·48, 0·86	S.c.e.	MeCN	TBAP	—	207
Biphenylquinone, 3,3′,5,5′-tetramethoxy-	0·51	S.c.e.	MeCN	TEAP	—	77
Dibenzoquinone (**12**)	0·35, 0·65, 0·88	S.c.e.	MeCN	TEAP	25	208
Dibenzoquinone (**12**)	0·38, 0·74, 1·29	S.c.e.	DMF	TEAP	25	208
Dibenzoquinone (**12**), 5,5′-dimethyl-	0·55, 0·72, 1·08	S.c.e.	MeCN	TEAP	25	208
Dibenzoquinone (**12**), 5,5′-dimethyl-	0·57, 0·77, 1·48	S.c.e.	DMF	TEAP	25	208
Dibenzoquinone (**12**), 5,5′-dimethyl-	0·50, 0·66, 1·23	S.c.e.	DMSO	TEAP	25	208
Triquinone (**13**)	0·49, 0·67, 0·73, 1·05	S.c.e.	MeCN	TEAP	25	208



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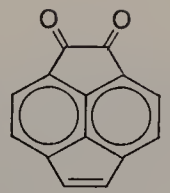

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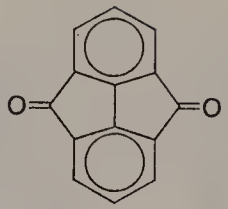

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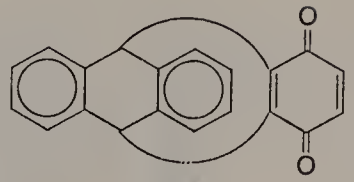

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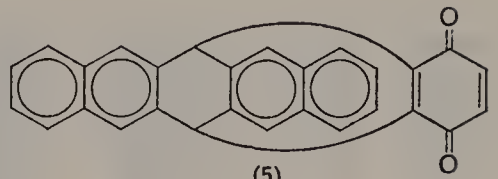

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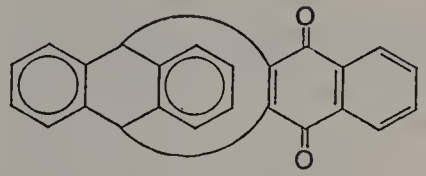

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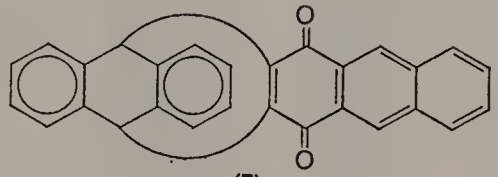

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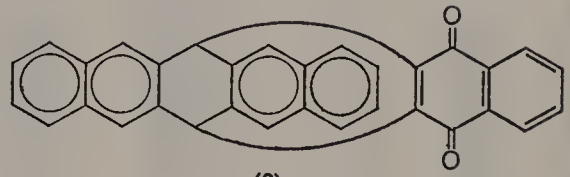

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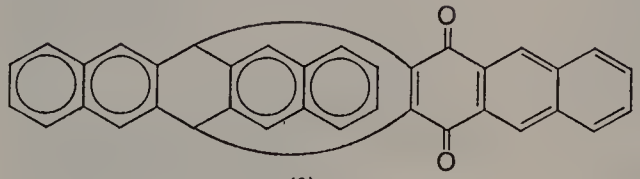

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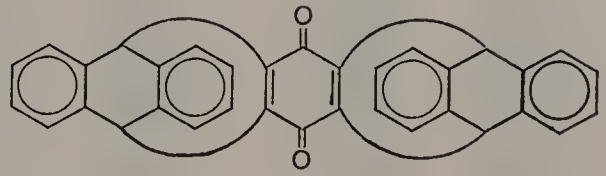

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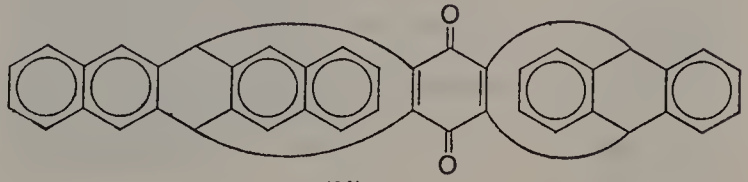

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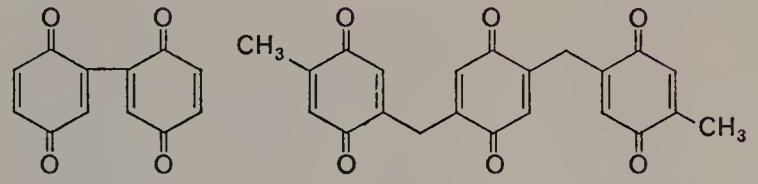
TABLE 1 (*cont.*)

Name	$-E_{\frac{1}{2}}$ (V)	Reference electrode[a]	Solvent[b]	Supporting electrolyte[c, d]	T[e] (°C)	Reference
Triquinone (**13**)	0·51, 0·71, 1·20	S.c.e.	DMF	TEAP	25	208
Triquinone (reduced) (**14**)	0·32, 0·68	S.c.e.	DMF	TEAP	25	208
Stilbenequinone, 3,3,5,5′-tetra-*t*-butyl-	0·04, 0·33	HgPool	DMF	TEAP	25	66
Stilbenequinone, 3,3′,5,5′-tetramethyl-	0·02, 0·17	HgPool	DMF	TEAP	25	66
Methylenequinone (**15**, R = H, R′ = CH_3)	1·28, 2·01	S.c.e.	DMF	TEAP	25	209
Methylenequinone (**15**, R = R′ = CH_3)	0·81, 1·42	S.c.e.	DMF	TEAP	25	209
Methylenequinone (**15**, R = CH_3, R′ = C_2H_5)	1·41,	S.c.e.	DMF	TEAP	25	209
Methylenequinone (**15**, R = R′ = C_5H_6)	1·11, 1·41	S.c.e.	DMF	TEAP	25	209
Methylenequinone (**15**, R = H, R′ = CH_2Br)	1·52	S.c.e.	DMF	TEAP	25	209
Methylenequinone (**15**, R = H, R′ = CN)	0·26, 0·50	S.c.e.	DMF	TEAP	25	209
Ubiquinone-1	0·84, 1·6	S.c.e.	MeCN	TEAP	—	68



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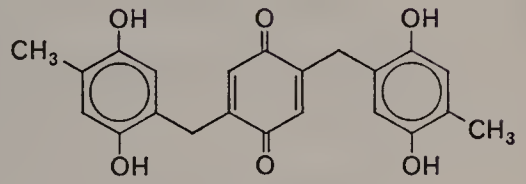
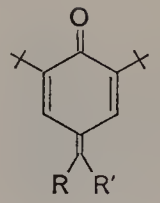
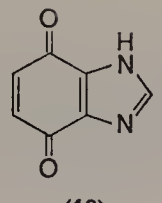


(14)

TABLE 1 (*cont.*)

Name	$-E_{\frac{1}{2}}$ (V)	Reference electrode[a]	Solvent[b]	Supporting electrolyte[c, d]	T[e] (°C)	Reference
α-Tocopherylquinone	0·56	S.c.e.	MeCN	$LiClO_4$	—	97
Vitamin E quinone	0·75	S.c.e.	DMF	TEAP	25	180
Benzimidazole-4,7-quinone (**16**)	0·44	S.c.e.	DMF	TEAP	—	210
Benzimidazole-4,7-quinone, 1-methyl-	0·67	S.c.e.	DMF	TEAP	—	210
Benzimidazole-4,7-quinone, 1-methyl-2-phenyl-	0·41	S.c.e.	DMF	TEAP	—	210
Benzimidazole-4,7-quinone, 1-methyl-2-dimethylamino-	0·67, 1·29	S.c.e.	DMF	TEAP	—	210
Benzimidazole-4,7-quinone, 1-methyl-2-chloro-	0·60	S.c.e.	DMF	TEAP	—	210
Benzimidazole-6,7-quinone, 1-methyl-	0·54	S.c.e.	DMF	TEAP	—	210
Benzimidazole-6,7-quinone, 2-phenyl-	0·38	S.c.e.	DMF	TEAP	—	210
Benzimidazole-6,7-quinone, 1-methyl-2-phenyl-	0·56	S.c.e.	DMF	TEAP	—	210
Benzimidazole-6,7-quinone, 1-methyl-2-chloro-	0·54	S.c.e.	DMF	TEAP	—	210
Benzimidazole-6,7-quinone, 1-methyl-2-dimethylamino-	0·64	S.c.e.	DMF	TEAP	—	210
Benzimidazole-5,6-quinone, 1-methyl-2-dimethylamino- (**17**)	0·71, 0·91	S.c.e.	DMF	TEAP	—	210
Benzimidazole-5,6-quinone, 1-methyl-2-(*p*-dimethylaminophenyl)-	0·48	S.c.e.	DMF	TEAP	—	210
Benzimidazolone-5,6-quinone, 1,3-dimethyl- (**18**)	0·63, 1·09	S.c.e.	DMF	TEAP	—	209
Benzimidazolone-4,7-quinone, 1,3-dimethyl-	0·59, 1·22	S.c.e.	DMF	TEAP	—	210
Naphth[2,5-*d*]imidazole-4,9-quinone, 1-methyl (**19**)	0·87	N.c.e.	DMF	TEAP	—	200, 211


(15)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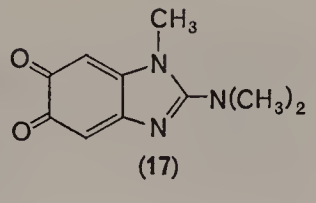
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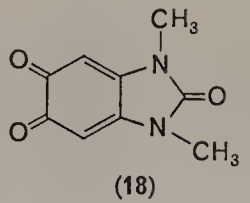
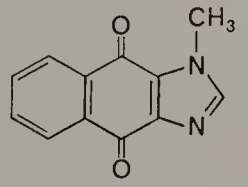
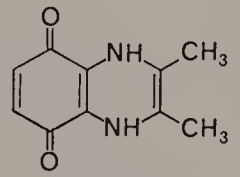
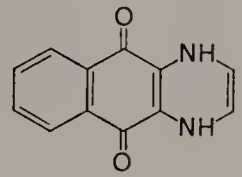
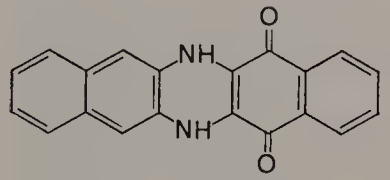
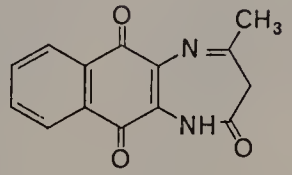
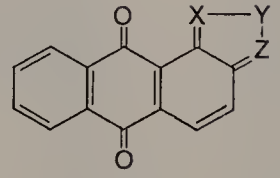
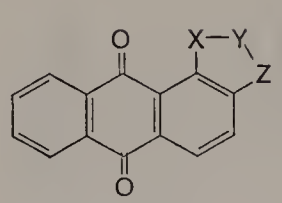

(18)

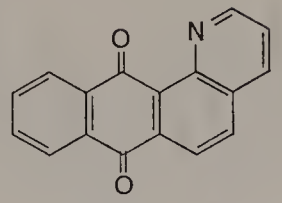
Naphth[2,5-*d*]imidazole-4,9-quinone, 1-methyl, 5,8-dihydroxy-	0·56	N.c.e.	DMF	TEAP	—	200
Naphth[2,5-*d*]imidazole-4,9-quinone, 1-methyl, 5-amino-8-hydroxy	0·59	N.c.e.	DMF	TEAP	—	200
Naphth[2,5-*d*]imidazole-4,9-quinone, 1-methyl, 5,8-diamino-	1·17	N.c.e.	DMF	TEAP	—	200
Quinoxaline-5,8-dione, 2,3-dimethyl-(**20**)	0·60, 1·37, 2·15	S.c.e.	DMF	TEAP	—	211
Benzo[*g*]quinoxaline-5,10-dione (**21**)	0·73, 1·37, 1·90	S.c.e.	DMF	TEAP	—	211
Benzo[*g*]quinoxaline-5,10-dione, 2-methyl-	0·76, 1·37, 1·96	S.c.e.	DMF	TEAP	—	211
Benzo[*g*]quinoxaline-5,10-dione, 2,3-dimethyl-	0·79, 1·45, 2·07	S.c.e.	DMF	TEAP	—	211
Benzo[*g*]quinoxaline-5,10-dione, 2-(*p*-dimethyl-aminostyryl)-	0·71, 1·36, 1·71	S.c.e.	DMF	TEAP	—	211
Benzo[*g*]quinoxaline-5,10-dione, 2,3-diphenyl-	0·81, 1·51, 2·14	S.c.e.	DMF	TEAP	—	211
Benzo[*g*]quinoxaline-5,10-dione, 2-hydroxy-3-phenyl-	0·49, 1·22, 2·08	S.c.e.	DMF	TEAP	—	211
Benzo[*g*]quinoxaline-5,10-dione, 2,3-dihydroxy-	0·59, 1·10	S.c.e.	DMF	TEAP	—	211
Dibenzo[*b*, *i*]phenazine-5,14-dione (**22**)	0·87, 1·53, 1·77	S.c.e.	DMF	TEAP	—	211
(**23**)	0·62, 1·36	S.c.e.	DMF	TEAP	—	194, 195
(**24**: X = N, Y = O, Z = N → O)	0·19, 0·86	S.c.e.	DMF	TEAP	—	194, 195
(**24**: X = N, Y = O, Z = N)	0·27, 0·97	S.c.e.	DMF	TEAP	—	194, 195
(**24**: X = N, Y = S, Z = N)	0·42, 0·97	S.c.e.	DMF	TEAP	—	194, 195
(**24**: X = N, Y = Se, Z = N)	0·43, 1·01	S.c.e.	DMF	TEAP	—	194, 195
(**24**: X = N, Y = NC_5H_6, Z = N)	0·57, 1·13	S.c.e.	DMF	TEAP	—	194, 195
(**25**: X—Y—Z = S—N=N)	0·43, 1·10	S.c.e.	DMF	TEAP	—	194, 195

TABLE 1 (*cont.*)

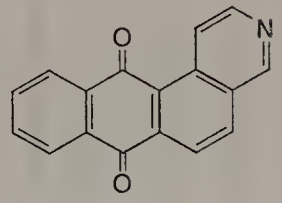
Name	$-E_{\frac{1}{2}}$ (V)	Reference electrode[a]	Solvent[b]	Supporting electrolyte[c, d]	T[e] (°C)	Reference
 (19)						
 (20)						
 (21)						
 (22)						
 (23)						
 (24)						
(25: X—Y—Z = N=N—S)	0·57, 1·06	S.c.e.	DMF	TEAP	—	194, 195
(25: X—Y—Z = N=N—NCH_3)	0·67, 1·19	S.c.e.	DMF	TEAP	—	194, 195
(25: X—Y—Z = S—$C(CH_3)$=N)	0·67, 1·35	S.c.e.	DMF	TEAP	—	194, 195
(25: X—Y—Z = N=$C(CH_3)$—S)	0·79, 1·21	S.c.e.	DMF	TEAP	—	194, 195
(25: X—Y—Z = N=CH—NH)	0·76, 1·10	S.c.e.	DMF	TEAP	—	194, 195
(25: X—Y—Z = N=CH—$N(CH_3)$)	0·88, 1·18	S.c.e.	DMF	TEAP	—	194, 195
(26)	0·69, 1·07	S.c.e.	DMF	TEAP	—	194, 195
(27)	0·62, 1·22	S.c.e.	DMF	TEAP	—	193, 194



(25)



(26)



(27)

[a] Abbreviations: s.c.e., saturated calomel electrode; n.c.e., normal calomel electrode; s.c.e. (Na) saturated NaCl calomel electrode; HgPool, mercury pool electrode.

[b] Abbreviations: DMF, *N*,*N*-dimethylformamide; MeCN, acetonitrile; DMSO, dimethyl sulphoxide; PC, propylene carbonate; NB, nitrobenzene; $MeNO_2$, nitromethane; Me_2CO, acetone; MeOEtOH, 2-methoxyethanol.

[c] Abbreviations: TEAP, tetraethylammonium perchlorate; TBAP, tetra-*n*-butylammonium perchlorate; TBAI, tetra-*n*-butylammonium iodide; TEAI, tetraethylammonium iodide; TMACl, tetramethylammonium chloride, TBABr, tetra-*n*-butylammonium bromide; TEABr, tetraethylammonium bromide.

[d] Concentration: 0·1M unless specified otherwise.

[e] No entry implies that the temperature was not given in the literature; room temperature is assumed.

[f] Peak potential, linear sweep voltammetry.

[g] Graphite electrode.

[h] −0·40 V versus $E_{\frac{1}{2}}$ ferrocene.

[i] −0·46 V versus $E_{\frac{1}{2}}$ ferrocene.

[j] −0·47 V versus $E_{\frac{1}{2}}$ ferrocene.

[k] −0·44 V versus $E_{\frac{1}{2}}$ ferrocene.

[l] −0·38 V versus $E_{\frac{1}{2}}$ ferrocene.

[m] −0·51 V versus s.c.e.

[n] −0·50 V versus s.c.e.

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CHAPTER 15

Polymeric quinones

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I. INTRODUCTION

This chapter considers the natural occurrence, synthesis, properties, and theoretical and practical importance of quinones incorporated into macromolecular structures or polymeric systems.

The presence of the macromolecular or polymeric structure confers new, distinctive, and sometimes unusual, properties on the quinone function as exemplified by changes in reactivity, electrochemical behaviour and in the development of semiconductor and catalytic properties.

Discussion is confined mainly to polyquinones in which there exists an *ortho* or *para* relationship of the carbonyl groups, but for the special case of conjugated polyquinones it has been extended to include polymers of quinonoid structure where the functional groups may also be —C=N—, or —C=C—.

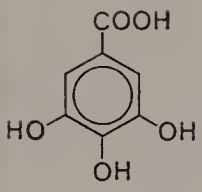
II. NATURALLY OCCURRING QUINONE POLYMERS

A. General

Simple quinone and quinonoid molecules, their reduction products and derivatives, are widely distributed in nature. In numerous cases such molecules can become polymerized, condensed or otherwise bound into macromolecular structures and they have been recognized through their chemical and physical properties, or from their occurrence in the products of degradation reactions. Thus mono-, di- and triquinones are found in moulds and fungi and quinone derivatives of perylene and coronene are present in certain aphids and plants[1]. Plants of the genus *Hypericum* contain red fluorescent pigments, which on ingestion cause animals to become light-sensitive, and which have been shown to be derivatives of *bis*-anthraquinone[2]. More highly polymerized structures which contain quinone groups, or groups readily convertible to quinones, include the tannins, lignins, humic acids, coals, melanins and other less definable components of plants and animals. These various groups of natural polymers will be considered in turn.

B. Tannins

The tannins are water-extractable constituents of the leaves, bark, roots and heartwood of various trees and plants, which are used for converting hides into leather[3,4]. As obtained, they are complex mixtures containing polyhydroxyphenols or derivatives thereof, and in many cases consist of polymeric condensed ring systems but the precise structures of the tannins are largely unknown. A molecular weight of 600–2000 appears necessary for satisfactory tanning action. Alkali fusion and dry distillation of tannins yield a variety of decomposition products mainly phenolic in character. These include catechol, pyrogallol, resorcinol, hydroquinone, *p*-hydroxybenzoic acid, gallic acid, **1**, and ellagic acid, **2**.



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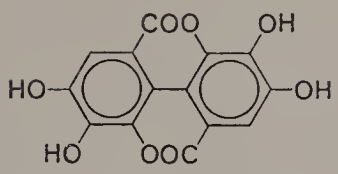

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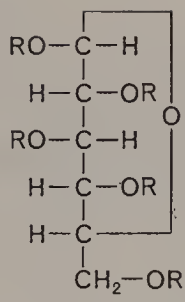
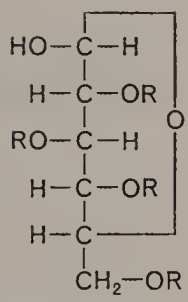




(R = 3,4,5-trihydroxybenzoyl)

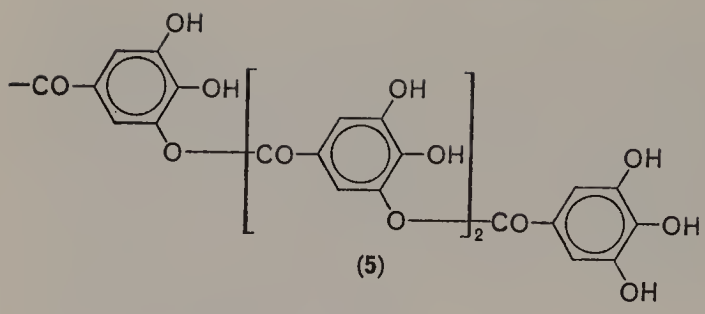
(3) (4)

Two main groups of tannins are recognized: the hydrolysable tannins, which are esters of a sugar, usually glucose, with one or more trihydroxybenzene carboxylic acids and the condensed tannins which are derivatives of flavanols. The former are those in which the complex molecule is hydrolysed by acids and enzymes to simpler units; the latter on similar treatment with acids are converted into more complex insoluble coloured products called phlobaphens.

Considerable progress has been made in elucidating the structure of gallotannin, an important hydrolysable tannin present in nut galls and sumach[4]. Paper chromatography[5] revealed that Chinese gallotannin is a mixture of closely related galloylglucose derivatives, which analysis showed to be octa- or nona-galloylglucose compounds. Elegant degradation work by Haworth and coworkers[6] showed this gallotannin to be based on units of β-penta-*O*-galloyl-D-glucose (**3**) and 2,3,4,6-tetra-*O*-galloyl-D-glucose (**4**). The additional gallic acid residues are linked to the base unit by depside bonds (for example **5**).

Exact knowledge of the structures of the condensed or flavanoid tannins is scanty. Freudenberg[7] proposed in 1920 that the basic unit of their structure was catechin, **6**, and this has been supported by isolation of catechin derivatives and dimers from degradative reactions. A variety of polycondensation mechanisms and structures have been proposed, a common feature being the presence of *o*-dihydroxybenzene units[3,4].

The tannins are amorphous substances which give deep colorations with ferric salts, are precipitated from solution by potassium dichromate, lead acetate and by alkaloids, and which precipitate gelatin from solution. The ability of tannins to form durable, and in many cases irreversible, compounds with proteins is the basis of their tanning action. The mechanism of the tanning action has not been clearly elucidated and may in part be related to quinone formation in the tannin with subsequent condensation with free hydroxyl or amino groups present in the hide



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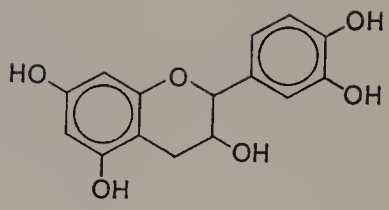
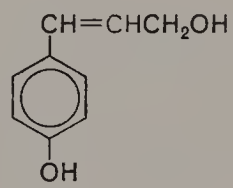


(6)

proteins. Thus, it has been found that when gelatin was treated with phenols under aerial oxidizing conditions the resultant precipitate became insoluble in boiling water as well as in dilute acids and alkalis[8]. Against the view that quinones are intermediates in the tanning process can be set the report[9] that optimum conditions for benzoquinone tanning require alkaline solutions of about pH 8–10, whereas tanning is normally carried out under acidic conditions. Present views are that tanning occurs by a hydrogen-bonding process with the amide groups of the protein and it has been shown[10] that tanning compounds able to form quinonoid resonance structures which favour hydrogen bonding are good tanning agents, whereas those condensates in which resonance cannot occur are poor tanning agents.

C. Lignins

The lignins[11,12] are complex three-dimensional macromolecular structures which form the cell walls of plants and the 'woody' tissue of trees. On the basis of extensive degradation and other studies they are considered to be polymers built up from a variety of primary monomeric units which include *p*-coumaryl alcohol, **7**, coniferyl alcohol, **8**, and sinapyl alcohol, **9**.



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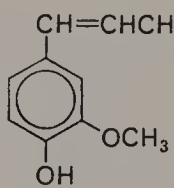

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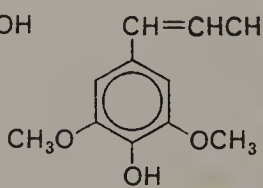


(9)

Although the object of much research the chemical structure of lignin is still uncertain. The complexity of the structure apparently derives less from the multitude of component units than from the variety of ways in

which these units may be linked together[13]. Certain tentative structures for lignin have been proposed by Freudenberg[14,15] and by Adler[16,17] in which *ortho*-related hydroxyl, methoxyl and ring carbonyl groups are present, and consequently provide pathways for quinone generation.

Lignins prepared by hydrolytic methods which involve some aerial oxidation have been shown to contain quinone groups. Thus, a lignin in a very early stage of decomposition was found to possess infrared absorption bands at 1648 and 1668 cm^{-1} indicative of *o*-quinone groups[18]. These disappeared on reduction with sodium dithionite. The initial and reduced lignins had the same electron spin resonance spectra and approximately the same concentration of free radicals (10^{16}–10^{17} spin/g). The oxidized lignin liberated iodine from potassium iodide solution which was not due to peroxide but might be due to quinone action.

The amount of quinone carbonyl groups in various lignins has been determined by selective reduction methods. Values of quinone carbonyls present range from 0 to 1·1 meq/g[19]. Further support for the presence of quinone or quinone precursor groups in lignins derives from the production of quinone nitropolycarboxylic acids as red-coloured products by the stepwise oxidation and hydrolysis of condensed lignin with aqueous nitric acid at 100°C[20–22]. The ammonium salts of these quinone nitropolycarboxylic acids have been used as plant growth stimulants.

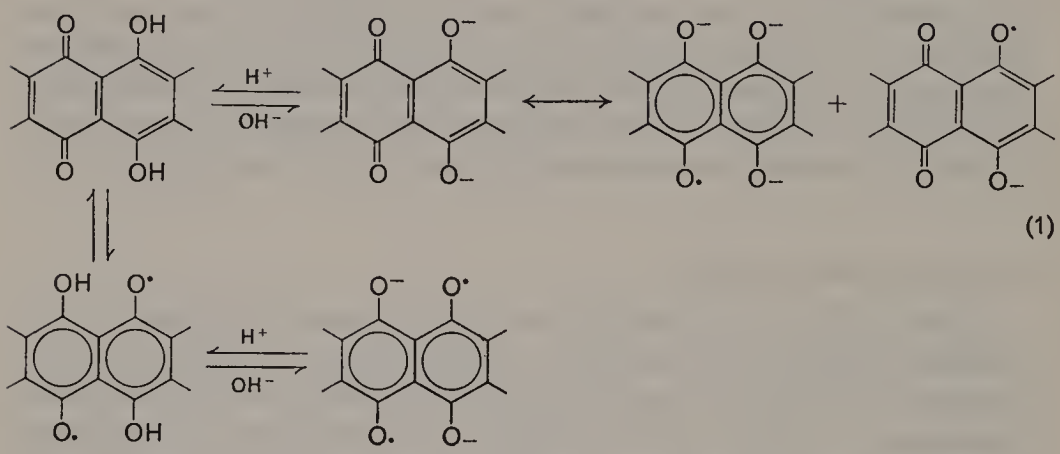
D. Humic Acids and Coal

Humic acids occur in soil[23,24] and may be generally defined as that polymer constituent of the organic matter present which has become resistant to microbial attack. Humic acids derive from decomposing plant matter—in the main from lignin. It is suggested that biological oxidation causes decomposition of the side-chains of the lignin macromolecule, together with demethylation and oxidation to quinone structures which can then polycondense with plant phenols, amino acids and other nitrogenous materials available in the soil[25].

Generally, the humic acids are regarded as amorphous, three-dimensional polymers of high molecular weight, built up of essentially aromatic and quinonoid rings, which also carry numerous acidic groups such as carboxyl and phenolic hydroxyl. Because of their properties humic acids contribute to soil stability and influence plant growth. The presence of acidic groups confers strong ion-exchange and chelating properties on them and they readily form complexes with metals and silicates[26]. Commercial humic acids and sodium humate are obtained from oxidized coals such as forms of lignite and bituminous coals.

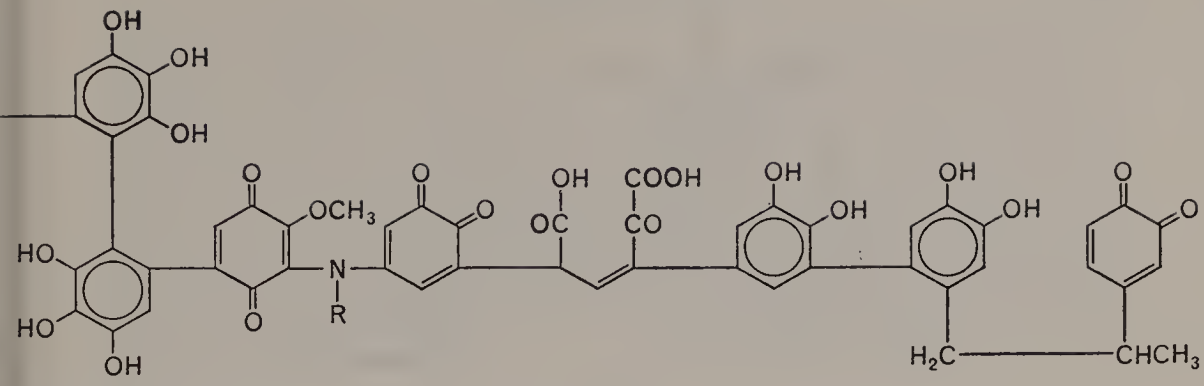
There is considerable evidence indicating the presence of quinone groups in humic acids. Thus humic acids derived from coal have been shown to give two main polarographic reduction waves with similar characteristics to polynuclear quinones[27]. Close similarities of the i.r. spectra of humates to those of hydroquinone polymers have been reported[28]. Comparison of the i.r. absorption spectra of solid sodium *p*-diphenoquinhydrone and of sodium humate have also revealed close similarities.

The presence of stable free radicals in soil humic acids has been established by e.s.r. measurements[29]. Conversion to the sodium salts increased the free-spin concentration by a factor of about 25, whilst acidification returned the free-spin content to about the original value. The e.s.r. results were interpreted as showing that humic acid contains quinhydrone and/or hydroxyquinone species which characteristically increase in radical content on addition of base (reaction 1).



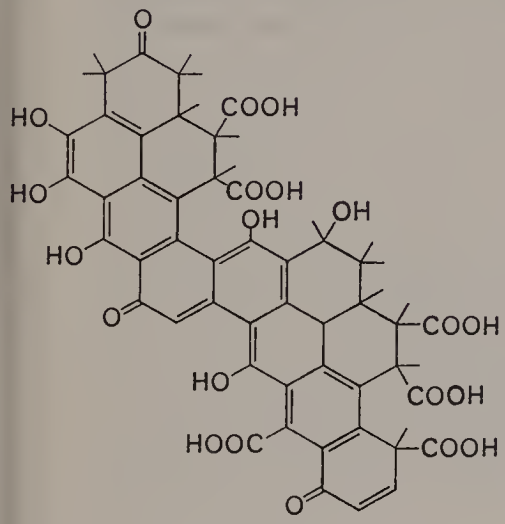
(1)

It is generally considered that no one specific structural formula will adequately represent humic acid. However, a number of structures have been proposed by Flaig, Kononova, Felbeck, Finkle and others, which account for many of the properties of the humic acids, and therefore are worthy of mention. Flaig's[25,30] proposed structure, **10**, is based on the assumption that lignin is the precursor of soil humic acids as mentioned above. The alternative structures of Fuchs[31a], **11**, and Dragunov[31b], **12**, for certain humic acids containing quinonoid groups, or *o*- or *p*-dihydric phenols in the reduced state, have been discussed by Kononova[31c], who considered the latter to be more consistent with the known facts. Felbeck[32] considered that heterocycles form an important part of the macromolecular structure and proposed structure **13**.

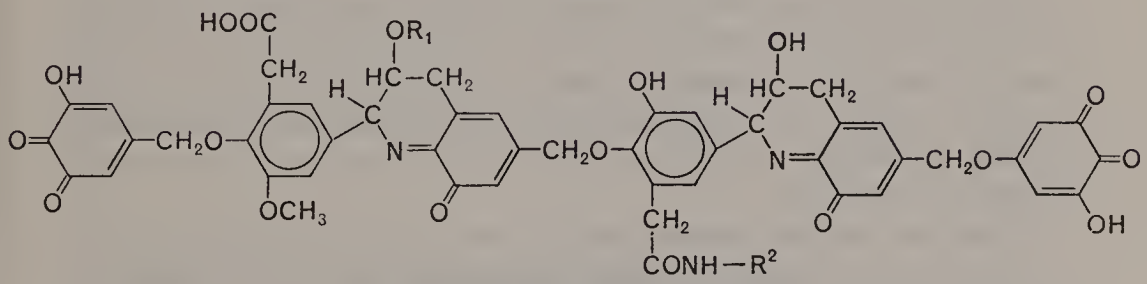


R = aminoacid residue

(10)

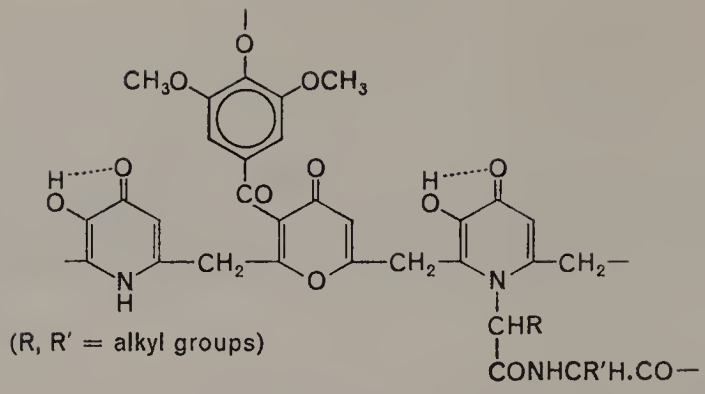


(11) Fuchs humic acid



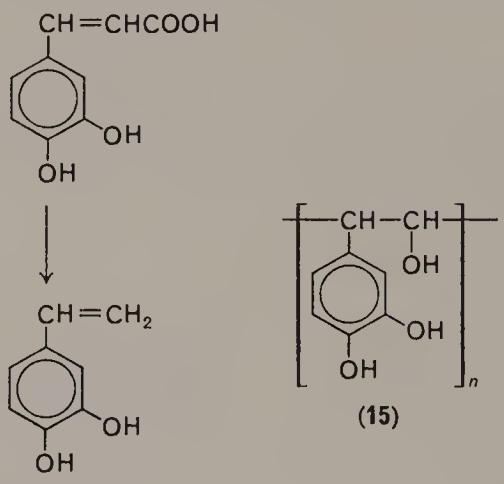
R_1 and R_2 are carbohydrate residues

(12) Dragunov humic acid



(13)

Finkle[33] found that decarboxylation of certain plant cinnamic acid derivatives to hydroxystyrene derivatives, **14**, was brought about by *Aerobacter*, and drew attention to the fact that polymers, **15**, based on this monomer had properties very similar to those of the humic acids.



(14) (15)

The variety of postulated structures for the humic acids, as in the case of other naturally occurring polymeric quinones, underlines the difficulty in establishing firm evidence of structure. The presence of quinonoid groups, however, is a common feature of the proposed structures, and probably explains the ability of humic acids to bind amino compounds present in the soil, as well as making a contribution to their metal-complexing properties.

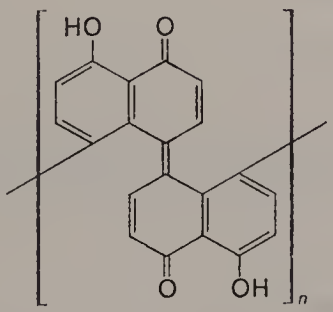
Coals also contain quinones and quinonoid groups and their presence has been established by a number of investigators[34,35]. The most convincing evidence comes from the polarographic study of oxidized coal products[27] or solvent extracts[36] in which two distinct reduction waves

can be identified which are characteristic of simple quinones. Other evidence is provided by examination of i.r. spectra of coal extracts before and after reductive acetylation[35,37] in which there is clear evidence of quinone hydrogen-bonded carbonyl absorption near 1600 cm^{-1}. Other supporting evidence is based on measurements of the X-ray diffraction pattern of coal, which are markedly similar to those of an 'artificial' coal prepared by coprecipitation of three polynuclear quinones from sulphuric acid solution[38]. The quinone content of certain lignite coals of Central Asia has been found to lie between 2–3·3 mg/g[39] on the basis of the quinone carbonyl groups present.

E. Other Natural Quinone Polymers

The melanins form another group of natural polymers of ill-defined structure which are believed to be complex aggregates of quinonoid pigment and several enzyme systems in a protein matrix[40]. They form the brown pigmentations of skin and hair, and occur in the cuticle and epidermis of insects[41]. The formation of melanins apparently can proceed through the intermediate formation of *o*-quinone structures such as 1-methylindole-5,6-quinone[42].

A black quinonoid polymer has been shown to be[43] a constituent of the cell-wall material of *Daldinia concentrica* sporophores. The powder which was obtained after exhaustive extraction of the ground sporophores with solvents was found to undergo reversible bleaching by reducing agents, but even in the reduced state no alkali soluble phenols could be removed. It was suggested that the cell-wall polysaccharides contained non-acetylated aminosugar residues which were cross-linked with monomeric or polymeric quinone oxidation products of the general structure **16**.



(16)

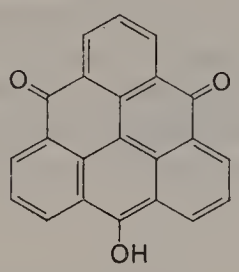
Recently[44], a hexachloro polynuclear quinone has been isolated from Australian soil as a crystalline red pigment thought to arise from the decomposing roots of eucalyptus.

III. POLYNUCLEAR AND CONJUGATED POLYQUINONES

A. Introduction

The polynuclear quinones were among the earliest group of polyquinone systems studied. This was because of their prominence as intermediates in the preparation of polynuclear aromatic hydrocarbons[45] and dyestuffs[46]. More recently, studies have centred on their generation during the coking of coals and the role they play in the coking mechanism[47]. Polynuclear quinones and conjugated polyquinones have been widely utilized for experimental and theoretical studies of the semiconductor, electronic and catalytic behaviour of conjugated quinone systems[48,49]. Certain quinonoid polymers such as the polyphenoxazines are thermally stable.

The materials considered in this section are those in which *ortho* or *para* quinone or quinonoid groups form integral units within a system of essentially aromatic or heteroaromatic rings which are annellated linearly or angularly. Three structural types can be distinguished. (i) Those in which the quinone groups form part of an extended polynuclear system. In some cases the two carbonyl groups exhibiting quinonoid properties may be linked by a series of conjugated double bonds forming a π-electron system, as in 12-hydroxytriangulene-4,8-quinone (**17**) and isodibenzanthrone (**18**). (ii) Those in which the quinone groups are regularly linked



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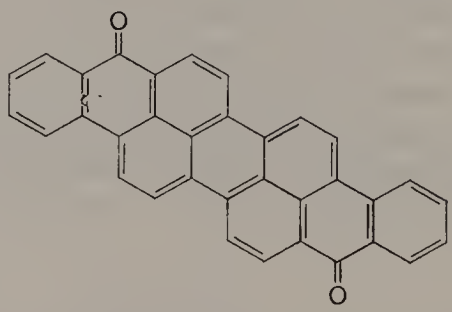


(18)

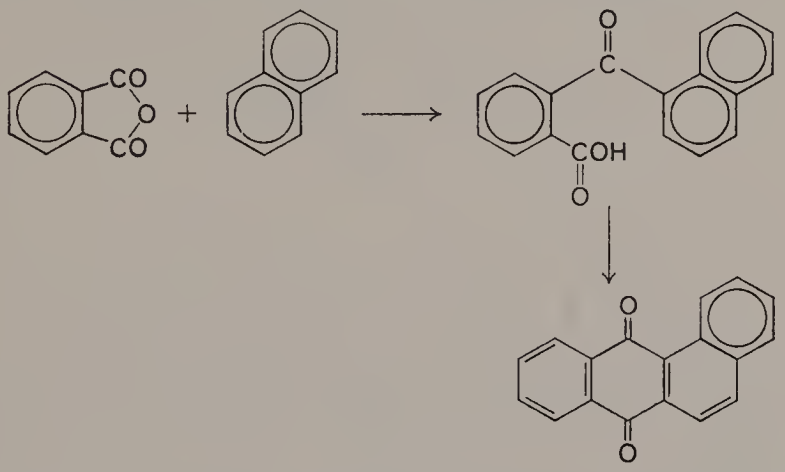
through conjugated bonds. (iii) Those in which quinonoid groupings form the prominent structural units. These structural groups are considered in more detail below.

B. Polynuclear Polyquinones

Several synthetic routes are available for the preparation of fused polynuclear quinones, the most important being the condensation of phthalic anhydride, pyromellitic dianhydride and similar aromatic anhydrides with various aromatic systems. Other methods involve

oxidation of the corresponding aromatic hydrocarbon, or its hydroxyl and amino derivatives, and by application of the diene synthesis utilizing butadiene and its analogues as the diene component.

In the presence of aluminium chloride, phthalic anhydride will condense with a wide range of aromatic hydrocarbons usually to form carboxy diaryl ketones which are then fully cyclized to the corresponding polynuclear quinone by heating with concentrated sulphuric acid (equation 2). The number of *p*-quinone groups in the system in some cases can be increased by using two or more moles of phthalic anhydride.



(2)

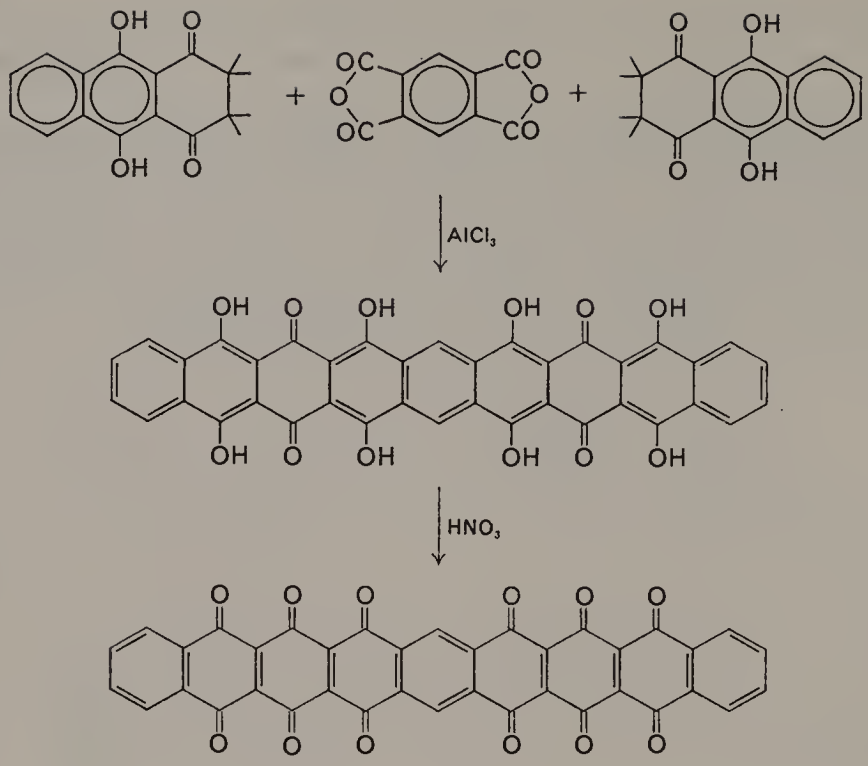
Condensation with hydroxy hydrocarbons proceeds more readily than with hydrocarbons, and milder condensing agents such as boric acid can be employed. Thus, by using pyromellitic dianhydride and leucoquinizarin a polynuclear hexaquinone, **19**, can be prepared[50].

Another variant[51] is condensation of dihydroanthracene tetracarboxylic acid dianhydride with benzene, followed by cyclization and oxidation to give the triquinone **20**.

Pohl and his group[52] have applied the anhydride condensation reaction to the preparation of a wide range of polynuclear quinone polymers. The chemical structures of the polymers were not characterized but they were considered to contain mainly quinone **21** and carbonyl groups (e.g. ketone, carboxyl) and only low amounts of lactone groups as in **22**.

These polymers were black, insoluble, infusible materials and contained a few p.p.m. of the metal of the catalyst used. They exhibited important semiconductor properties (see section VI.C).

Oxidation of hydrocarbons may also be used for preparing polynuclear quinones[45]. Thus chromic acid oxidation of isodibenzoanthrone **23** gives the triquinone indoquinoneanthrene **24** which can be further reacted with hydrazine to form the quinonoid diazine **25**.



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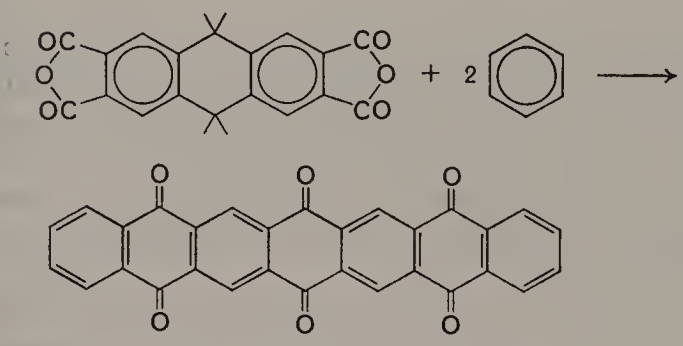

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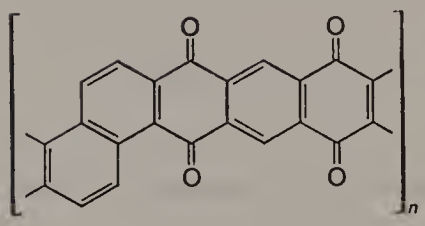

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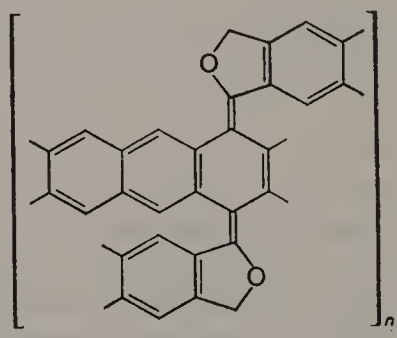

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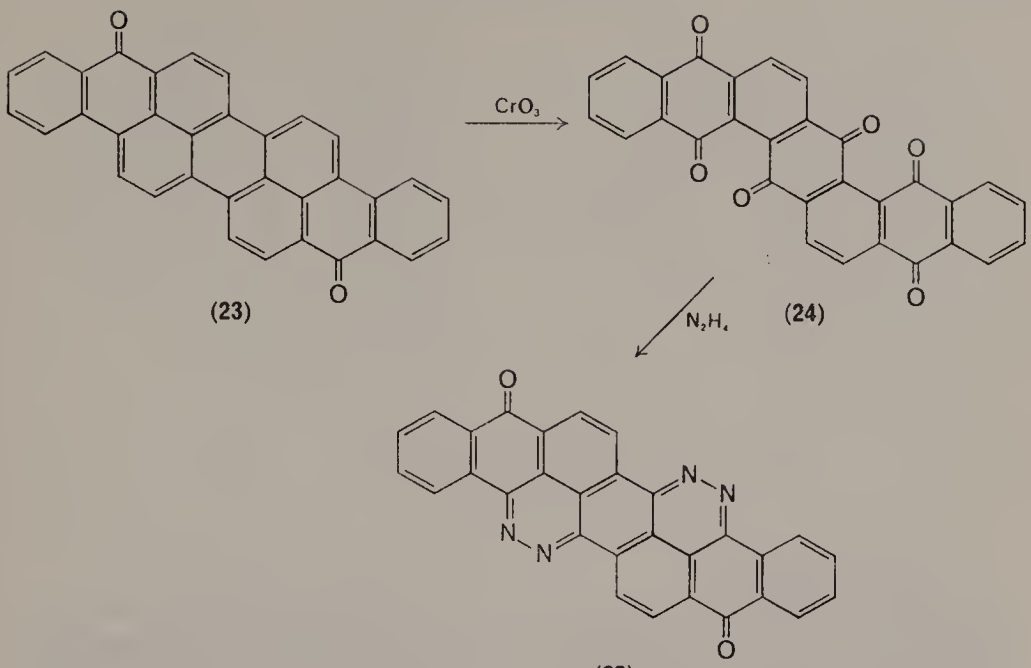


(23) (24) (25)

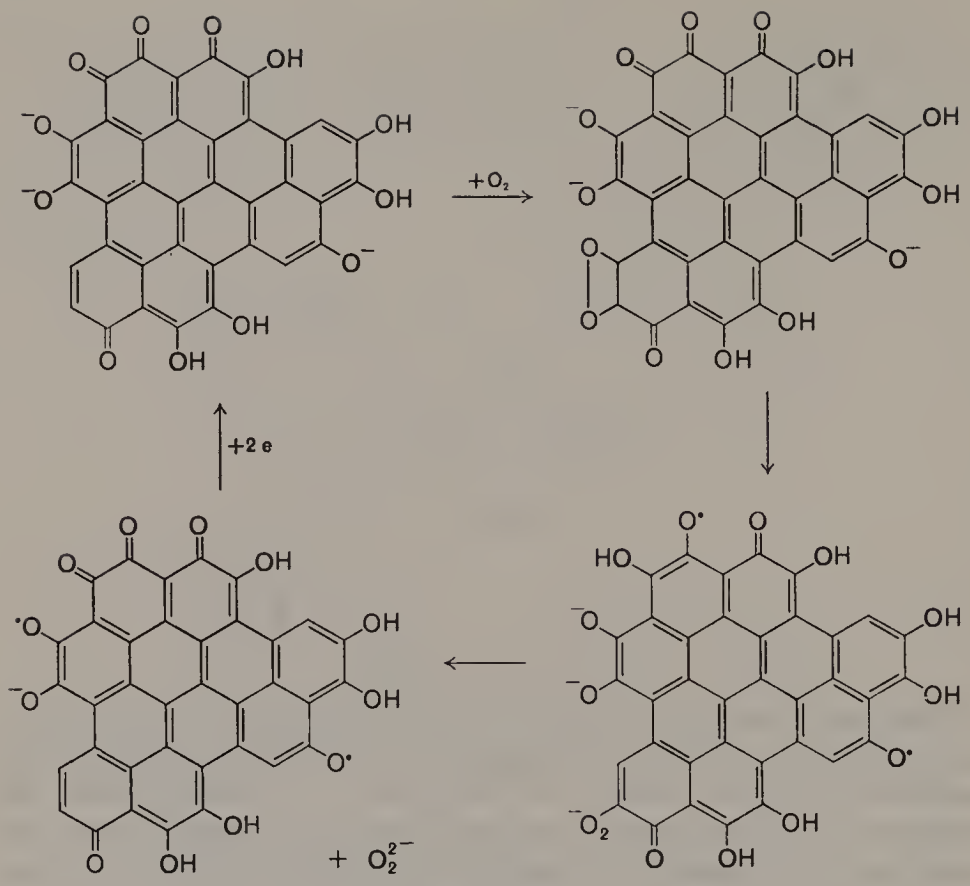
The pyrolysis and coking of coals are thought to involve formation of polynuclear quinone type compounds[47], and the formation of quinone and quinonoid groupings during the preparation of carbon blacks and activated carbons is commonly adduced to explain the reactions they will bring about. The presence of structures such as **26** in H-carbons (i.e. those active carbons that adsorb mineral acid but not alkali) has been proposed to explain its behaviour as an oxygen electrode in alkaline solutions[53].

Some polynuclear quinones have been prepared by condensation reactions. 1,4-Naphthoquinone, for example, on heating with pyridine and glacial acetic acid in nitrobenzene forms the triquinone, triphthaloylbenzene (**27**)[54]. The diene synthesis has been applied to the preparation of polynuclear quinones[55] and is of general application where quinonoid double bonds are exposed.

C. Conjugated Polyquinones

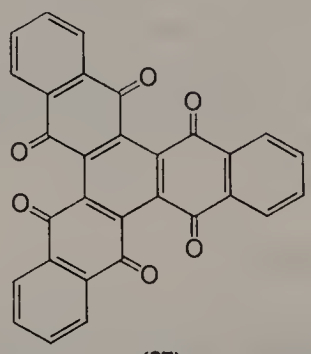
Conjugated polyquinones exhibit unusual properties such as photodynamism[2], photochromism[56] and semiconduction[52] and consequently their synthesis has received increasing attention.

Dimeric and polymeric quinones which are linked through double bonds have been studied by a number of workers. Apparently the first such dimeric quinone, **30**, was described by Hunt and Lindsey[57], who prepared it from the tetramethoxystilbene derivative **28** by demethylation



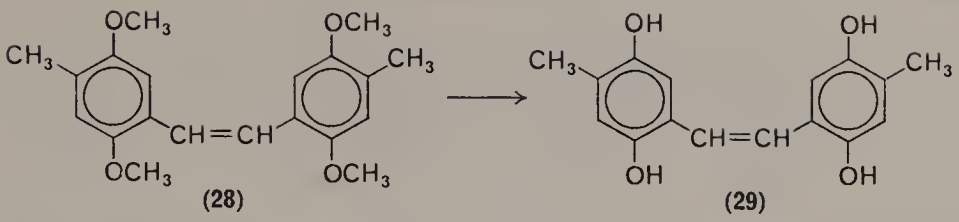
(26)

(After Garten and Weiss[53])

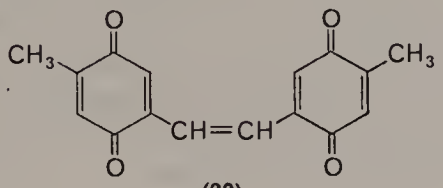


(27)

with pyridinium chloride to give the tetrahydroxy compound **29** which was oxidized to the diquinone by means of silver oxide in dimethoxyethane. The diquinone was unstable to light and air, and the i.r. spectrum and electrochemical behaviour indicated ring conjugation.

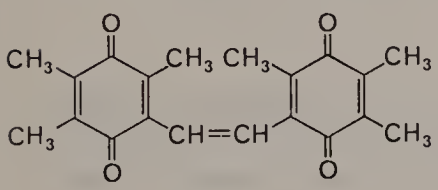


(28) (29)



(30)

Forster and Manecke[58] examined the synthesis of the corresponding fully methylated diquinone **31** using the Wittig reaction to prepare the stilbene derivative **32**. However, on demethylation cleavage occurred into 4,6,7-trimethyl-5-hydroxybenzofuran (**33**) and trimethylhydroquinone.



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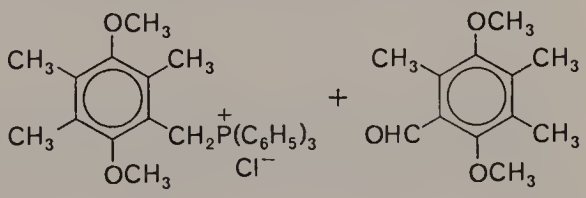

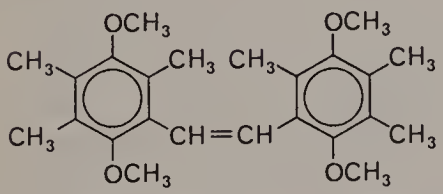

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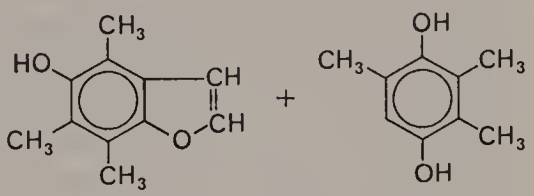
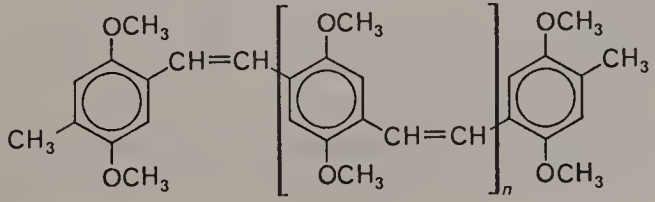
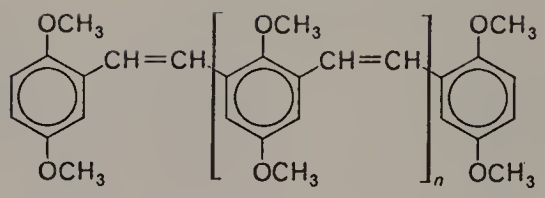


(33)

The Wittig reaction was also employed[59] to prepare a series of oligomers ($n = 1$–4) and polymers of the general formula (3), and also oligomers ($n = 0, 1$) and a polymer of the general structure (4).



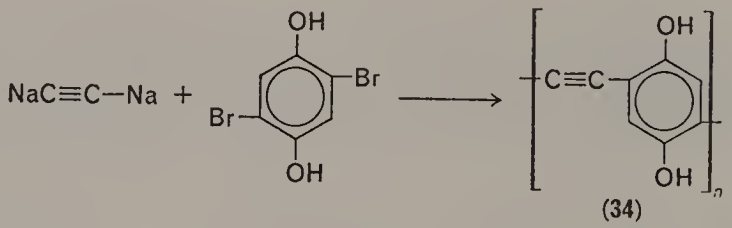
(3)



(4)

However, because of side-reactions and difficulty in obtaining complete demethylation, the corresponding hydroquinone compounds could not be fully characterized. The hydroxy analogue of formula (3) ($n = 1$) was air sensitive and rapidly darkened to a black-brown colour.

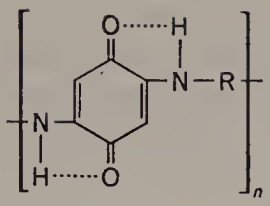
A polyethynylhydroquinone (**34**) has been prepared by reacting disodium acetylide with 2,5-dibromohydroquinone[60]. The polymer was an insoluble black powder which could be reversibly oxidized and reduced and also showed semiconductor properties.



(**34**)

Berlin and coworkers[61] have studied a series of conjugated quinones prepared by reacting aromatic diamines with *p*-benzoquinone or chloranil in hot ethanol or dimethylformamide with an acid acceptor present (sodium acetate) to give polymers of the general structures **35** and **36**, which can also exist in a tautomeric form such as **37**. The polymers were obtained as brown to black powders which were soluble in concentrated sulphuric acid and formic acid to give deep-blue or violet solutions. They had considerable solubility in dimethylformamide, but solubility in other solvents was poor. The dimethylformamide-soluble polymers would react with cupric acetate to give copper-containing polymers believed to have the chelated structure **38**[61]. The polyphenyleneaminoquinones exhibit a narrow electron spin resonance line of high intensity corresponding to 10^{17}–10^{18} free electrons per gram and are semiconductors. In contrast, polyaminoquinones prepared from aliphatic diamines show no paramagnetic properties.

Other conjugatively linked quinones which have been studied by Berlin and coworkers are the polyarylenequinones (**39**)[62] and the polyphenylazoquinones (**40**)[63]. Both series are prepared by reacting *bis*-diazotized aromatic diamines such as *p*-phenylenediamine, benzidine, substituted benzidines and 4,4′-diaminostilbene with benzoquinone or



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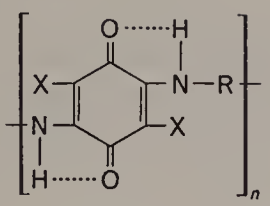
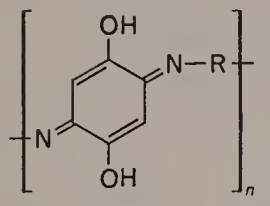


(36)

(R = $-C_6H_4-$, $-C_6H_4C_6H_4-$ etc.)
(X = Cl, CH_3COO-)



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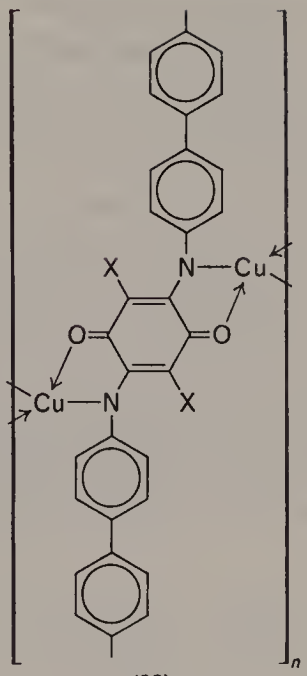

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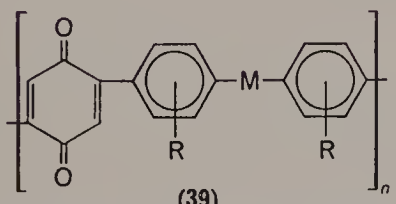
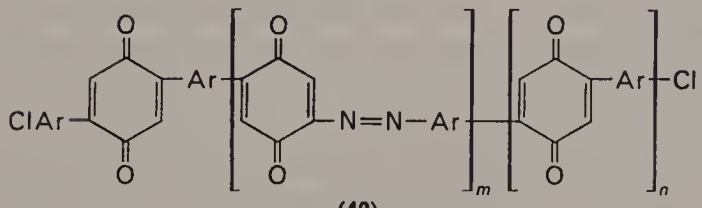


(39)

M = $-CH=CH-$, or is absent
R = H, $-HSO_3$, $-CH_3$



(40)

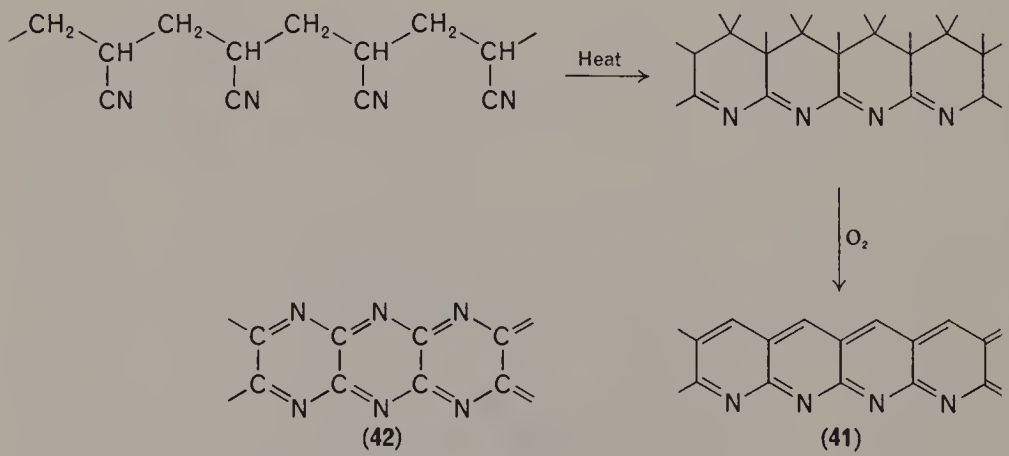
Ar = Arylene group

chloranil. Thus, with benzoquinone polymer structure **40** is thought to arise, the azo groups being retained due to incomplete decomposition of the diazo compound. In other cases, such as when benzidine-3,3′-disulphonic acid is used, structures of substantially the polyarylenequinone type are obtained and only very low amounts of nitrogen are retained.

D. Quinonoid Polymers

Quinonoid polymers are those polymers which exhibit quinonoid structures or possess quinonoid properties. A wide range of such polymers both aromatic and heteroaromatic has been reported in the literature. However, in this section only quinonoid polymers which illustrate special methods of preparation or which exhibit properties of particular interest, such as thermal stability or semiconductivity, will be considered.

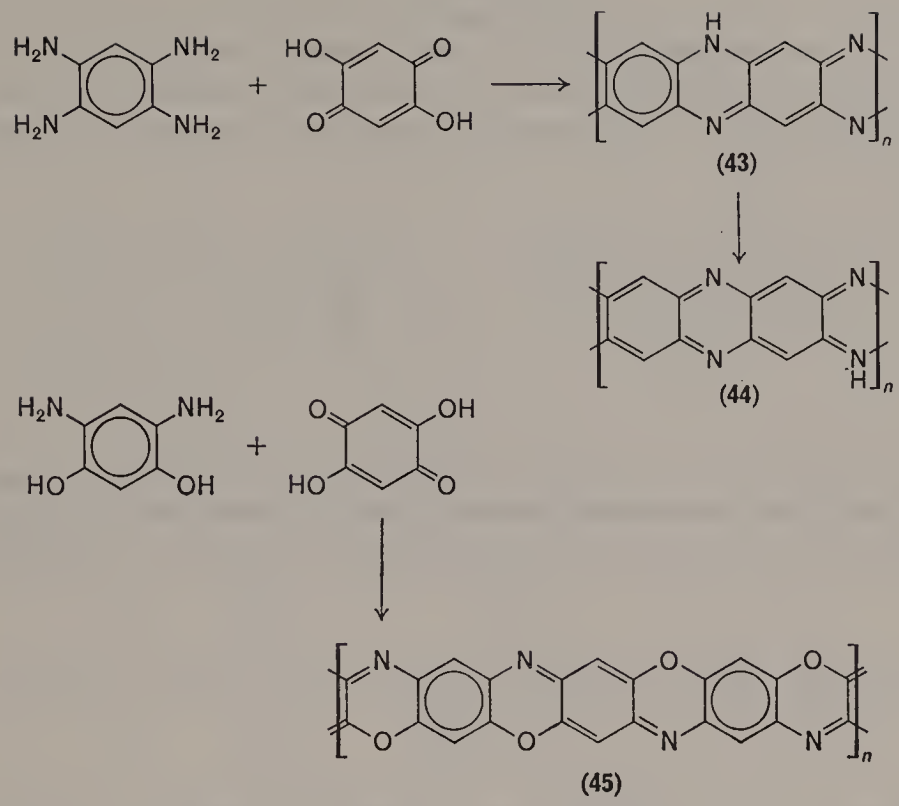
The high thermal stability of graphitized polyacrylonitrile fibre is well established[64], but if pyrolysis of the fibre is carried out in air at lower temperatures (400–500°C) black polymers, believed to have structure **41** and containing nitrogen in the ring, are obtained[65]. These polymers contain free electrons and exhibit semiconducting and catalytic properties which are discussed more fully in section VI. The orthoquinonoid structure is similar to that proposed for paracyanogen[66], **42**.



(42) (41)

A number of the so-called 'ladder' polymers possess quinonoid structures. Examples of these are the polyhydroquinoxalines (**43**), the polyquinoxalines (**44**) and the polyphenoxazines (**45**) prepared by Stille and coworkers[67].

The polyhydroquinoxaline **43** is believed to be the first product of the condensation of stoicheiometric amounts of the hydrochloride of 1,2,4,5-tetraminobenzene and 2,5-dihydroxy-*p*-benzoquinone in solvents such as dimethylacetamide, hexamethylphosphoramide and polyphosphoric acid.

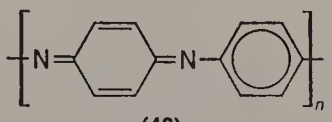


The structure of the black polymer formed was assumed by analogy with the product of the simple monomeric reaction. Oxidation on heating the polymer in air was assumed to give the polyquinoxaline **44**. A rather similar series of reactions provided the polyphenoxazines. In this case 4,6-diaminoresorcinol was condensed with 2,5-dihydroxy-*p*-benzoquinone (or its diacetate) in hexamethylphosphoramide.

Aniline black is a deep-black polymeric product obtained by oxidation of aniline with potassium dichromate or potassium chlorate[46b]. In an alternative preparation cyclohexa-1,4-dione was condensed with *p*-phenylenediamine and then aerially oxidized[49]. Although its structure has not been established it is thought to be a conjugated polymer of the type shown, **46**. The chemistry of aniline black was examined by Willstater and coworkers and by Green and coworkers who showed that there were several distinctive oxidation stages involving progressive oxidation from a colourless leuco compound through to an ungreenable aniline black[46b]. Similar quinonoid polymeric dyes which also contain sulphur are obtained by oxidation of aniline, diphenylamine and triphenylamine with sulphuric acid[68]. Aniline black has been shown to possess free electrons, giving both narrow line and broad line e.s.r. signals[61]. Its semiconductor properties

have been studied, as well as its catalysis of hydrogen peroxide decomposition and dehydrogenation of hydrocarbons (see section VI).

Structurally similar polymers, **47**, have been prepared by heating 1,4-naphthoquinone with toluenediisocyanate in the absence of air at 250°C[52].



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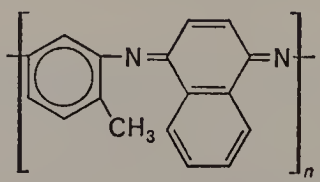
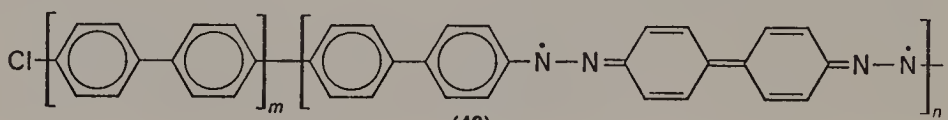


(47)

Another group of conjugated polymers which probably possess quinonoid structures in the chain are the polyazophenylenes studied by Berlin and coworkers[69]. These were prepared by treatment of *bis*-diazotized benzidine or substituted benzidines with ammoniacal cuprous salts.



(48)

Brick-red to brown polymers were obtained, **48**, which were soluble in concentrated sulphuric acid but not very soluble in organic solvents. Chlorine apparently formed the chain end groups. Most of the polyazophenylenes are of high thermal stability and survive temperatures of 300°C. The e.s.r. spectrum showed three types of signal, and the polymers had high free-electron spin values ranging from 10^{18} to 10^{19} spins/g. The quinonoid structure of the polymer chain was deduced from the i.r. absorption spectrum. Some rather similar polymers have been obtained by replacing benzidine in the reaction by 4,4′-diaminodiphenylmethane or by 4,4′-diaminobenzil[70].

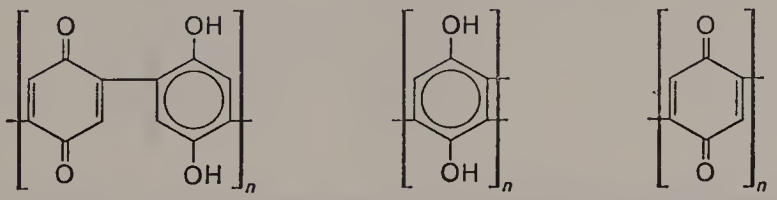
IV. POLYMERIC QUINONES

A. Polymers with Directly Linked Quinone Groups

Treatment of mono-, di- or polyhydric phenols or of aminophenols in alkaline solution with aerial oxygen, potassium persulphate solution or hydrogen peroxide at temperatures below 60°C yields dark-brown amorphous polymers[71]. 1,2-Benzoquinone under similar treatment likewise gives amorphous polymers. These polymers were called 'synthetic humic acids' because of the similarities of their properties, such as redox

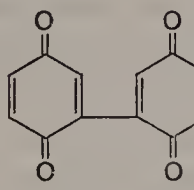
character, solubility in alkali and precipitation by acids, and of their chlorinated and nitrated products, with one another and with the natural humic acids.

The structure of these polymers was investigated by Erdtman[72], and later with coworkers[73], who established that they contained directly linked hydroquinone and quinone groups as well as diphenylene oxide structures. The polymeric products were usually prepared by shaking a suspension of *p*-benzoquinone in alkaline solution (sodium hydroxide or sodium acetate) in an inert atmosphere for a prolonged period, then acidifying with mineral acid and extracting the hydroquinone with ether. The moist polymers were easily soluble in alkali, giving green or brown solutions which readily absorbed oxygen from the air to form deep-brown solutions. Erdtman proposed that the alkali polymerized *p*-benzoquinone had a linear or three dimensional structure based on units such as series (5).



(5)

Directly linked di-, tri- and tetraquinones (**49–51**) which were separately synthesized were shown to yield typical synthetic humic acids when treated with alkali.



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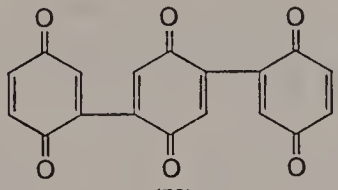

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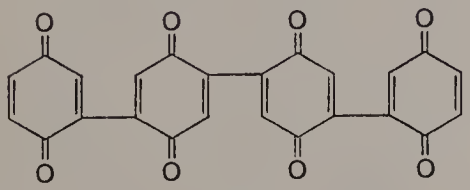

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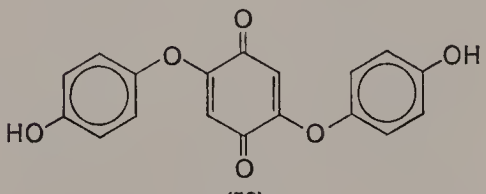
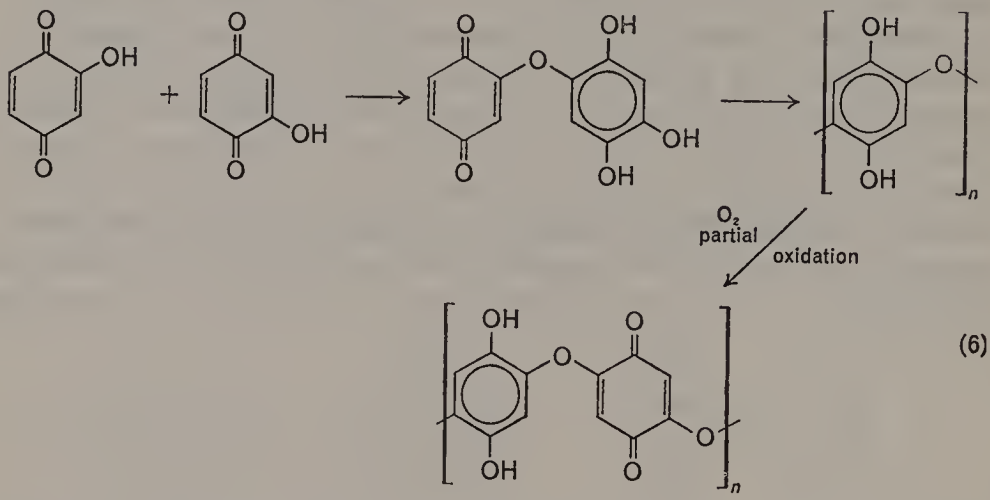


(52)

Diels and Kassebert[74] obtained a quinone trimeride, **52**, from benzoquinone by the action of pyridine, but in view of the ready alkaline hydrolysis of this compound to hydroquinone and 2,5-dihydroxyquinone,

Erdtman[73] has discounted the possible existence of this structural unit in the polymers.

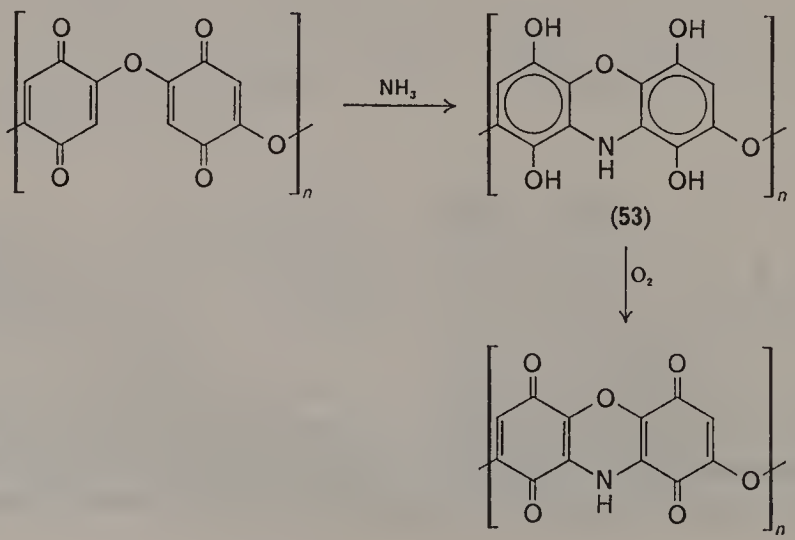
It has been established that a primary product of alkali treatment of *p*-benzoquinone is 2-hydroxy-*p*-benzoquinone[75], and Flaig[76] has proposed that since hydroxy-*p*-benzoquinone is not stable in aqueous solution it undergoes polycondensation by the reactions shown (6). Flaig[76] also



(6)

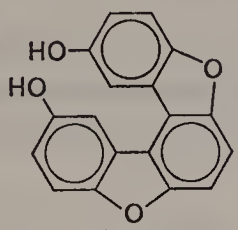
showed that when oxidation of hydroquinone was carried out in strong ammonia solution a polymer containing nitrogen was obtained, which was considered to have structure **53** on the basis of its nitrogen analysis.

Attention has also been drawn to the ring-opening effect of alkaline oxidation on 4,6-di-*t*-butylpyrogallol[77] to yield 2,4-di-*t*-butyl-4-oxalocrotonic acid which could also be involved in the formation of the synthetic humic acids.



Mineral acids will also cause dimerization and polymerization of quinones[72]. Thus the main product from *p*-benzoquinone is an amorphous mixture of at least partly quinonoid substances. Erdtman[78] has proposed that they are formed mainly by 2,5 (or 2,6) condensation of the quinone nuclei and that the trimeride which is also found to be present owes its formation to a competing reaction involving 2,4-condensation followed by dehydration to the stable product **54**. The alternative structure **55** was eliminated on the basis of direct comparison with an authentic sample.

Shand and Thomson[79] have pointed out that ring cyclizations of diquinones **56**→**57** not only proceed under acid conditions but also thermally and by u.v. irradiation.



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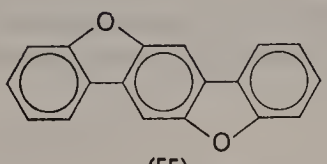

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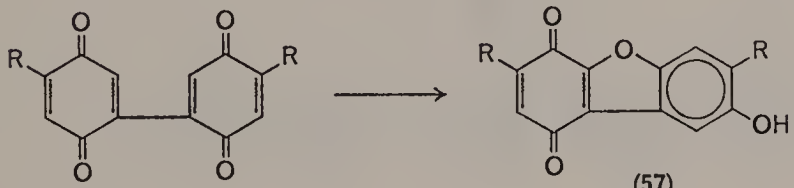
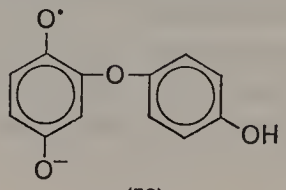


(56) (57)

The exact mechanisms of the hydroquinone and quinone polymerizations have not yet been established. However, there are certain lines of evidence which point to the intermediate formation of semiquinone anions which subsequently dimerize and polymerize by free-radical combination processes. It is well known that phenols will undergo a wide variety of coupling reactions under oxidative conditions which are similar to those of semiquinone radicals[80]. Thus, when aqueous sodium hydroxide is added to an alcoholic solution of *p*-benzoquinone (or duroquinone) in the presence of air a dark-green–yellow solution results which exhibits a strong paramagnetic signal (e.s.r.) thought to be due to formation of a semiquinone species, possibly that of hydroxybenzoquinone[81]. Anderson and coworkers[82] have made a more detailed e.s.r. study of the development of paramagnetic semiquinone free radicals produced by aerial oxidation of hydroquinone in alcoholic potassium hydroxide. The results suggested that the radicals dimerize or otherwise react in concentrated

solution to form radicals linked through oxygen, whilst dibenzosemiquinone radicals are produced from the benzoquinone under reducing conditions. The primary coupling products suggested are **58** and **59**, including their various possible substituted versions depending on the starting material, the reaction mechanism and the displacement of substituents.



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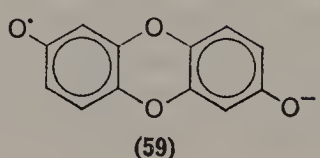
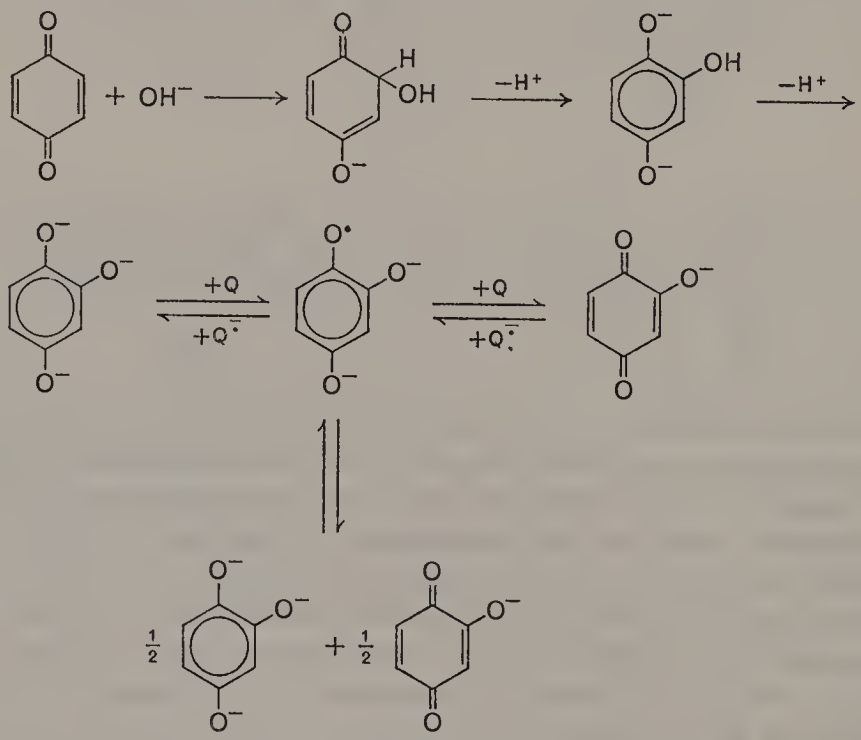


(59)

On the basis of a kinetic study of the reactions of *p*-benzoquinone with alkali at 22°C Eigen and Mathies[83] have put forward the reaction scheme shown (7). An initial reaction between the quinone and hydroxyl ions is



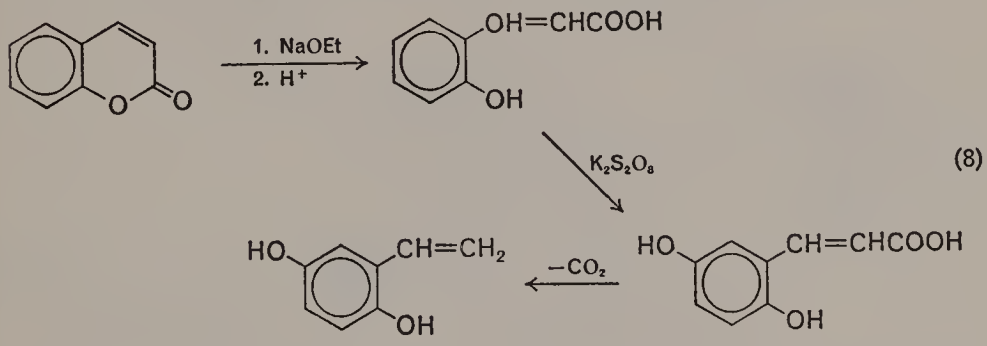
(7)

(Q = benzoquinone)

thought to result in formation of hydroxyhydroquinone, which then undergoes redox reactions with the *p*-benzoquinone leading to the formation of *p*-benzosemiquinone, hydroxy-*p*-benzoquinone and hydroxy-*p*-benzosemiquinone. These reactive intermediates could be expected to link up to form polymeric products of the types described above.

B. Polymerized Quinones

Quinones are well-known inhibitors of free-radical polymerization of vinyl monomers[84], although apparently anthraquinone has little affect on the molecular weight of the chain in styrene polymerization[85]. Vinyl hydroquinone is sensitive to aerial oxidation and consequently radical polymerization of it tends to be hindered by the presence of the quinone, and only low molecular weight polymer is obtained[86]. Much higher degrees of polymerization can be attained by protecting the hydroxyl group with another group which can readily be removed after polymerization. Suitable groups which have been used are acetyl[86], benzoyl[86], methyl[87], tetrahydropyranyl[88], methoxymethyl[89] and 1-ethoxyethyl[90], although in the last two instances formaldehyde and acetaldehyde are liberated in the hydrolysis stage, and may further react with the polymer. The initial synthesis of vinyl hydroquinone[86] was carried out by the series of reactions shown (8) but alternative routes have been reported[91].



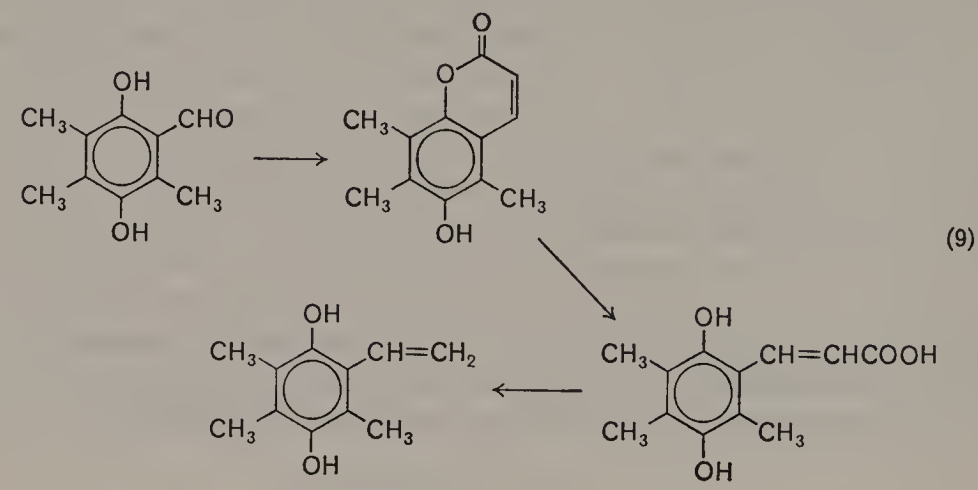
(8)

Polyvinylhydroquinone is not very hydrophilic and therefore copolymers of vinylhydroquinone dibenzoate with α-methylstyrene and divinylbenzene have been prepared which could be sulphonated to confer a greater degree of hydrophilic character on them[92]. Since methylated and other substituted quinones show a greater stability towards inorganic oxidants than the unsubstituted benzoquinone, various synthetic methods have been developed to incorporate these into a polymeric matrix[93–95], which are shown in the reaction sequences (9–11).

Spinner and coworkers[96] circumvented the necessity to attach the polymerizable double bond directly to the hydroquinone, by linking the latter to the styrene molecule via a sulphone bond. The hydroxyl was protected by a pyranyloxy group during the polymerization reaction (12).

Manecke and coworkers[97] found that neither 2-methyl-3-vinyl naphthoquinone nor 2,3-dimethyl-5-vinyl naphthoquinone could be polymerized when converted to the corresponding diacetates. However, when the

latter was converted to the epoxide the product could be readily polymerized. The oxide bridge was then removed by treating with potassium iodide in aqueous acetic acid (reaction 13).



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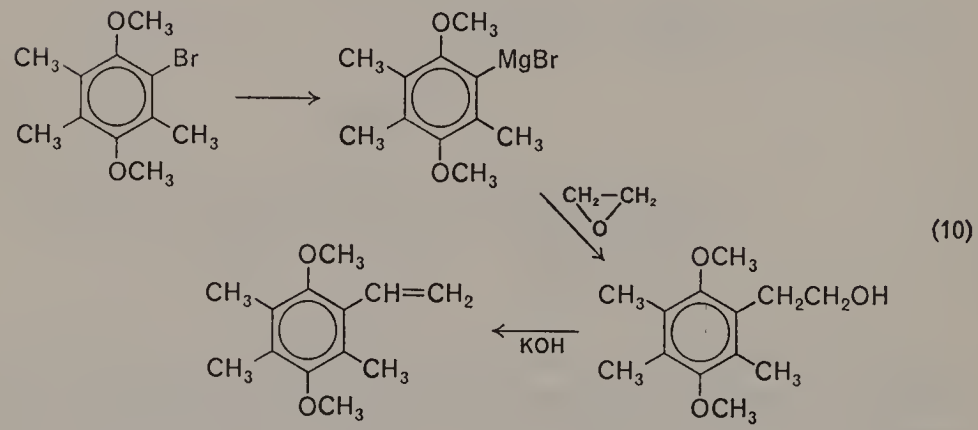

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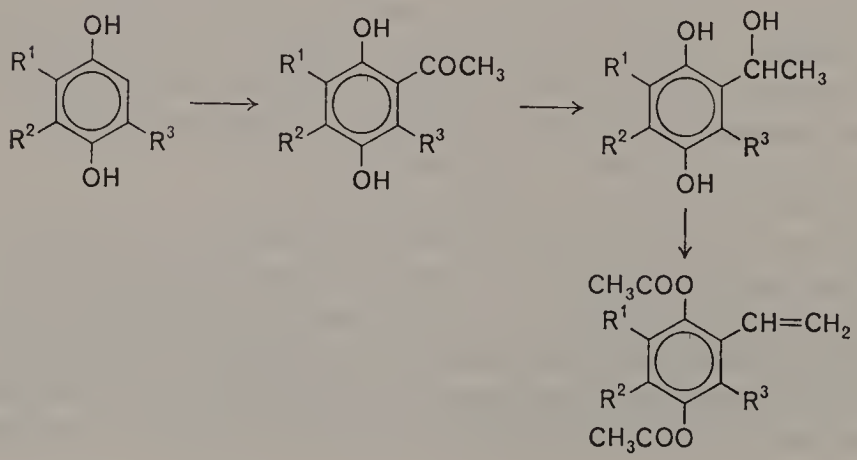

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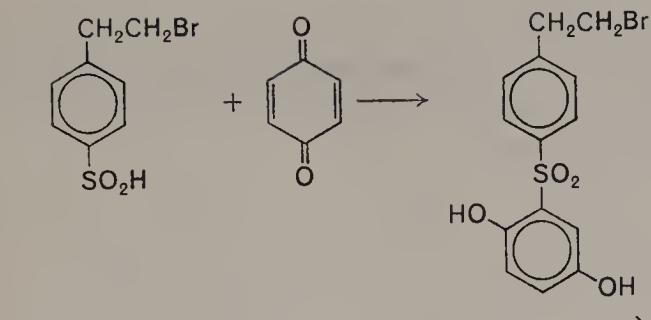

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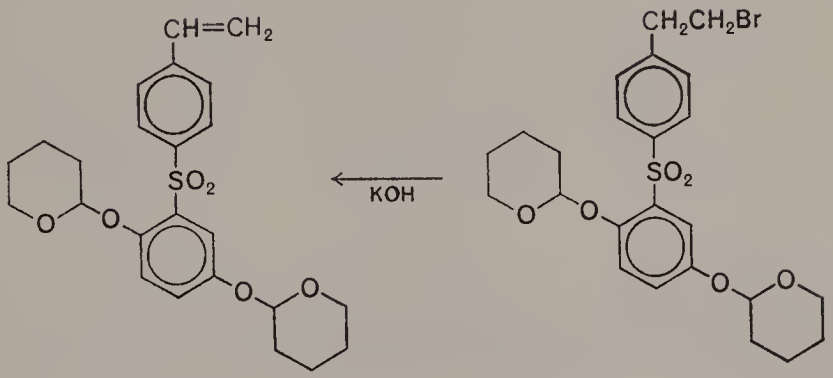

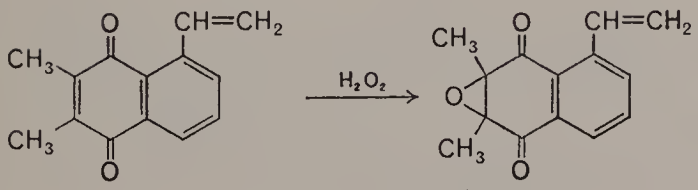

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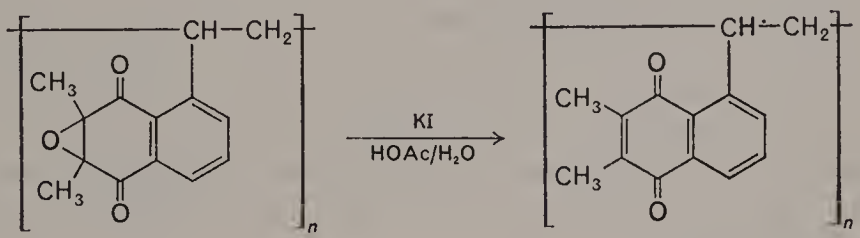
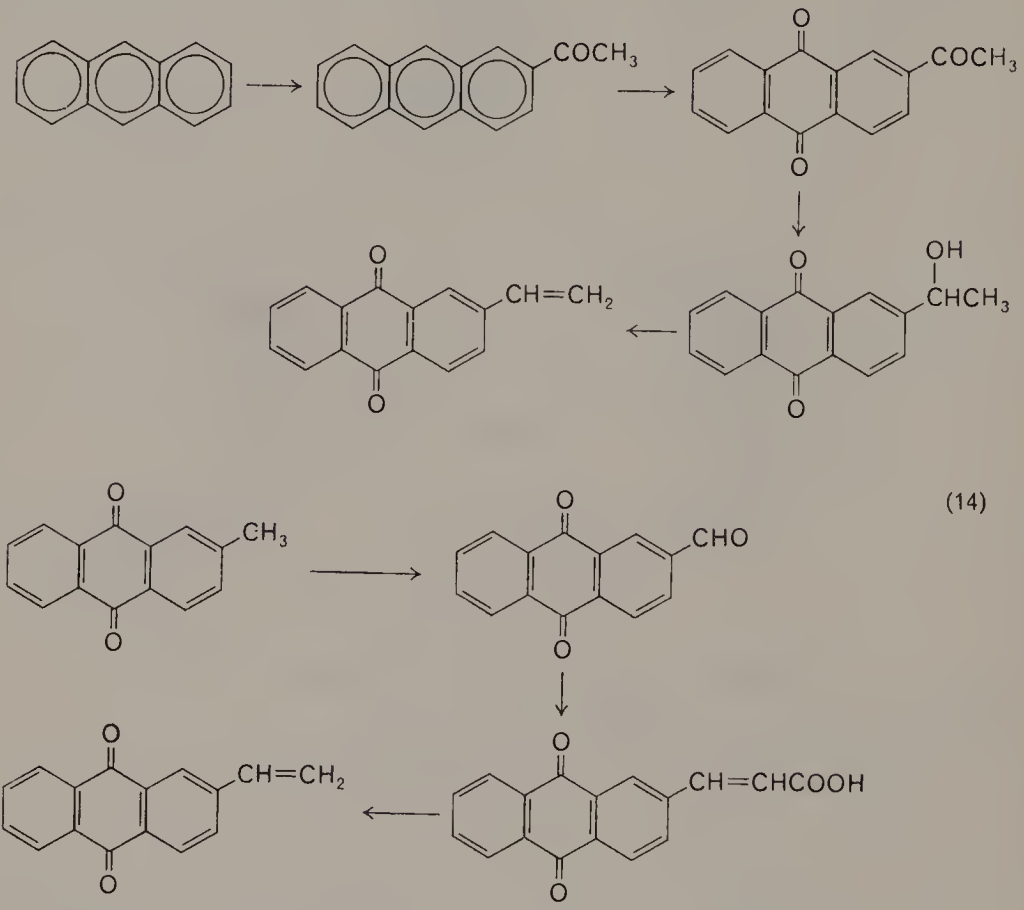


Routes have also been examined to the polyvinylanthraquinones. 1-Vinylanthraquinone has been prepared by Diels–Alder addition of 1,3,5-hexatriene to 1,4-naphthoquinone and subsequent oxidation, but was found to be thermally non-polymerizable[98]. Several routes to 2-vinylanthraquinone have been reported[99]. The simplest method involves

dehydrogenation of 2-ethylanthraquinone by passage over palladized asbestos at 600°C. Oxidation of 2-methylanthraquinone to the aldehyde, conversion to the 2-acrylic acid followed by decarboxylation to 2-vinylanthraquinone is an alternative route.

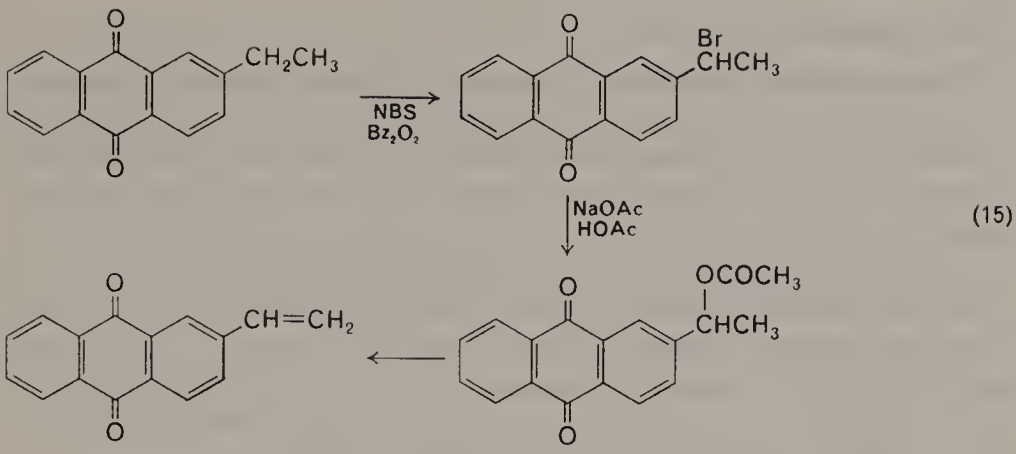


(14)

Manecke and Storck[100] prepared 1- and 2-vinylanthraquinone from anthracene or from anthraquinone by a variety of routes (reaction 14). They also used 2-ethylanthraquinone as starting material which they converted to the vinyl compound by the reaction sequence (15).

2-Vinylanthraquinone readily undergoes radical polymerization with high conversions and can be copolymerized with styrene and divinylbenzene. The copolymers can be sulphonated to improve their hydrophilic character[100].

Polymers and copolymers based on various vinylpyrazoloquinones have been reported by Manecke and coworkers[101]. Thus 1,3-dipolar addition of vinyl diazomethane to benzoquinone, 2,3-dimethylbenzoquinone and naphthoquinone gave the vinyl pyrazoloquinones (**60–62**, R = H) which could be copolymerized. The polymers and copolymers



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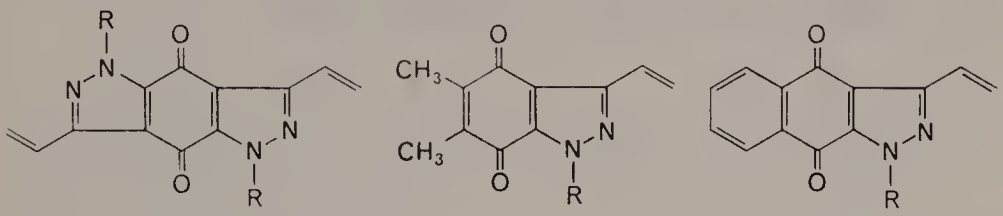


(60) (61) (62)

could be *N*-sulphalkylated ($R = (CH_2)_3SO_3K$) to give water-swellable polyquinones by treatment with propane sultone. The water-swellable copolymers obtained were claimed to be very stable chemically and thermally.

Some typical values of redox and ion-exchange capacities of polymerized quinones are given in Table 1.

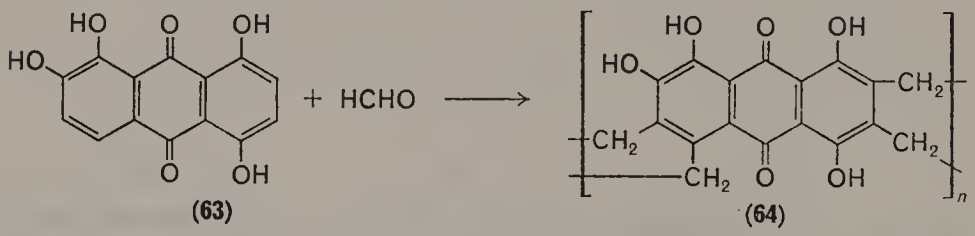
TABLE 1. Typical redox and ion-exchange capacities of polymerized quinones

Polymer	Redox capacity (meq/g dry resin)	Ion-exchange capacity (meq/g dry resin)	Reference
Sulphonated copolymer of vinylhydroquinone, α-methylstyrene and divinylbenzene	5·7	3·9	139
Sulphonated copolymer of 2-vinylanthraquinone, styrene and divinylbenzene	4·8	2·0	100
Sulphoalkylated copolymer of 3-vinylpyrazolonaphthoquinone and 3,6-divinyl-*bis*-pyrazolobenzoquinone	5·0	2·7	101

C. Polycondensed Quinones

The preparation of polymeric quinones by polycondensation reactions provides an alternative synthetic method which is versatile and prolific.

A very widely applied method utilizes the acid- or base-catalysed condensation of *o*- or *p*-dihydric phenols, or hydroxyquinones, such as quinalizarin (**63**) and chrysazin, with formaldehyde. The degree of cross-linking can be controlled by varying the molar ratio of formaldehyde, and by adding phenol or resorcinol to the reaction mixture as a diluent and cross-linking agent. Thus two- or three-dimensional networks of the types **64** and **65** can be obtained. Treatment with oxidants such as ferric or ceric salt solutions converts the polymers to the polyquinone form, which can be reduced again with sodium dithionite solution.



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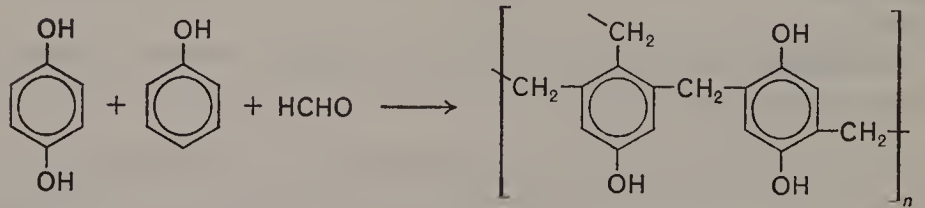


(65)

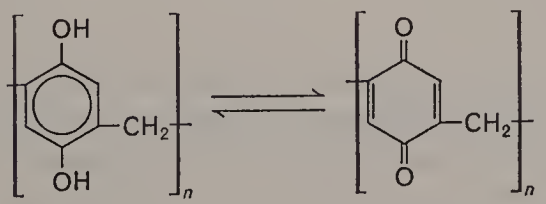
The earliest report of the condensation of phenol and formaldehyde with polyhydroxy benzenes was that of Griessbach and coworkers[102] who described a regeneratable redox resin. Condensates of phenol–formaldehyde–hydroquinone have been studied in detail by Manecke and coworkers[103,104]. By using phenolsulphonic acid as one component, water-swellable polymers were obtained[105]. A range of quinones and hydroxy quinones such as juglone, 2-hydroxyanthroquinone, alizarin, anthrarufin, quinalizarin, chrysazin and purpurin have been utilized[103,106]. Formaldehyde as such, or in the form of paraformaldehyde or hexamethylene triamine, has been most commonly used as the cross-linking agent. Other aldehydes such as acetaldehyde, paraldehyde, benzaldehyde, furfural and glyoxal may be used to replace all or some part of formaldehyde in the condensation[107]. Practical conditions for the preparation

of hydroquinone–resorcinol–formaldehyde polymers have been examined[108]. Macroporous polycondensates with improved redox reaction kinetics (i.e. faster acting) have been obtained by Shostak and Ergozhin[109]. Some typical redox capacities of polycondensed quinones are given in Table 2.

TABLE 2. Typical redox capacities of polycondensed quinones

Polycondensate components	Ratio	Redox capacity (meq/g dry resin)	Reference
Hydroquinone Phenol Formaldehyde	1 1 3	6·8	103
Juglone Phenol Formaldehyde	1 1 3	4·5	103
Hydroquinone Resorcinol Formaldehyde	1 1 2	4·4	108

A convenient way of preparing methylene- and dimethylene-linked quinone polymers has been reported by Hunt and Lindsey[110] in which 1,4-di(chloromethyl)-2,5-dimethoxybenzene was directly condensed with 2,5-dimethoxybenzene by refluxing the two compounds together in glacial acetic acid. Subsequent demethylation gave the polyhydroquinone which could be reversibly oxidized to the polyquinone form (reaction 16). By treating 1,4-di(chloromethyl)-2,5-dimethoxybenzene with a sodium dispersion in dioxan the dimethylene-linked polymer was obtained which could likewise be demethylated and oxidized to the polyquinone (reaction 17).



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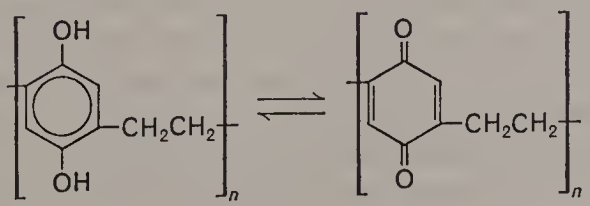
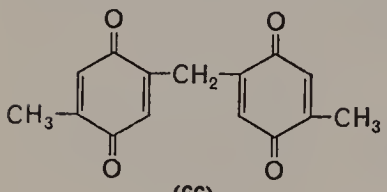


(17)

Because of the difficulties of studying the properties of the formaldehyde condensation products directly, a number of studies have been carried out on low molecular weight dimeric, trimeric and tetrameric quinones with analogous structures to those of the polymer chain unit (see section V.B). Thus Lindsey and coworkers[110] synthesized the polymer model compounds **66** to **71** by direct condensation of the mono- or *bis*-2,5-chloromethyl-1,4-dimethoxybenzene with 1,4-dimethoxybenzene or derivatives to form dimers and trimers. Demethylation gave the corresponding hydroxy compounds which could be oxidized with acid ferric ammonium sulphate, or by refluxing with ethanolic benzoquinone.



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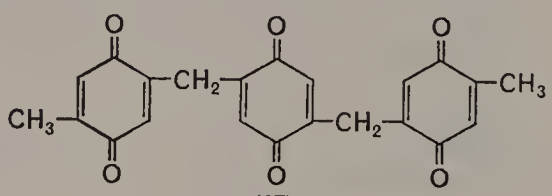

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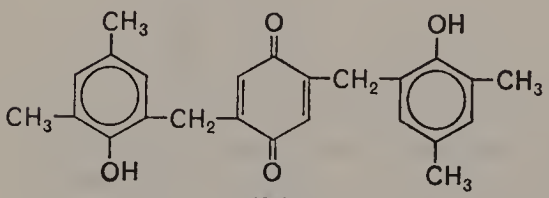

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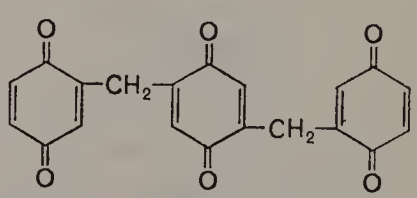

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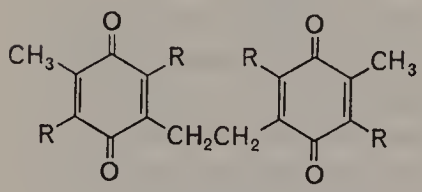
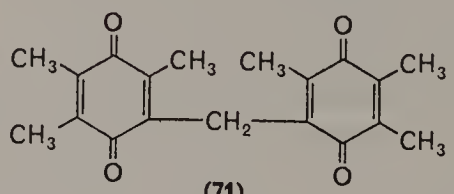


(R = CH_3— or Br)

(70)



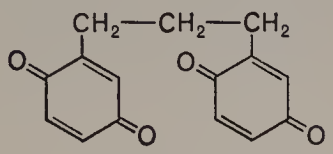
(71)

Manecke and Forster[104] similarly synthesized oligomers by controlled condensation of phenol, hydroquinone and formaldehyde to give chain segments carrying hydrogen, methyl or chloro substituents. These compounds were also used for potentiometric studies (see section V.B).

A series of model chain units (**72–74**) corresponding to the polyvinylquinone system were synthesized by Moser and Cassidy[111], and were examined spectroscopically and potentiometrically (see section V.B).

Another route to the polyquinones has utilized a polypeptide chain as backbone with hydroquinone groups pendant to it[112]. Thus polycondensation of 4-(2,5-diacetoxybenzyl)-oxazolidine-2,5-dione (**75**) by

treatment with alkali in dioxan gave the protected hydroquinone polymer **76**, which on hydrolysis gave the polyhydroquinone **77**.



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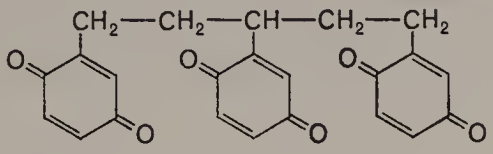

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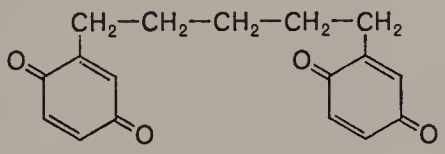
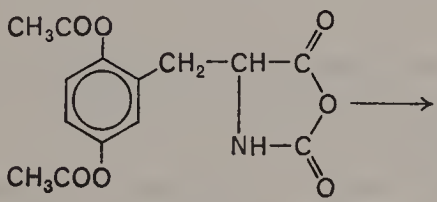


(74)

The 3,4-dihydroxyphenyl polymer was prepared by a similar route. The 2,5-dihydroxy polymer was hygroscopic whilst the 3,4-dihydroxy polymer was not. Copolymers were prepared by copolycondensation with the *N*-carboxy anhydride of γ-benzyl glutamate. Conversion to identifiable polyquinones was not reported[112].

A polyester chain carrying pendant anthraquinone groups has been reported[113]. Initially 2-formylanthraquinone was reacted with diethyl-malonate to give diethyl anthraquinonyl-2-methylenemalonate (**78**), which readily condensed with aliphatic diols and glycerol to give a polyester polyquinone of structure **79**.

Haas and Schuler[114] showed that peroxidation of the diacetate of allyl hydroquinone provided the epoxide derivative which could be poly-condensed under the catalytic action of zinc chloride–aluminium isopropoxide to give poly-3-(2,5-diacetoxyphenyl)propylene oxide. The



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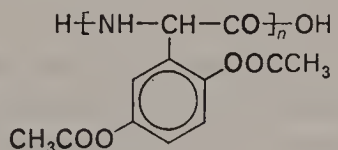

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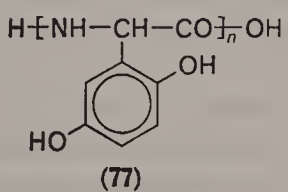
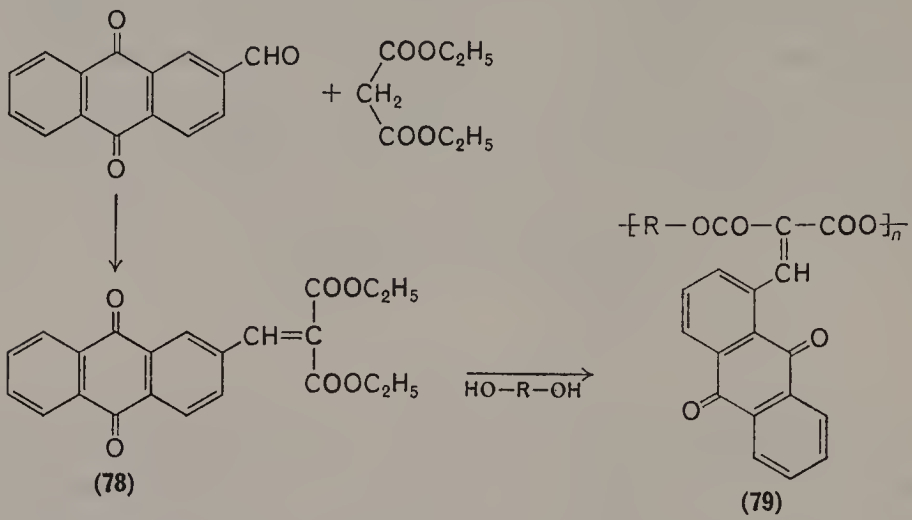


(77)

acetate groups were removable by alkaline hydrolysis to give the polyhydroquinone, which was susceptible to aerial oxidation under these conditions.



(78) (79)

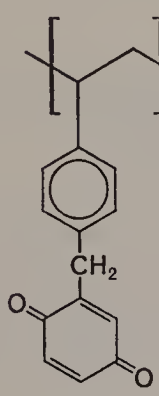
D. Polymer Supported Quinones

Quinones and hydroquinones have been attached to a variety of polymer frameworks by chemical reaction, often under mild conditions. The main difficulties are achieving high reaction yields and the avoidance of side-reactions, particularly cross-linking.

One of the earliest reports of this synthetic approach was that of Sansoni[115], who converted polyaminostyrene to the diazonium salt which was then reacted directly with *p*-benzoquinone. Dyestuffs such as methylene blue and thionine could be similarly attached. The reactions of aryldiazonium salts with benzoquinone have been studied by Brassard and L'Ecuyer[116]. Dorfner[117] extended the scope of the reaction by coupling diazotized polyaminostyrene with *p*-benzoquinone, 1,4-naphthoquinone and anthraquinone. Hydroquinone has also been utilized in this reaction to give polymers of high redox capacity, stable to strong oxidants and reducible by alkaline dithionite[118]. The polyquinone form was found to oxidize Fe^{2+} and methylene blue.

Kun[119] developed alternative methods of bonding the quinone system to the polystyrene matrix. Conventional gel and macroreticular styrene-divinylbenzene polymers were chloromethylated with chloromethyl ether using a Friedel–Crafts catalyst, and the chloromethylated polymer treated with hydroquinone, benzoquinone or 1,4-dimethoxybenzene in the presence of further Friedel–Craft's catalyst. The dimethoxy compound was subsequently demethylated by means of hydriodic acid. The polyquinones so obtained were of the type **80** and **81**. The polystyrene backbone

renders the polymers hydrophobic in character, and they were made more hydrophilic by limiting the initial amount of hydroquinone reacting with the polymer and converting the surplus chloromethyl groups to hydrophilic quaternary groups, e.g. by reaction with trimethylamine **82**[120]. An alternative method was sulphonation of the hydroquinone groups[121].



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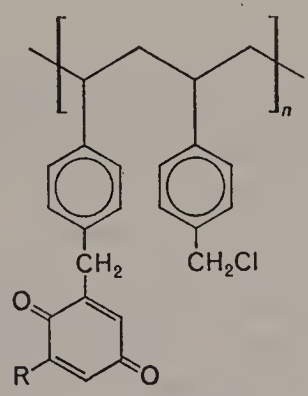

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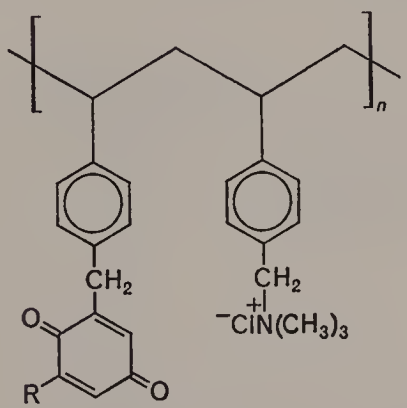
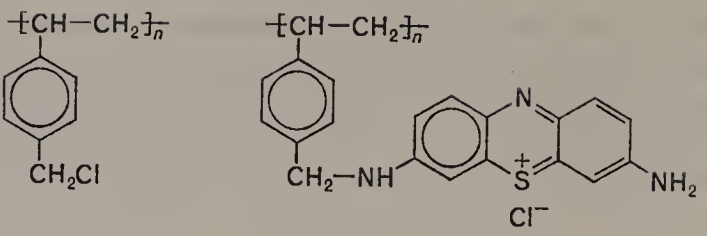


(82)

Russian workers have described the preparation of similar polyquinones from chloromethylated polystyrene and styrene-disopropenylbenzene copolymer[122]. A commercial polymeric quinone with a structure approximating to **82** (R = *t*-butyl) has been marketed[123].

Manecke and Kossmehl[124] have reacted a chloromethylated cross-linked polystyrene with thionine and with trimethylthionine to prepare blue-coloured polymers containing quinonoid dye structures **83**, and possessing good redox capacities (ca. 4 meq-g).

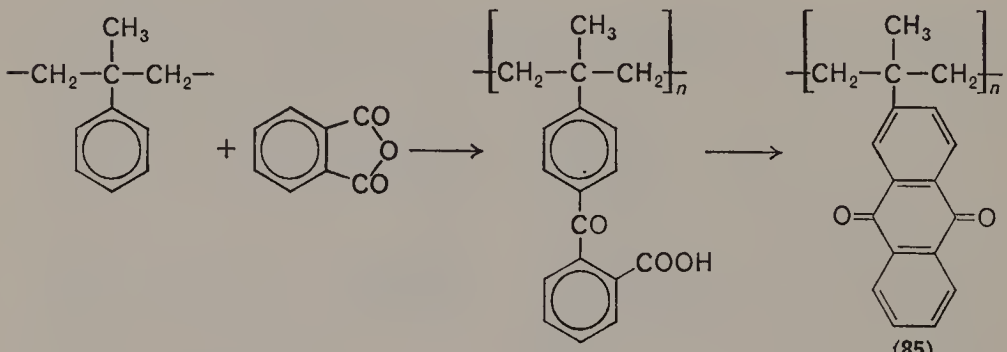
Reaction of phthalic anhydride with poly-(α-methylstyrene) in the presence of aluminium chloride gave poly[*p*-(*o*-carboxybenzoyl)-α-methylstyrene] (**84**) which on heating in syrupy phosphoric acid cyclized to



(83)

give the poly[2-(α-methylvinyl)-anthraquinone] polymer (**85**). The low redox capacity of the product (0·5 meq/g) indicated that only a low introduction of anthraquinone groups had occurred[124].

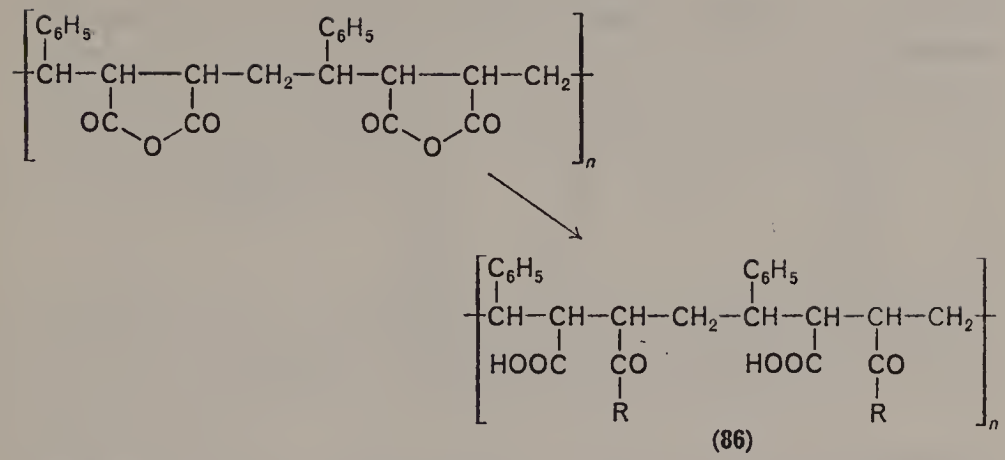
Kern and Schulz[125] utilized a styrene–maleic acid copolymer which they reacted with β-aminoanthraquinone in tetrahydrofuran in an autoclave at 160°C for six hours. A pale-yellow polymer of the general structure **86** was obtained which was soluble in tetrahydrofuran, pyridine and dimethylformamide and possessed oxidizable–reducible groups. A quinonoid grouping was introduced into the polymer by reaction with 7-amino-phenthiazone-2.



(84) (85)

An interesting route to the polyquinones was developed by Taylor[126], who reacted 6-hydroxy-3,4-dihydrocoumarin and similar compounds with poly(vinylamine) and poly(ethylenimine) by refluxing the components together in aqueous methanol. Polymers of the general structure **87** were obtained which were stable to alkalis and were proposed for use as anti-fogging or antistain agents in photographic emulsions.

Polyvinyl alcohol[127, 108] and polyacrylic acid[127] have also been used as supports for anthraquinone and benzoquinone groups. Thus in acidified methanolic or dimethyl sulphoxide solution 2-formylanthraquinone condenses with polyvinyl alcohol to give a polyacetal structure carrying pendant anthraquinone groups (**88**). These groups were reducible by solutions of titanous salts or sodium dithionite, and reoxidizable with air.



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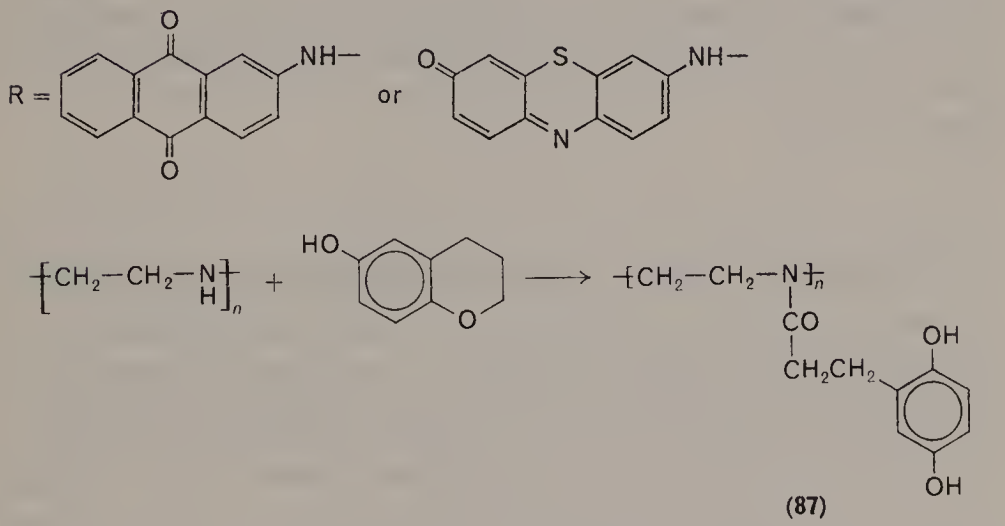
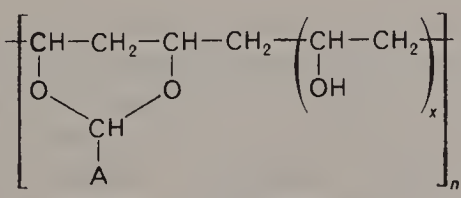


(87)

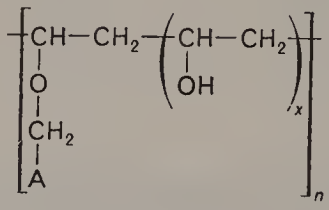
The acetal bonds were rather easily cleaved by acids. Izoret[127] has also described polyquinones prepared by reacting the tosylate of 2-hydroxymethylanthraquinone with polyvinyl alcohol to give **89**, and by reacting 2-hydroxymethylanthraquinone with polyacrylic acid to give polymers of the type **90**. Tetrachlorobenzoquinone has been reacted with a sodium



(88)

(A = anthraquinonyl-2)

derivative of polyvinyl alcohol to give a polyquinone of good redox capacity[128].



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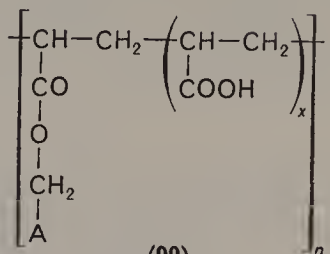


(90)

(A = anthraquinonyl-2)

Kamogawa[129] methylolated polyacrylamide and an acrylamide-vinylpyridine copolymer with formaldehyde under alkaline conditions. The products were reacted with hydroquinone or phenothiazine to give redox polymers which could be potentiometrically titrated with ceric sulphate solutions.

V. ELECTROCHEMICAL BEHAVIOUR OF POLYQUINONES

A. The Polymeric Quinone–Hydroquinone Electrochemical System

The reversible electrochemical behaviour of the quinone–hydroquinone system can be represented by the following series of reaction equations:

$$Q + e \rightleftharpoons Q^- \quad \text{(semiquinone anion)} \qquad \text{(A)}$$

$$Q^- + e \rightleftharpoons Q^{2-} \quad \text{(quinol dianion)} \qquad \text{(B)}$$

$$Q^{2-} + 2\,H^+ \rightleftharpoons H_2Q \quad \text{(quinol)} \qquad \text{(C)}$$

Reactions (A) and (B) can occur as discrete steps under aprotic conditions whilst reaction (C) requires the presence of a proton donor (usually water). Under certain conditions (e.g. strongly alkaline solution) the semiquinone anion may also exist as a metastable species in aqueous media[130].

Consequently, the electron acceptor ability of a quinone may be determined in two ways: (i) by measurement of its electron affinity and (ii) by measurement of its standard oxidation–reduction potential (E^0). Electron affinity measurements are valid for aprotic media and are more usefully considered under section VI, whereas oxidation–reduction potentials are generally determined under aqueous or partially aqueous conditions.

The standard oxidation–reduction potential (E^0) of a quinone–hydroquinone system under aqueous conditions can be measured potentiometrically and provides a measure of the free-energy change ΔG^0 accompanying the interconversion of the two species. These quantities are related by equation (D)

$$\Delta G^0 = -nFE^0 \qquad \text{(D)}$$

When the conversion takes place in solution the free-energy change is dependent on a number of factors such as pH of the solution, the molecular and electronic structures of the oxidized and reduced forms, as well as environmental effects such as interactions with the solvent and other species present[131].

At moderate concentrations of hydrogen ions the quantitative effect of pH on the mid-point potential (E_m) of a simple quinone–hydroquinone system is described by the modified Nernst Equation (E)[132]

$$E_m = E^0 + 0{\cdot}0591 \ln [H^+] \qquad \text{(E)}$$

The characteristic mid-point oxidation–reduction potential (E_m) of the simple system at a specified hydrogen ion concentration can be readily determined by potentiometric titration, and hence the standard oxidation–reduction potential established.

In principle a polymeric quinone should behave similarly and on potentiometric titration can be expected to follow a typical two-electron titration curve (curve 1, Figure 1). The titration is normally carried out in a half-cell with addition of the oxidant to the polymeric hydroquinone, which is either in solution or in suspension. In some cases, due to sluggish response of the system, a mediator (e.g. isopropylhydroquinone) is added which will rapidly establish equilibria with both polymer and electrode. Considerable detail on the methods of measurement has been given by Cassidy and Kun[133].

However, contrary to expectation the measured potentiometric titration curve for many polymeric quinones deviates considerably from the typical two-electron shape (curves 2 and 3, Figure 1)[100, 111]. The curve can be used to determine three characteristic potentials of the polymer system, the mid-point potential (E_m) at the 50% oxidation stage and the two index potentials E_{i_1} and E_{i_2} which represent the differences between the mid-point potential and the 25% (E_{25}) and 75% (E_{75}) oxidation potentials. That is, $E_{i_1} = E_{75} - E_m$ and $E_{i_2} = E_m - E_{25}$. For a symmetrical two-electron titration curve $E_{i_1} = E_{i_2} = 14{\cdot}1$ mV[132b]. The titration curves for the polymeric systems are frequently non-symmetrical with wide variations in the values of E_{i_1} and E_{i_2}[133, 134].

The cause of the non-symmetricality of these titration curves has been ascribed to a number of individual 'polymer effects' such as semiquinone formation, complexation with the oxidant or reductant, quinhydrone formation, dimerization and tautomerism (e.g. formation of quinone-methide structures). Another cause may be associated electrode effects[134].

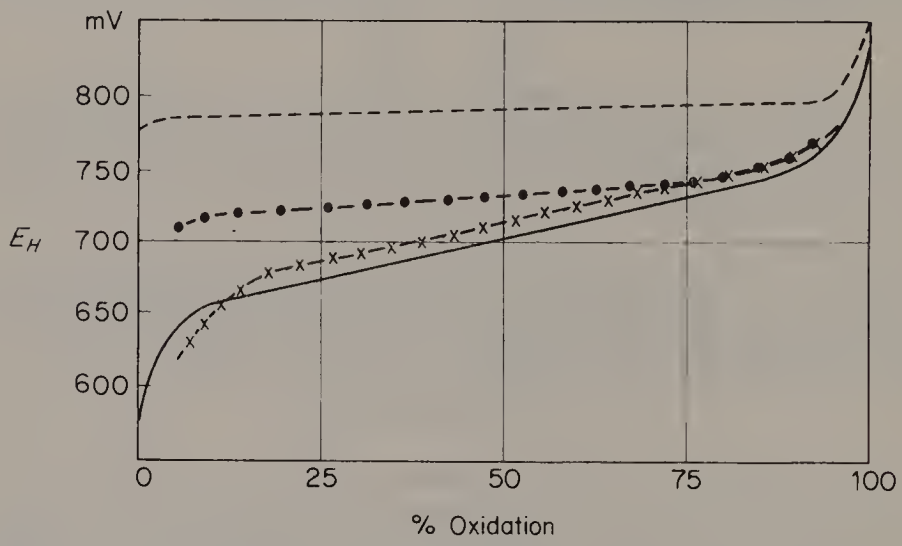


FIGURE 1. Potentiometric titration curves. (1) ——, Typical two-electron curve; (2) – – –, sulphonated polyvinylhydroquinone; (3) – · – · –, poly-2,5-dihydroxy-4′-vinyldiphenylsulphone; (4) —x—x—, hydroquinone–phenol–formaldehyde polymer (1 : 1 : 2).

Cassidy and coworkers[111, 133b] have described the striking colour change which occurs when a sulphonated polyvinylhydroquinone is oxidatively titrated. On first addition of oxidant a pink colour appears which intensifies up to the mid-point of the titration, and then becomes more and more yellow, finally giving the clear yellow of polyvinyl-*p*-benzoquinone at completion of the oxidation. The origin of these colour changes has been discussed[133b].

Apart from variation in the shape of the potentiometric titration curve, the measured mid-point potential of a polymeric quinone is found to be much higher than that measured for the corresponding monomeric reference quinone system[135]. As pointed out by Lindsey[136] and by other workers[133, 135, 137], the oxidation–reduction mid-point potentials of polymeric quinones are dependent on a number of factors, the more important of which can be broadly classified as structural, configurational and environmental. These are expanded in more detail in Table 3, though it should be recognized that the classification shown is arbitrary to some extent since some factors (e.g. semiquinone formation) can obviously fall into more than one category.

Structural features of polymeric quinones which affect the electrochemical behaviour of the system as a whole arise from the structure of the functional quinone unit, the type of nuclear substituent on the ring and the nature of the bridging groups since these, as in simple substituted quinones, materially affect the electron affinity of the unit. It is known, for

TABLE 3. Factors affecting mid-point potentials of polymeric quinones

1. Structural:	(i) Nature and degree of bridging groups
	(ii) Type and degree of nuclear substitution
	(iii) Nearest-neighbour interactions
	(iv) Molecular weight of polymer
	(v) Electrostatic field effects
	(vi) Complexation or addition of cations or anions
	(vii) Presence of non-functional chain members (copolymers)
	(viii) Solubility of polymer system
	(ix) Side-reactions (e.g. xanthene formation)
2. Configurational:	(i) Stereochemical disposition of quinone groups
	(ii) Chain coiling—uncoiling
	(iii) Semiquinone formation
	(iv) Inter- and intra-chain quinhydrone formation
	(v) Internal hydrogen bonding
	(vi) Steric effects
	(vii) Charge-transfer complexes
3. Environmental:	(i) Hydrogen ion concentration
	(ii) Nature of titration solvent medium
	(iii) Presence of neutral salts
	(iv) Differences in composition of macromolecular and bulk solvent phases
	(v) Type and normality of oxidant or reductant
	(vi) Presence of a mediator
	(vii) Electrode effects
	(viii) Liquid junction potentials

example, that increasing the degree of methyl substitution of *p*-benzoquinone results in a fall in the oxidation–reduction potential and similarly with increasing polynucleicity[47]. Helfand[138] has pointed out that in some polyquinones interactions between neighbouring quinone groups may be quite strong, as shown by deviation in the shape of the titration curve of the polymer compared to that of a suitable monomer model. Helfand[138] developed, on a mathematical basis, a theoretical treatment of polymeric quinone titrations and showed that above a certain limit the degree of polymerization did not affect the course of the titration. Below this limit the observed behaviour depended on the degree of reduction of the polyquinone system. Electrostatic field effects may be important where the

polymer chain is also a polyelectrolyte (e.g. is sulphonated)[139]. The properties of polyelectrolytes are known to differ from both non-polymeric electrolytes and non-ionized polymers. Their properties mainly depend on the average electrostatic potential of the polyelectrolyte macromolecule, its contribution to the electrostatic free energy of the system and its effect on the average dimensions of the macromolecule. Because of the coulombic forces present, polyelectrolyte systems incorporating quinone groups can be expected to exhibit a modified E_m value. Indeed, it has been experimentally shown[139] that the effect of a sulphonated polystyrene matrix is to raise the E_m of the copolymeric quinone. When the quinone was non-bonded to the sulphonated matrix only a small positive increase in E_m occurred. In the presence of molar potassium chloride the mid-point potential of the sulphonated polyvinylhydroquinone fell to that of the monomeric system. It was not confirmed that this was due to an electrostatic screening effect since other salts did not bring about this effect[139].

Other structural effects arising from complexation, presence of non-functional chain members, occurrence of irreversible side-reactions and effects arising from the molecular weight and solubility of the polymer system have been considered as influencing the redox behaviour of the polyquinone system[133, 139].

Configurational features which exert an effect on the interconversion of the bonded quinone–hydroquinone couple arise in the polymeric system because of the greater degree of regularity and lower degree of flexibility of the macromolecular structure compared with a random association of monomeric units[136]. Thus, in the polymer there are inherent constraints placed on the spatial orientation of the quinone groups which may arise from primary bonding (cross-links) or from secondary bonding (hydrogen bonds, charge-transfer interactions, quinhydrone formation) or through purely steric factors (bulky substituents). Consequently, the degree of electronic interaction between the polymer chain structure and each individual quinone group, causing variation in electron-acceptor ability, will be related to the degree of flexibility of the chain and the orientational freedom of the quinone group. These factors can also tend to stabilize semiquinones when formed by hindering delocalization of the unpaired electron, and preventing dismutation or dimerization of the semiquinone. Variation in the value of E_m may be associated with coiling and uncoiling of the polymer chain during change in the ratio of reduced and oxidized groups along the chain in the course of titration[93, 139].

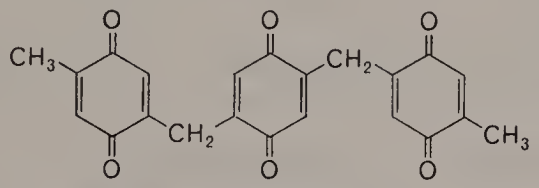
Many of the environmental factors influencing redox behaviour which are listed in Table 3 are valid for both monomeric and polymeric quinones. However, the macromolecular environment can bring about concentration

and species alterations within the macromolecular cells compared to the bulk solvent phase, which can lead to variation in the solute and solvent interaction between monomeric and polymeric quinone groups[136, 140]. Neutral components of the solvent phase may also affect the potential, for example the depressing effect of potassium chloride on the E_m value of a sulphonated polyvinylhydroquinone system already mentioned. Other aspects of environmental effects have been discussed by Cassidy and Kun[133]. Evidence has been presented that adsorption of the oxidized polymer on to the electrode during potentiometric titration is responsible for increased potentials. In the presence of detergent the monomer value was approached[134].

Table 4 shows some representative E_m values for different polymers measured under varied conditions.

B. Electrochemical Behaviour of Polyquinone Chain Segments

As indicated in the previous section, the potentiometric titration curve for many polyquinones deviates considerably from the shape of a normal two-electron curve. An important approach to the study of the factors causing this deviation has been based on examination of the electrochemical behaviour of oligomeric quinones which have analogous structures to the polymeric quinone.



(18)

The synthesis and redox behaviour of a variety of di-, tri- and tetrafunctional *p*-hydroquinone, 1,4-naphthoquinone and 9,10-anthraquinone systems have been reported but have not been systematically studied[45, 141]. Apparently the first systematic studies were published by Hunt, Lindsey, Savill and Peover[110, 142], who studied the electrochemical behaviour of mono-, di-, tri- and polyfunctional quinones with structures corresponding to those thought to be present in polyquinones derived from hydroquinone–formaldehyde and hydroquinone–phenol–formaldehyde condensates. Polarographic reduction of the quinone segments in aqueous–ethanolic solutions established that two-electron additions were made successively to each quinone unit. Thus reaction (18) showed a two-electron step and a complex four-electron wave, which could be analysed into two two-electron components (Table 4, No. 12). The titration curves for both the methylene-bridged diquinone and the two triquinone molecules revealed larger index potentials than for normal two-electron addition

TABLE 4. E_m Values of monomeric and polymeric quinone–hydroquinone systems

Quinone or polyquinone	Conditions[a]	E^0_m (mV)	Reference
1. Polyvinylhydroquinone, linear sulphonated	0·4N H_2SO_4 Neutral salt absent	789	86
2. Copolymer of vinylhydroquinone and α-methylstyrene, linear	0·106N H_2SO_4 + LiCl	643	139
3. Isopropylhydroquinone	0·106N H_2SO_4 + LiCl	630	139
4. Copolymer of vinylhydroquinone and α-methylstyrene, linear, sulphonated	1M KCl + H_2SO_4 (1 ml per 250 ml)	646	139
5. As 4	As 4 but neutral salt absent	849	139
6. Isopropylhydroquinone	As 4 but neutral salt absent	636	139
7. Poly(vinyl-3,4,6-trimethylhydroquinone)	In 90% acetic acid	420 (approx.)	93
8. Tetramethylhydroquinone	1 : 1 Acetic acid–0·5N H_2SO_4	456	93
9. Polycondensate of hydroquinone, phenol and formaldehyde (1 : 1 : 3)	*N*-H_2SO_4	628	142
10. Chain segment corresponding to 9, (68)	Polarographic	650	142
11. Poly-(2,5-dihydroxy-*p*-phenylenemethylene)	*N*-H_2SO_4	730	142
12. Trimeric quinone, chain segment corresponding to 11 (18)	Polarographic	624, 652 703	142
13. Sulphonated poly(2-vinylanthraquinone)	0·1N H_2SO_4 + mediator	178	100
14. Anthraquinone 2-sulphonic acid	In 50% aqueous acetic acid	183	100
15. 2-Isopropyl anthraquinone	In 50% aqueous acetic acid	124	100
16. Polyvinylpyrazolonaphthoquinone (*N*-sulphoalkylated)	Polarographic	130	101
17. 4-Quinonyl-4′-isopropyldiphenylsulphone	1 : 1 Acetic acid + 0·085N H_2SO_4	740	96
18. Poly-(2,5-dihydroxy-4′-vinyldiphenylsulphone)	In 80% acetic acid	753	96

[a] Potentiometric titration, except where stated.

and the mid-point potentials were much more positive than the reference monomer 2,5-dimethyl-*p*-benzoquinone. The central quinone nucleus (reaction 18) was considered to undergo the first two-electron addition, the high reduction potential being due to the strong electronegative

character of the two adjacent quinonyl groups and the much lower reduction potential of the third group resulting from the lower electronegativity of the adjacent hydroquinone group[142].

These electrochemical studies led to the conclusion that the anomalous redox behaviour observed during titration of polyquinones linked through methylene bridges could be qualitatively interpreted in terms of nearest-neighbour interactions, whilst the redox behaviour of the di- and triquinone segments suggested that other interactions in addition to nearest neighbours might be important. The shapes of the curves for the corresponding polymeric quinones significantly deviated from the theoretical shape for a two-electron process (index potentials of 35 mV compared to the normal value of 14 mV). However, the form of the polymer titration curve and its mid-point potential was not thought to have direct meaning since it was statistically dependent on factors such as extent of hyperconjugation between the methylene bridge protons and the quinone–hydroquinone nuclei which in turn appeared to depend on steric factors. Consequently, as reduction of the polymer proceeded those quinone groups having the most positive redox potential would be reduced first.

In aprotic solvents such as acetonitrile reduction of the same mono-, di- and triquinones proceeded by one-electron additions with formation of multiradical structures[142]. The spread in the first half-wave potentials of the three overall reduction steps was greater than the corresponding spread of the two-electron potentials in the protic solvent. E.s.r. measurements of the partially reduced quinone species indicated delocalization of the unpaired electron between directly coupled quinones but charge-transfer between quinones linked through a methylene bridge did not occur to any appreciable extent.

Similar studies of model monomer, dimer and trimer molecules related to hydroquinone–phenol–formaldehyde polymers by Manecke and coworkers[135,143] showed that benzyl-type substituents lowered the oxidation potential with respect to the reference *p*-hydroquinone by 47 ± 4 mV. The effects of both methyl- and benzyl-type substituents on the hydroquinone were claimed to be additive.

For *bis*-hydroquinone systems bridged by a *p*-xylylene grouping ($-CH_2-C_6H_4-CH_2-$) the symmetrical potentiometric curve deviated only slightly from the shape expected for a normal two-electron change. However, the corresponding *tris* hydroquinone oligomer gave an asymmetric curve with considerably steeper slope. Manecke[135] claimed that only relatively small interaction effects occurred in the oligomer systems which were inadequate to explain the potentiometric behaviour of the polymers.

Moser and Cassidy[111] also carried out electrochemical studies on oligomeric hydroquinone chain analogues of polyvinylhydroquinone (**72–74**). During potentiometric oxidation the hydroquinone groups appeared to react independently, which differed from that found for sulphonated polyvinylhydroquinone. When oxidized in aqueous acetic acid (1%) the *bis* and *tris* compounds developed a red colour which attained its maximum intensity at the mid-point. This behaviour was similar to that found for polyvinylhydroquinone polymers, and was thought to arise through quinhydrone formation.

Mills and Spinner[144] have made a detailed analysis of the redox behaviour of difunctional hydroquinone–quinone systems in which they show that the two overall oxidation potentials of the system are related to fundamental 'internal' oxidation potentials by a characteristic tautomeric equilibrium constant. The 'internal' oxidation potentials could be derived from the data available for the simple quinone–hydroquinone analogues and consequently made it possible to calculate the overall oxidation potential of specified dimeric hydroquinones. The analysis also permitted a direct numerical evaluation of intramolecular inductive effects due to nearest-neighbour interactions. The shapes and positions of the titration curves of the dimeric hydroquinones were related to the different values of the interaction effects. The possibility of analysing and predicting redox behaviour in monomeric, oligomeric and polymeric *p*-hydroquinone–quinone systems was envisaged by application of these methods.

C. Reaction Kinetics of Polymeric Quinones

The utilization of polymeric quinones as practical oxidation–reduction agents has focused attention on the necessity of ensuring that electron or hydrogen transfer at the polymeric redox sites should occur at reasonably fast rates. Since the presence of the polymer matrix complicates the reaction kinetics it is useful initially to consider the factors which influence transfer reactions with monomeric quinones.

The specific reaction rate constant of a simple monomeric quinone for a given substrate depends on a number of factors which include nature of solvent, pH, temperature and nature of the intermediate and other species present. Vetter[145] and Hale and Parsons[146] have measured the rate constants for the reduction of *p*-benzoquinone under carefully controlled conditions. Both authors found that the reduction proceeded by two one-electron transfers of almost equal activation energy. Hale and Parsons also established that the value of the free energy of activation was consistent with the Hush[147]–Marcus[148] theory of electron-transfer

reactions. Variation in the rate constant with the molecular size of the quinone was ascribed to the change in the free energy of formation of the semiquinone.

A number of correlations of the redox reaction rate with the oxidation–reduction potentials of the reactants has been reported. Gershinowitz[149], for example, deduced a theoretical relationship between reaction rate and the free energy of formation of the activated state which could be written in the form

$$0{\cdot}03 \log (k_1/k_1') = E_{OB} - E_{OD}$$

where k_1 and k_1' are the specific reaction rate constants for the reaction between the substance A and the oxidizing agents B and D. E_{OB} and E_{OD} denote the normal oxidation–reduction potentials of B and D. This equation was identical with that derived from experimental results by Conant and Pratt[150]. Other linear free-energy equations have been derived which are applicable to the dehydrogenation reactions of *o*- and *p*-quinones[151, 152], but these are useful for special cases only. The more general and more detailed theory developed by Marcus[153] which relates reaction rate with the free-energy changes occurring has been shown to give calculated results in agreement with the experimental measurements.

Braude and coworkers[151, 152] measured the rate constants of hydrogen transfer from organic substrates, such as dihydroaromatics, dihydropyridines, hydrazobenzenes, etc., to quinones of high electron-affinity of varied structures which included *o*-, *p*- and polynuclear quinones. In the majority of cases the hydrogen-transfer reaction was shown to be bimolecular and to obey a second-order rate equation up to at least 80% completion. The reaction was considered to proceed by a two-step heterolytic mechanism involving a rate-determining transfer of hydride ion from the hydrocarbon to the quinone followed by rapid proton transfer between the resulting conjugate acid of the aromatic hydrocarbon and the hydroquinone anion. In some cases a charge-transfer complex was formed between the reactants which led to a modification of the reaction kinetics[152]. Wallenfels and Gellrich[154] obtained rather similar results when they measured the rate constants for hydrogen transfer from various dihydropyridines to a restricted group of quinones.

Whilst the factors discussed above are generally relevant to the oxidation–reduction reactions of all types of quinones, the immobility and separation of functional quinone groups within a polymer matrix introduce additional factors affecting the reaction rate. Apparently the most important factors are the diffusion rates of the reactants and the internal equilibration rate.

Consideration[136] of literature evidence strongly suggests that in polymeric quinones the rate of the oxidation–reduction reaction is dependent on diffusion controlled processes similar to those operative in the case of ion-exchange resins[155]. These are (i) diffusion of reducing species in, and oxidized species out, through the Nernst film covering the redox beads, (ii) diffusion of the same species through the polymer network to and from the redox sites, or alternatively electron and proton migration to and from the reaction sites, (iii) electron plus proton transfer at the redox site. Diffusion of reactants into and within a polymeric matrix is linked to the swelling and hydrophilic properties of the polymer. Manecke has pointed out that the behaviour of a sulphonated anthraquinone polymer is completely analogous to that of a normal cation-exchanger based on polystyrene[135]. Kun and Kunin[121] have examined the redox kinetics of a series of polymers of the general structures previously shown (**81**, **82**, $R^1 = Cl$, $R^2 = H$), in which the degree of cross-linking was varied and the polymers were prepared with a macroreticular structure. They found that on increasing the hydrophilic character of the matrix, that is by making $R^1 = -N(CH_3)_3Cl$ or $R^2 = HSO_3$, the reaction rates and the available redox capacities significantly increased. Also, decreasing the particle size increased the reaction rate, which is similar to the observation of Sansoni[115]. Although the macroreticular structure of the polymer complicated interpretation of the results, Kun and Kunin[121] concluded that the low rates observed and the marked effect of introducing ionic groups indicate the rate-controlling step to be particle diffusion rather than Nernst-film diffusion. Similar results have been reported by Russian workers[156].

Oxidation–reduction reactions in solution can be catalysed by addition of other species. The oxidation of $Fe^{2+} \rightarrow Fe^{3+}$ for example is accelerated in the presence of chloride ions[157]. Luttinger and Cassidy[139] found that in the presence of 1 M potassium chloride the rate of oxidation of a sulphonated polyvinylanthraquinone by ceric ion (Ce^{4+}) was increased tenfold over that observed in the absence of neutral salt. No effect was noted in the presence of sodium acetate, sulphate or citrate anions, H^+, sulphuric or acetic acid. Manecke and Bahr[105] similarly found that addition of dimethylbenzoquinone or potassium chloride to the titration cell led to higher oxidation rates of a polymer, prepared by condensation of hydroquinone, phenolsulphonic acid and formaldehyde, with Ce^{4+}. In subsequent studies[100] on sulphonated polyvinylanthraquinone polymers it was found that on addition of a mediator such as anthraquinone-2-sulphonic acid to the solution, the reaction between the oxidant and polymer proceeded more rapidly and the potential of the polymer was established in a shorter time

on titration. The theory and utilization of mediators have been discussed by Cassidy and Kun[133].

The rate of equilibration of the polymeric quinone system can also exert an influence on the apparent rate of reaction. Cassidy and coworkers[133,158] established that there is an immediate stoicheiometric oxidation of the hydroquinone groups in a linear polymeric hydroquinone during electromeric titration, whereas attainment of a steady electrode potential for the system was comparatively slow. A similar behaviour has been observed[159] in the case of sterically hindered quinones such as 2,5-di-*t*-butyl-1,4-benzoquinone. Cassidy and Kun[133] and Moser[160] have postulated that in the polymer matrix where the hydroquinone groups are permanently separated, there is initially a rapid localized oxidation (*b*) followed by a much slower redistribution of electrons within the macromolecular structure (see Figure 2 (*c*)) and thence a slow redistribution of

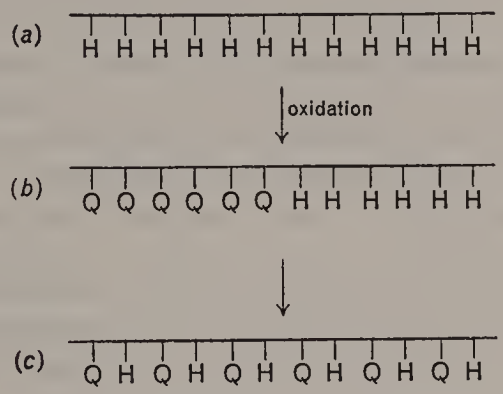


FIGURE 2. Equilibration stages.

electrons between different macromolecules (*d*). It is very probable that the rates of processes (*c*) and (*d*) are increased by the presence of certain salts or mediators.

VI. ELECTRONIC PROPERTIES OF POLYMERIC QUINONES

A. General

The electron acceptor–donor relationship of the quinone–hydroquinone system is fundamental to its distinctive electrochemical behaviour as well as the remarkable solid-state properties shown when incorporated into a macromolecular solid. Such materials are characterized by semiconductive and photoconductive properties and by catalytic activity.

The ability of a quinone in its ground state to accept electrons is quantitatively expressed as its electron affinity value. The electron affinity of a quinone can be defined as the energy liberated when an electron adds to the molecule in the gaseous state and is normally expressed in electron volts (eV). However, since direct measurement in the gas phase has attendant difficulties[161], electron affinity values of quinones are more usually indirectly determined from charge-transfer spectra[162] or from the linearly related first half-wave reduction potential of the quinone measured polarographically under aprotic conditions[163]. Pullman[164] has shown that the electron affinity of a quinone bears a simple relationship to the calculated energy of its lowest empty molecular orbital. It is therefore possible to calculate electron affinities from quantum mechanical data.

Similarly, the electron donor ability of an aromatic system can be represented quantitatively by its first ionization potential, which can be defined as the energy required to remove the most weakly bound electron of the molecule in the gaseous state. The first ionization potentials of molecules can be directly related to the energy of the highest filled molecular orbitals which are also calculable by quantum mechanical methods[165]. The presence of oxygen and nitrogen atoms can reduce the ionization potential of a molecule, whilst the ability of quinone to be converted to semiquinone forms stabilized by unpaired electron delocalization can provide a more mobile π-electron system which is reflected in the electrical and catalytic behaviour of the solid.

Information on the electronic transitions and interactions of coupled quinones may be obtained by studying their visible and u.v. spectra.

B. Electronic Spectra

The electronic spectra of *p*-benzoquinone and its derivatives were studied by Orgel[166] who identified the three absorption maxima at 410, 282 and 250 mμ as arising respectively from $n \rightarrow \pi^*$, $\pi \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions. The effect on the electronic spectrum of incorporating quinone groups into a macromolecular or polymeric structure has received little systematic study. Pullman and Diner[167] carried out some semiempirical molecular orbital calculations for polyquinones of increasing polynucleicity, which they used to interpret the spectral behaviour of the quinones. Existing data showed that an increase in the number of quinone functions in a linearly fused ring system led to a hypsochromic shift (blue-shift) of the longwave absorption band. In the case of angularly fused polyquinones a bathochromic effect (red-shift) occurred. The molecular orbital calculations indicated that in some polyquinones (e.g. heptacene diquinone) the *n*-electron energy level fell below that of the

π-electron level, and consequently the longwave absorption band was due to a $\pi \rightarrow \pi^*$ transition and not $n \rightarrow \pi^*$. These results explained the observed shifts of the longwave band.

The light absorption properties of molecular arrays of π-electron systems when linked, particularly in polymers, have been the subject of theoretical discussion[168, 169]. However, this has mainly been applied to polynucleotides and linked quinones have not been considered. Experimental studies of the spectra of quinones linked by methylene and ethylene bridges have been made by Lindsey and coworkers[110]. The data showed that in these systems ring interactions caused marked deviations from the oscillator-strengths-sum rule leading to intensity losses and hypochromism. Moser and Cassidy[111] found that when the quinone groups were linked by a chain of three or more methylene groups there was little interaction between the π-electron systems.

C. Semiconductor and Photoconductor Properties

As already indicated in section III, there are a number of polyquinones and quinonoid polymers which exhibit semiconductor and photoconductor properties. These can be grouped as follows:

1. Crystalline polynuclear quinones and analogues.
2. Polyacenequinones.
3. Polyaminoquinones.
4. Polyarylenequinones.
5. Polyphenylazoquinones.
6. Polysemiquinones.
7. Polymeric dyestuffs such as aniline black.
8. Polyarylenes.

The syntheses and inferred structures of these polymers have been discussed in section III. The majority are characterized by high free-electron spin values and by relatively low resistivity values which vary exponentially with temperature. The semiconductor properties can also apparently confer unusual chemical reactivity on functional groups attached to the polymers, and enable the polymers to form unusually stable charge-transfer complexes with strong electron donors or acceptors[170, 171]. Some of the polyquinones have been shown to be photoconductive[171].

The e.s.r. spectra of nearly all the above conjugated polymers, either as prepared or after further heat treatment, display a characteristic narrow line, the intensity of which corresponds to free-electron spin concentrations of 10^{16} to 10^{21} spin/g. The e.s.r. signal is little affected by oxygen for polymers which have not been heated above 300–400°C, but for polymers

heated above 500°C line broadening and a decrease in the free-spin concentration occur. In addition to the narrow e.s.r. line the spectra of some of the polymers, such as the polyaminoquinones, show broad absorption lines of great intensity, which disappear abruptly on cooling to 80 K. This behaviour is analogous to that of antiferromagnetic substances and has also been observed in nucleic acid preparations. The observed behaviour was suggested to be due to the presence of a single system of strongly interacting unpaired electrons constituting an orderly array of magnetic dipoles[172].

TABLE 5. Paramagnetic and semiconductor properties of polyquinones

Type of polyquinone	Electron free spins (per g)	Resistivity (ohm cm)	E_a Conduction activation energy (eV)	Reference
Polynuclearquinones (e.g. violanthrone)	—	10^{10} (288 K)	—	173
Polyacenequinones	10^{18}	10^{3}–10^{7} (300 K)	0·15–0·42	174
Polyaminoquinones	10^{17}–10^{18}	10^{10}–10^{16} (300 K)	0·88–1·0	69
Polyarylenequinones	9×10^{17}	10^{10}–10^{20} (300 K)	0·7–1·25	61, 69
Polysemiquinones	6×10^{19}	10^{9} (473 K)	1·00	175
Aniline black polymer	—	10^{10} (300 K)	—	52

In Table 5 the main data relating to the various groups of polyquinones listed above are summarized. It will be noted that the resistivities of the polymers vary between 10^3 and 10^{20} ohm cm at around room temperature. These values lie well insider the range usually classified as insulators and only at the lower resistivity end ($R < 10^{10}$ ohm cm) can the polymers strictly be called semiconductors.

On the basis of the limited amount of data yet available it appears that the electrical properties of these polymers depend on both the structure of the macromolecule and the structure of the material[171]. Conducting polymers are distinguished by macromolecules possessing an extended conjugated π-electron system which permits extensive charge delocalization over the macromolecule. As the number of π-electrons increases the ionization potential will tend to decrease and the electron affinity increase.

There will also be an increase in the polarizability of the system, in which strong internal polarization can be induced by the presence of hetero-atoms (e.g. oxygen, nitrogen, metals), edge-atom substituents or possibly by different sized macromolecules in the layer planes. Most of these expected features should confer improved electrical properties on the polymer, particularly as the conjugated system becomes more extended.

The dependence of electrical behaviour on the bulk structure of the polymeric material has been shown in a number of ways, particularly from the improvement resulting from a more ordered packing of the macromolecules[177] and from increasing pressure on the material[174]. Dulov and coworkers[179] have shown that introducing methylene bridges into the polymer chain improves the conductivity, which they interpret as arising from the improved flexibility of the polymer chain which enables closer and more ordered packing of the macromolecules to occur and thereby improves interlayer transfer of charge. Longer bridges such as $-CH_2CH_2-$ were found to restrict the conjugation path length and conductivity was reduced. Semiconducting polymers show enormous increases in conductivity with pressure, increased pressure leading to a reduction in the activation energy. The basis of this effect has been discussed[178].

Possible semiconduction mechanisms in organic polymers have been widely discussed. Two which have received considerable attention are the 'biradical' theory and the 'charge-transfer' theory.

The biradical theory propounded by Berlin[180] assumes that biradicals are formed in the longest conjugated macromolecular structure through local unpairing of π-bonds, followed by singlet–triplet transitions by thermal excitation, the double radicals remaining stabilized by non-coplanarity of structure or other steric factors. The formation of biradicals on heat treatment of the polymer explains the increase in the electron free-spin concentration and the improved conductivity due to decrease in the conduction activation energy. This theory has received further support from quantum mechanical calculations[181].

That donor–acceptor action promotes electrical conduction in polymers has been verified experimentally[174]. This lends weight to the theory[182] that charge-transfer states are present in the polymers giving rise to radical-ion centres. The charge-transfer either can occur between two neighbouring macromolecules or it can involve charge capture by more remote molecules, traps or crystal defects. Formation of polarized states involving charge-transfer is thought to be promoted by (i) an extensive conjugated π-electron system, (ii) polydispersity, which produces differences in electron affinity and ionization potential between the

macromolecules, (iii) polarization of the molecules, (iv) disorder and structural defects in the material, which permit local interactions between molecules and the formation of traps[171].

Photoconductivity in solids arises when light of a wavelength corresponding to a fundamental absorption band is absorbed by the material. Excitons or excited states are generated which lead to increased numbers of current carriers and improved conductivity. Some of the polyquinones have been shown to be photoconductive, and in most cases the photoconductivity has been shown to be electronic in origin[183]. Thus polyacenequinone polymers were found to be photoconductive[174].

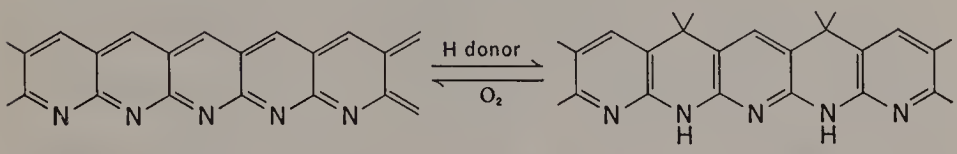
D. Catalytic Properties

Many of the conjugated quinone and quinonoid polymers described in section III have been shown to possess catalytic properties. Thus, the decomposition of hydrogen peroxide is catalysed by pyrolysed polyacrylonitrile[184], polyaminoquinones[185] and aniline black[186]; the decomposition of formic acid is catalysed by pyrolysed polyacrylonitrile[187], polyquinones[188], aniline black[188], polyquinoxalines[188], etc. Other reactions catalysed by these types of polymers are dehydrogenations and dehydrations[49, 188, 189], autoxidations[189, 190], decomposition of hydrazine and nitrous oxide[188, 189] and isomerizations[49, 188].

In some of these studies it has been possible to demonstrate a direct correlation between the catalytic activity of the organic polymer and the electron free-spin concentration as determined by e.s.r. measurements[49, 188, 191]. The catalytic activity of inorganic semiconductors is usually interpreted as a property which arises from their ability to function as conductive matrices for electrons and holes. A similar theory has been applied to the polymer catalysts, the semiconduction mechanism operating through the extended system of conjugated double bonds present in the polymer[192].

The work of Manassen, Wallach and Khalif[49], however, provides strong evidence that it is the presence of quinonoid groups and not extended π-electron systems which are essential for the catalysis of dehydrogenation reactions. They showed that if vapour-phase dehydrogenations (such as cyclohexene $\rightarrow$ benzene) are carried out over a thermostable polymer containing quinone units, hydrogen transfer from the substrate to the polymer occurs. Thus, the red polymer prepared by treating diazotized benzidine with benzoquinone, during the catalytic hydrogen transfer reaction changed in colour to yellow-brown and the characteristic quinone carbonyl absorption band at 1660 cm^{-1} in the i.r. spectrum disappeared. After aerial re-oxidation this band reappeared

together with the red colour. Similar results were established for pyrolysed samples of polyacrylonitrile and polycyanoacetylene, and aniline black. All three catalysts were considered to function by hydrogen atom abstraction from the substrate leading to conversion of quinonoid to hydroaromatic structures, e.g. reaction (19). In the case of pyrolysed polyacrylonitrile, acidic sites were also thought to be present on the catalyst leading to hydride ion transfer.



(19)

The catalytic polymers apparently did not liberate hydrogen, nor transfer hydrogen to the substrate and, when in the reduced condition, could be regenerated by air at about 140°C with formation of water. Catalysed reactions could be carried out in an air stream which maintained the activity of the catalyst. Non-quinonoid-type polymers and compounds were shown to be catalytically inactive. The correlation between dehydrogenation activity and electron spin values can be expected for the quinonoid polymer where semiquinone structures are possible, whereas there is no fundamental reason for a correlation with semiconduction properties.

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CHAPTER 16

Non-benzenoid quinones

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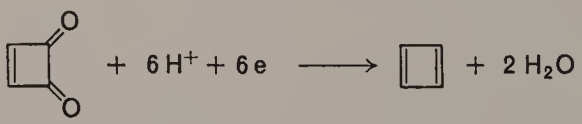
I. INTRODUCTION

Your reviewer, who is not an expert in the field covered, accepted the editor's invitation to produce a review of compounds that might reasonably be covered in this area. He defined the limit of the enquiry by excluding compounds where the carbonyl groups were attached to six-membered or extended six-membered rings and which might be thought to be benzenoid in character. He sought a reasonable definition of this class of compounds and the most comprehensive one was provided by Professor Trost who defined a non-benzenoid quinone as any dicarbonyl species whose two-electron reduction product would generate a non-benzenoid aromatic.

On reflexion the author considered that the use of the word 'aromatic' was unduly restrictive in this context since it implied the reduction product would have to conform to Huckel's $4n+2$ electron rule whereas there were compounds that might legitimately be included in this class whose reduction products did not conform to the rule. He therefore modified the latter part of the definition to 'any dicarbonyl species whose two-electron reduction product would generate a cyclic non-benzenoid structure containing conjugated double bonds'.

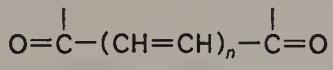
Thus we can write the following equation for the reduction of cyclobutenequinone



where two electrons are required for the reduction of the quinone. This definition gives the classes of compounds discussed in sections II and III, viz. the simple even- and odd-membered ring systems.

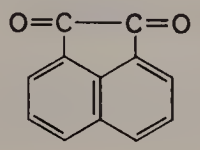
Other dicarbonyl systems still conforming to the above general definition can be generated by considering the ways in which carbonyl groups can become cross-conjugated. The requirements for this type of system are (i) that both carbonyls should be directly joined to one another

or through a mobile electron system and (ii) that each carbonyl should be attached to a carbon containing mobile electrons. Thus we can generate a further class of compounds from the system



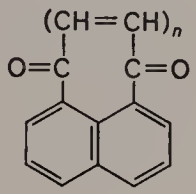
and any conjugated system capable of linking across the free valences would produce the type of system we have in mind.

For example, we can take the acenaphthene quinone system

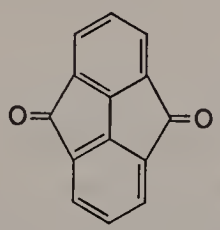


which could be extended by a many-fold extension of the aromatic ring in various ways.

We might also construct further systems from the generating formula



in which we could build up 1,2-, 1,4-, 1,6-, 1,*n*-mobile-electron carbonyl systems attached to an aromatic system. Apart from the simple ring systems discussed in sections A and B we can get larger ring systems such as



All these other types of dicarbonyl systems are discussed in section IV.

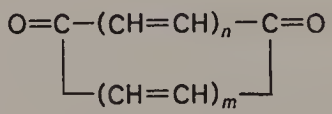
Having limited the class of compounds in the above way your reviewer then attempted to write an interesting but not exhaustive review of compounds in this class. He decided to indicate synthetic methods but not to give a detailed account of them; he would note chemical properties

of interest; he would observe the physical properties of these compounds especially in relation to physical properties normally met with in the quinone system such as oxidation–reduction potentials, colour and the ability to form radical ions and, while recording these properties, would indicate but not include calculations of a theoretical nature. He hopes he has neither overestimated nor underestimated work in this area and would apologize to any worker in this area who feels his work may have been misrepresented.

II. EVEN-MEMBERED RINGS

A. Generating Formula

The quinones in this class may be regarded as being generated from the system



in which either n or m, but not both, may be zero.

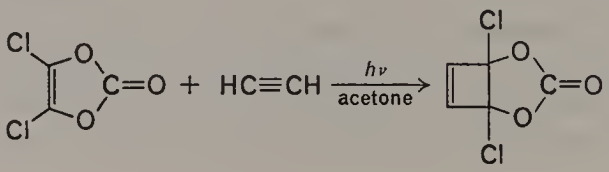
The case $n = 0$, $m = 1$ generates cyclobutenequinone, i.e. the class of four-membered rings. For the situation $n+m = 2$ we have the case $n = 2$, $m = 0$ which yields *ortho*-benzoquinone and $n = 1$, $m = 1$ yields *para*-benzoquinone. If we now take the situation $n+m = 3$ then we generate the eight-membered ring which can have either a 1,2- or a 1,4-dicarbonyl function. If we take the situation $n+m = 4$ then we generate a ten-membered ring with a 1,6 dicarbonyl function and larger symmetrical rings will produce 1,8 and 1,10 cases and so on.

If instead of —C=C— we take —C≡C— then new possibilities are introduced, though whether or not such compounds would strictly belong to the class we have in mind is not clear.

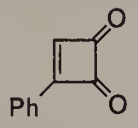
B. Four-membered Rings

1. Cyclobutenequinone and derivatives

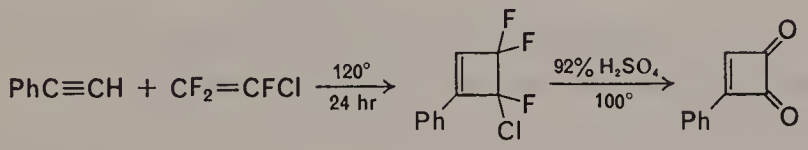
a. Preparation. The parent compound of this class cyclobutenequinone or cyclobutenedione has only recently been prepared by the following route[1].



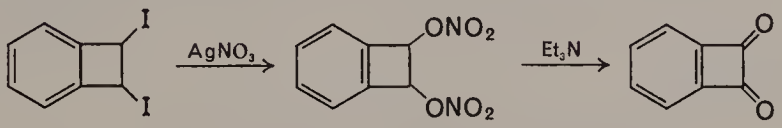
The cycloadduct is a rather unstable liquid (B.P. 41–42°C at 0·05 Torr) formed in 10–15% yield. Hydrolysis of the adduct at 60° in 60% acetone–water gives cyclobutenedione as a light-yellow solid (M.P. 40–41°C). The compound



was prepared[2] by the following route

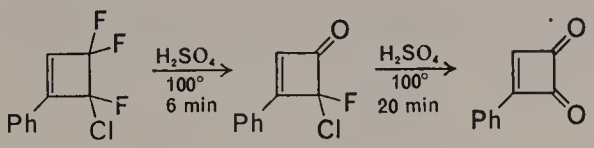


The benzo compound was formed[3] through the route

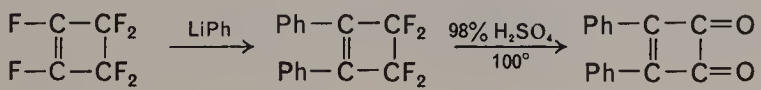


A later paper[4] gives more generalized procedures for preparing cyclobutenedione derivatives.

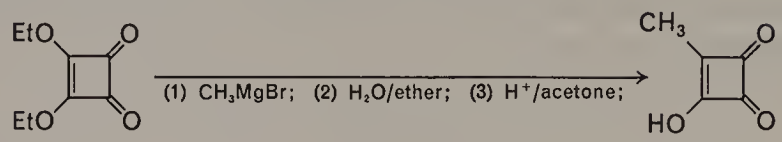
In these syntheses the cycloadducts of perhaloethylenes with phenylacetylene were used as starting materials. Thus, from trifluorochloroethylene and phenylacetylene heated in a sealed tube at 125° for 20 h there was obtained 1,1,2-trifluoro-2-chloro-3-phenylcyclobutene which was then hydrolysed.

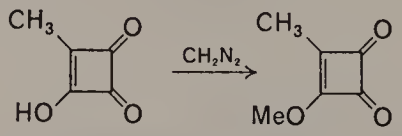


The synthesis of the diphenyl compound has been described by the following route[5]



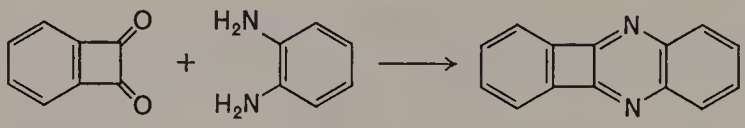
The methylcyclobutenedione and its methoxy derivative have been prepared according to the schemes below[6]



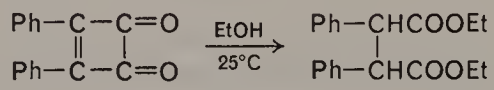


b. Chemical properties. The following by no means exhaustive series of reactions of cyclobutenedione and its derivatives was noted:

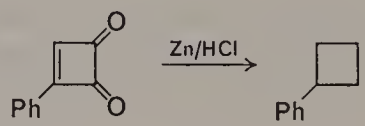
Condensation[4]:



Esterification[5]:

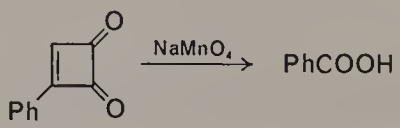


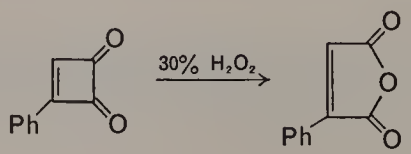
Reduction[4]:



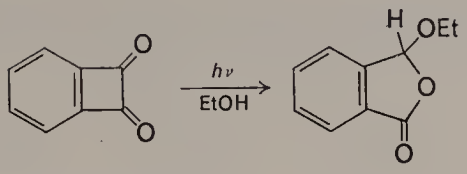
However, phenylcyclobutenedione is apparently not reduced[3] by reagents such as hydrogen over platinum to the corresponding hydroxy compound.

Oxidation[4]:

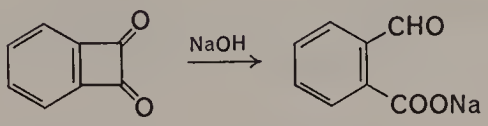




Photolysis[7]:

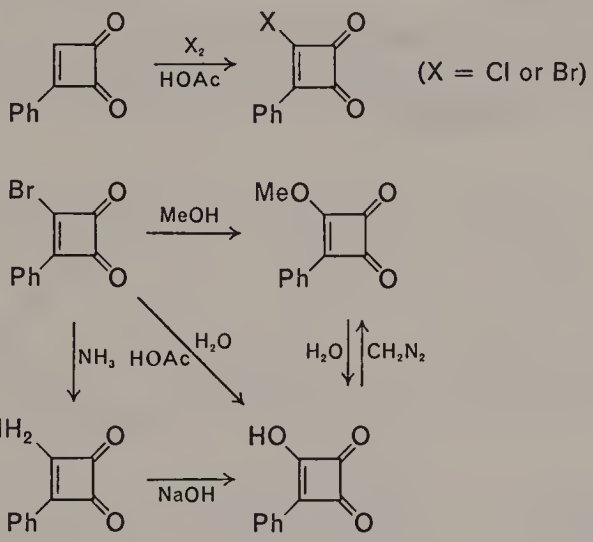


Ring opening[3]:



Blomquist and La Lancette[8] report that with phenylcyclobutenedione and diphenylcyclobutenedione treatment with hydroxide results in cleavage of the 2,3-bond.

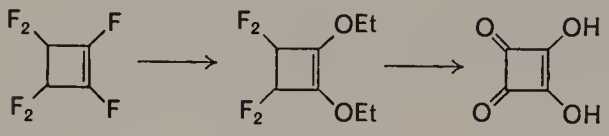
Substitution[4]:



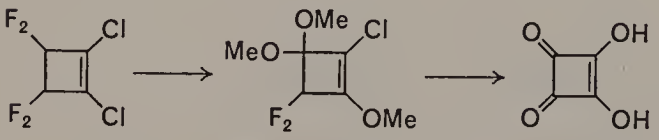
c. Physical properties. The physical properties of these compounds are mildly quinonoid in character. Thus phenylcyclobutenedione separates as yellow crystals and has a u.v. spectrum with a maximum of 287 mμ in ethanol. Heats of combustion, resonance energies, dipole moment data and acid dissociation constants of this compound and its derivatives are also recorded[4].

2. Squaric acid

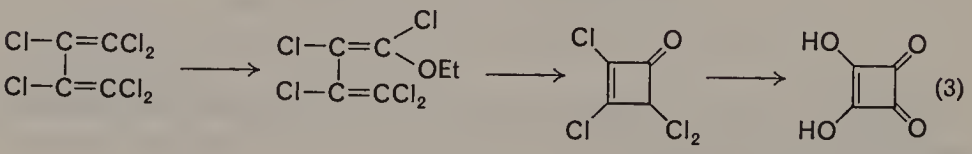
a. Preparation. The properties of this compound have been the subject of review[9] and the following preparative methods described.



(reference 10) (1)



(references 11, 12) (2)

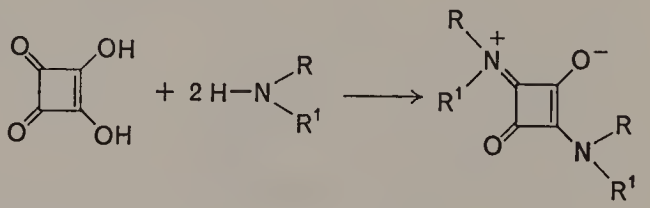


(3)

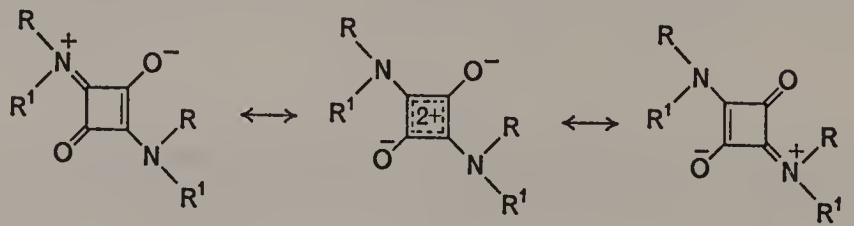
(reference 9)

b. Chemical properties. Again, without being exhaustive, a selection of reactions is described.

Condensation[13]: Gauger and Manuke report the condensation products of squaric acid with primary and secondary amines to produce a new class of betainic squaric acids



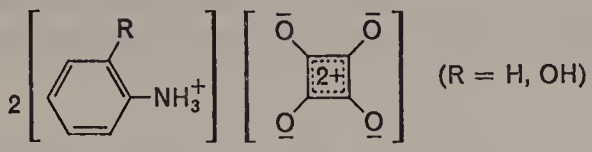
The product formed can be written in further resonance forms



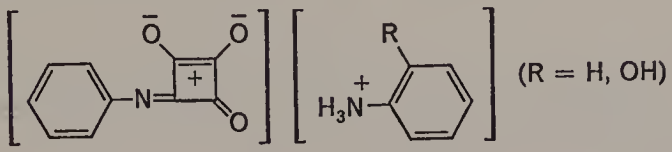
(R = H, alkyl or aryl) (R¹ = aryl)

The structure of these compounds has been confirmed by i.r., n.m.r. and mass spectroscopic measurements.

As intermediates the following squarates were isolated,



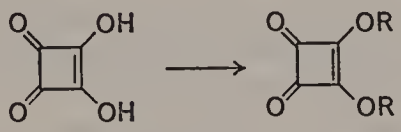
as well as the compounds



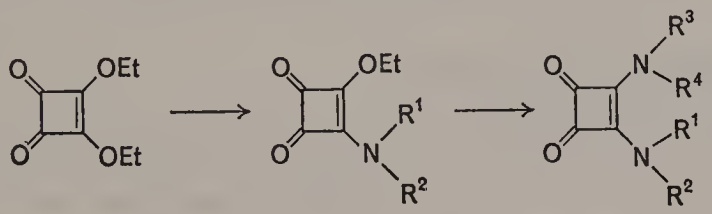
and these compounds were transformed into the corresponding squaric acid 1,3-bisamides by stepwise condensation.

A further paper[14] describes the preparation of copper chelates of the squaric acid 1,3-bisamides with aromatic substituents containing donor groups in the *ortho* position.

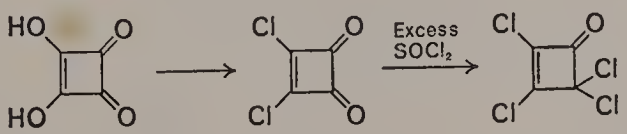
Esterification[9]: diethyl and dibutyl esters are formed by the reaction of the acid with excess alcohol,



the diesters reacting with amides to give squaramides, e.g.

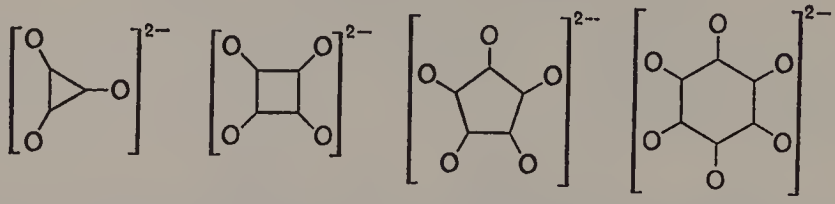


Halogenation[15]: the reaction of squaric acid with thionyl chloride and catalytic amounts of *N*,*N*-dimethylformamide has been recorded.



c. Physical properties. Squaric acid is a white dibasic acid. A precise determination of the ionization constants of squaric acid has been made

and values of pK_1 1·2 and pK_2 3·5 recorded[16]. A large number of substituted squaric acids have also been studied and their pK's recorded[17]. An extended account of the properties of the ions $C_nO_n^{-m}$ has been given[18].



The series is of interest, though the existence of the three-membered ring compound has not been recorded.

Results from simple LCAO-MO calculations on anions of the $C_nO_n^{-m}$ group correlate with observed properties of known members of this group. Calculations have also been carried out on a large number of theoretically possible anions with related but more complex structures.

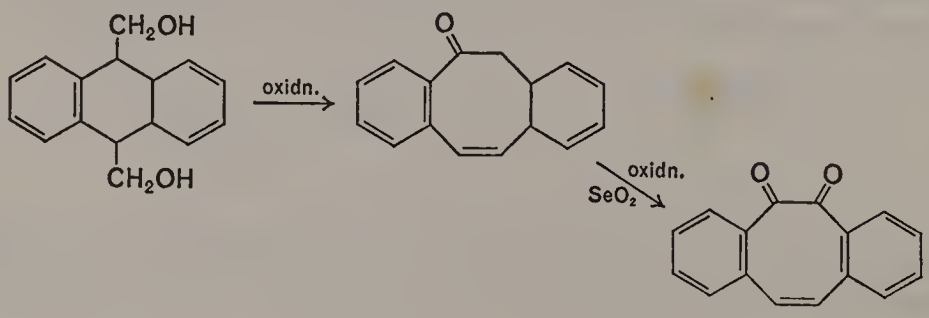
In a subsequent paper[19] the infrared spectra of solid $K_2C_4O_4$ and $K_2C_5O_5$ and the Raman spectra of their aqueous solutions were studied. Spectra indicate planar symmetrical structures (D_{4h} and D_{5h}) for the ions. Vibrational assignments were made on the basis of these structures and a normal coordinate treatment was carried out using a Urey–Bradley force field. The resulting force constants supported the view that these ions constituted members of an aromatic series.

In subsequent papers[20, 21] complexes of these ions with divalent and trivalent metal ions were prepared and characterized.

C. *Eight-membered Ring Systems*

1. Cyclooctatrienequinone

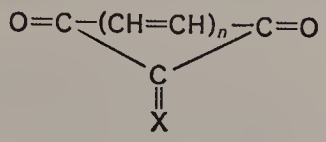
An article has been written which contains a very good account of the theory of such compounds and of attempts that have been made to prepare them[22]. In this paper the following synthesis is reported:



III. ODD-MEMBERED RINGS

A. Generating Formula

These compounds may be regarded as being generated from the formula



where n can be 0, 1, 2, 3, etc., the larger rings producing dicarbonyl systems with 1,2-, 1,4- and 1,6-function respectively. In accord with our earlier definitions, the only restriction is that X must not produce an immobile electron system on the carbon attached to the two carbonyls and we have chosen to regard compounds where X is oxygen as belonging to this class.

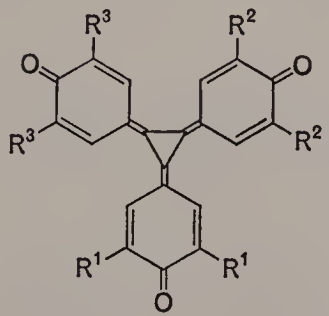
B. Three-membered Ring Systems

The generating compound of this class is cyclopropanetriquinone

which has not been prepared as yet. However, triquinocyclopropanes, which are an approach to this system, are known[23].

1. Cyclopropanetriquinone derivatives

a. Preparation. Triquinocyclopropanes are generated from the corresponding tris-(*p*-hydroxyaryl)cyclopropenium salts[23]. When these are dissolved in benzene and treated with potassium hexacyanoferrate(III) solution, deprotonation and oxidation occur simultaneously, the benzene layer turning deep-blue and producing



where R^1, R^2 and R^3 are alkyls.

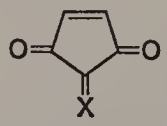
b. Chemical properties[23]. Treatment of the blue-green solutions of the triquinocyclopropanes with hydroquinones resulted in orange solutions. The electronic spectra of the solutions indicated that the products were diarylquinocyclopropenes and this was confirmed by a quantitative preparative experiment.

c. Physical properties. The compounds are soluble in non-polar solvents and insoluble in polar solvents. All the compounds are highly coloured and the i.r., n.m.r. and u.v. spectra all support the proposed symmetrical structure.

C. Five-membered Ring Systems

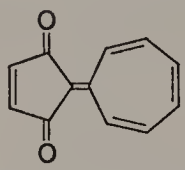
1. Cyclopentenequinone and derivatives

The parent compound in this class may be regarded as

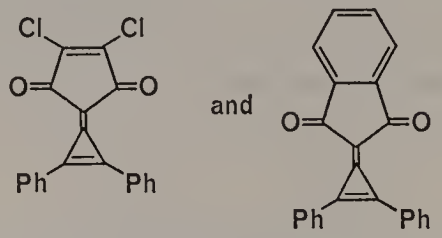


in which quinonoid properties are achieved by the attachment of a mobile electron system as X.

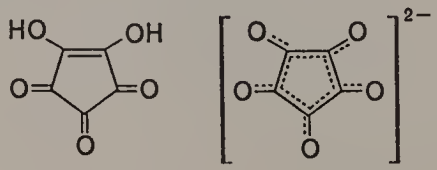
An example of this class is fulvalmixene-1,4-quinone, of which the synthesis has been described[24]. The substance crystallizes in red plates



whose absorption spectrum has been recorded. It undergoes addition at the 2,3-position. In the same class we record the compounds[25]



a. Croconic acid. Croconic acid is a yellow substance which has been known for a long time[26]. A structural investigation[27] suggests the formulae

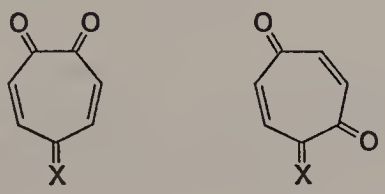


for the acid and the ion and a comparison between this species and squaric acid has been noted earlier in this review. The reduction of croconic acid either by hydriodic acid and red phosphorus or electrochemically gives the pinacol of croconic acid[28].

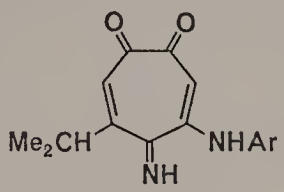
D. Seven-membered Ring Systems

1. Cycloheptadienequinone and derivatives

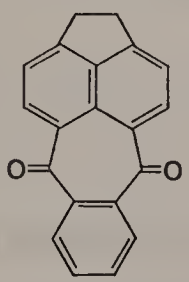
The parent compounds in this class may be regarded as



in which quinonoid properties are again achieved by the attachment of a mobile electron system as X. The compounds thus have the possibility of both 1,2- and 1,4-function. An interesting member of this class recorded in the literature[29] was the compound

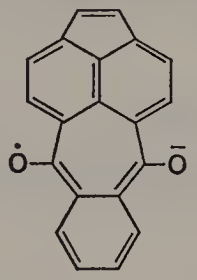


a. 5,12-*Dihydroacepleiadene*-5,12-*dione*[30]. This was the best example available of a seven-membered ring showing quinonoid properties. The compound 5,12-dihydroacepleiadene-5,12-dione undergoes reactions leading to the formation of stable radical ions in a manner similar to pyracylo-quinone to be discussed in the subsequent section.

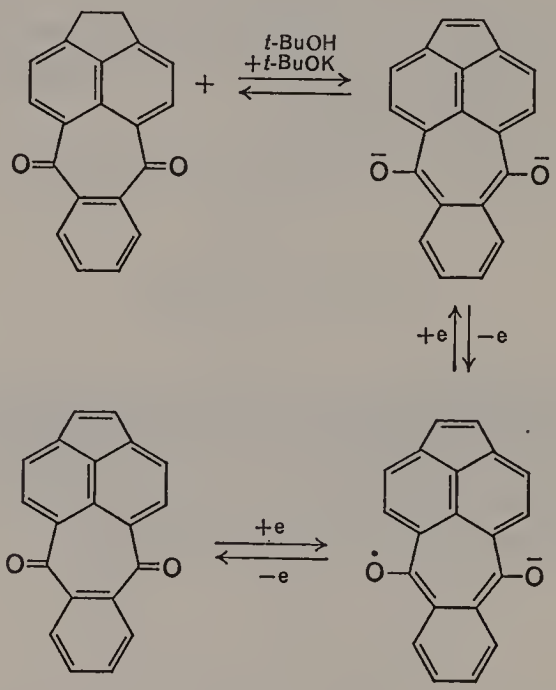


Treatment of a 1×10^{-2}M solution of the above dicarbonyl compound in dimethyl sulphoxide with a $2{\cdot}5 \times 10^{-2}$M solution of potassium *t*-butoxide

solution gives a deep-blue solution containing a paramagnetic species as evidenced by a strong e.p.r. signal.



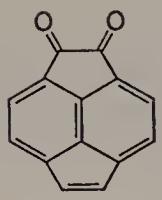
An identical e.p.r. signal was obtained when a 1×10^{-2}M solution of 5,10-dihydroacepleiadylene-5,10-dione in dimethyl sulphoxide was treated with 2×10^{-2}M potassium *t*-butoxide in dimethyl sulphoxide. The total investigation gave evidence for the equilibrium scheme below.

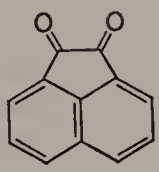


IV. OTHER DICARBONYL SYSTEMS

A. 1,2-Dicarbonyl Systems

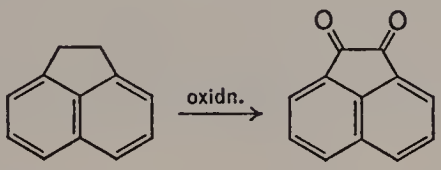
The compounds which we will discuss in this class are pyracyloquinone and acenaphthenequinone





I. Acenaphthenequinone

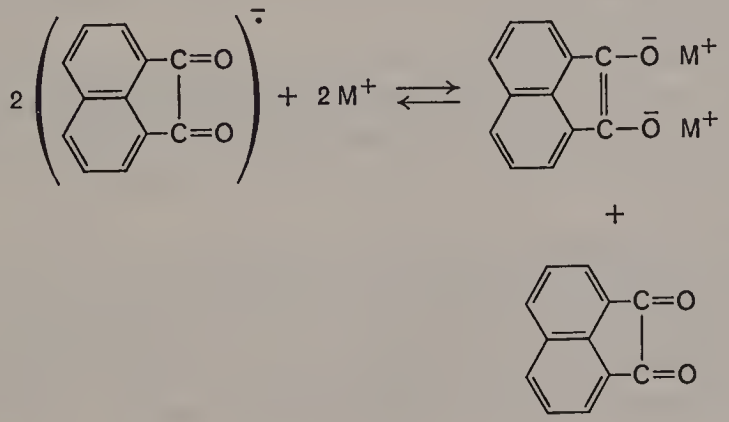
a. Preparation. This compound is well known and the reaction



is recorded in most organic texts. Heilbron records information on bromo[31a], hydroxy[31b] and nitro[31c] derivatives of acenaphthenequinone. A definitive synthesis has also been described[32]. Acenaphthenequinone can be prepared from acenaphthene by oxidation with chromic acid, calcium permanganate or by air in the presence of catalysts in various solvents.

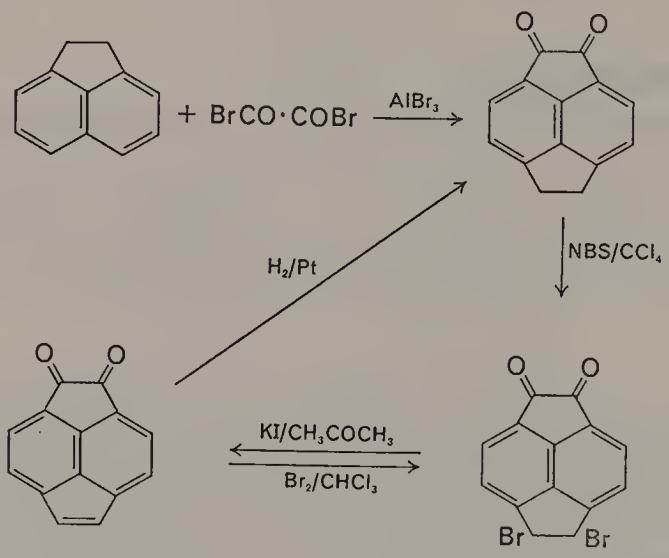
b. Chemical properties. Structures have been assigned to the products of the reaction of acenaphthenequinone with ethylene glycol[33] and the reactions of acenaphthenequinone and ammonium acetates in the presence of aryl aldehydes have been recorded[34].

c. Physical properties. Acenaphthenequinone is capable of forming radical ions and the equilibrium between these radical ions and metal ions has been determined, it being possible to measure an equilibrium constant for the reaction[35].



2. Pyracyloquinone

a. Preparation. Following a preliminary report on pyracyloquinone[36] a definitive account of the synthesis and chemistry of this interesting compound has been given[37]. The following synthetic and reactive scheme is described:



The diketopyracene was prepared by Friedel–Crafts acylation with oxalyl bromide. The compound does not tautomerize under acidic or basic conditions to dihydroxypyracylene or a derivative. Bromination with *N*-bromosuccinimide followed by debromination with iodide ion produced pyracyloquinone.

b. Chemical properties. Attempts to reduce pyracyloquinone chemically to a derivative of pyracylene all failed. Among methods used were trimethyl phosphite, zinc in acetic acid, zinc in acetic anhydride and sodium and lithium in liquid ammonia followed by acetylation or alkylation with methyl iodide.

Pyracyloquinone undergoes Diels–Alder reactions with both cyclopentadiene and with 2,6-diphenyl-3,4-benzofuran. Irradiation of pyracyloquinone produces either acenaphthene-5,6-dicarboxylic anhydride or acenaphthylene-5,6-dicarboxylic anhydride, depending on reaction conditions.

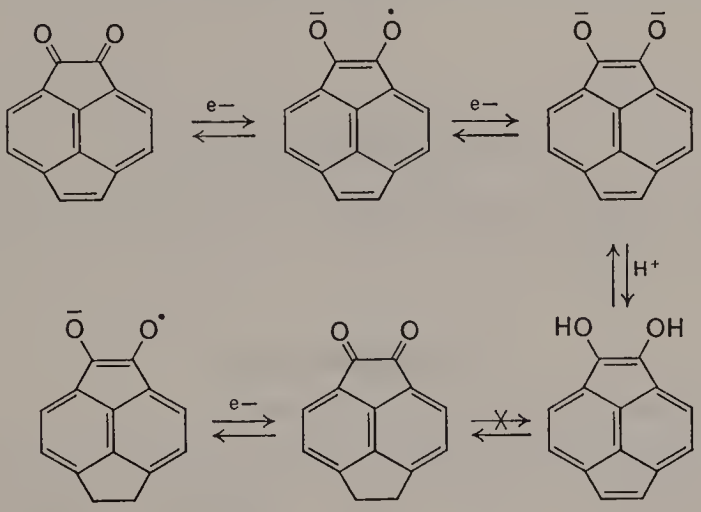
c. Physical properties. The spectral properties of pyracyloquinone are in complete agreement with the above structure. The i.r. spectrum shows a pair of peaks at 1735 and 1685 cm^{-1} due to the diketone moiety. The energy separation between these peaks is about 30 cm^{-1} less than any of the diketopyracene derivatives. This decreased energy is associated with

increased strain in the diketo bridge. The u.v. spectrum of the pyracyloquinone contains the following peaks.

max. mμ	log ε
230	4·47
247	4·19
307	4·25
314	4·23
346	3·85

This spectrum agrees well with one predicted from theoretical calculation.

In an earlier paper the formation of radical ions from pyracyloquinone by treatment of the substance with 0·1 M potassium tertiary butoxide in dimethyl sulphoxide was described[38] and also the following equilibrium system:

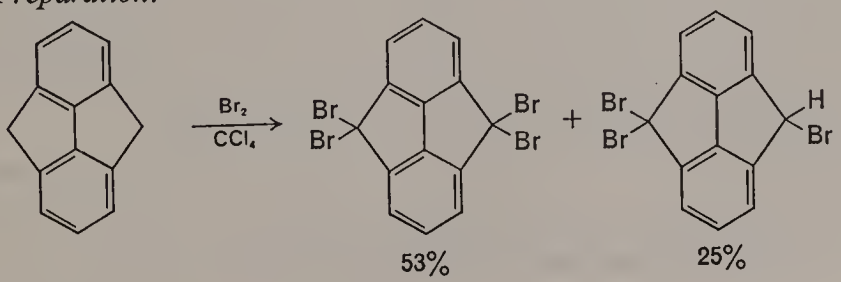


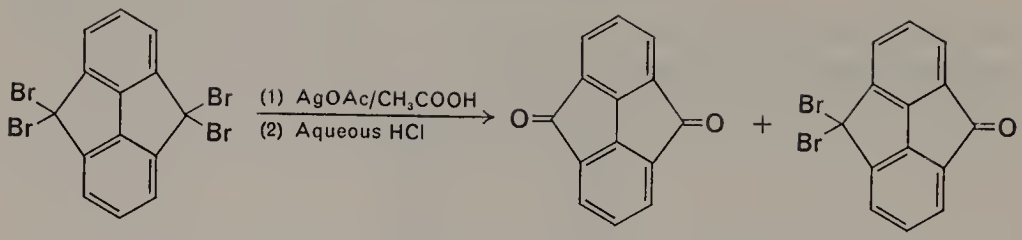
B. Other Dicarbonyl Systems

The compound discussed in this class is the dibenzo[*cd,gh*]pentaleno-4,8-quinone[39].

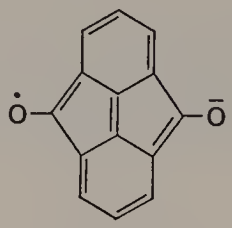
1. Dibenzo[*cd,gh*]pentaleno-4,8-quinone

a. Preparation.





b. Properties. Electrolytic reduction of the dibenz[*cd,gh*]pentaleno-4,8-quinone in DMSO containing 0·1M tetra-*n*-butylammonium perchlorate produced the radical ion



V. ACKNOWLEDGMENT

The author wishes to thank Professor B. M. Trost for assistance in the preparation of this review.

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31a. I. Heilbron in *Dictionary of Organic Compounds*, Vol. 1, Eyre and Spottiswoode, London, 1965, p. 415.
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CHAPTER 17

The addition and substitution chemistry of quinones

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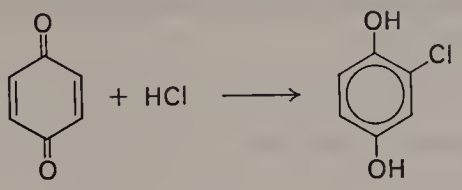
I. INTRODUCTION

From the very beginnings of modern organic chemistry the chemistry of the quinones has formed a lively section of our discipline. Wöhler himself carried out a 1,4-reductive addition reaction (equation 1) quite typical of the chemistry to be described in the present chapter[1]. In our day, the prolific Fieser continues to add to his extensive contributions to quinone chemistry[2].



(1)

Between these two reference points has come an army of scientists producing a bewildering array of synthetic and mechanistic facts and speculation. Even in the more limited areas of addition and substitution chemistry the scientific scope is both broad and deep. Consequently, a great many very difficult choices have had to be made in preparing this chapter. While every effort has been made to treat all of the major areas of activity, in a number of cases only one or two leading papers have been dealt with in detail. Where this course has been necessary, those papers with the greatest mechanistic detail have been discussed and checked to see that adequate references to other aspects of the work are provided.

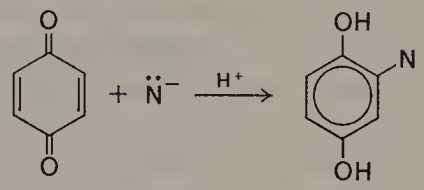
The general pattern selected for the chapter has been to treat most of the non-quinonoid reactants in separate subsections. While the details of the mechanisms are very similar in many cases, and a unified treatment is attractive, the best and most complete studies are still centred on discrete and rather narrow areas. The encouragement of research to examine the interrelationships to be found in this old, but partially tilled, field is certainly a desirable objective. Within each of the sections there are basically three major subsections: (i) a very brief historical introduction, (ii) a detailed discussion of the current mechanistic picture, and (iii) a summary of the synthetic scope of the reaction type. Where a particular area has received detailed treatment, some in more than one subsection, some further sections have been included for clarity. Finally, in a few cases a brief note or two has been added at the end of a section. These notes are simply a recognition that an interesting piece of work has been reported, but not yet studied in sufficient detail for discussion.

Mention should be made of two other aspects of this review. First, benzo-, naphtho-, 1,2- and 1,4-quinones have been included where data are available. The higher, polycyclic quinones do not show addition and substitution chemistry of the types treated here (with exceptions such as carbonyl reactions) and, therefore, are largely omitted. Second, the rather large patent literature: after a careful study of the actual patents it was decided that relatively little is lost by not citing these materials. Much of the patent literature is related to practical modifications and improvements in such industries as dyes, photography, plastics, etc.

II. NUCLEOPHILIC ADDITION CHEMISTRY OF QUINONES

A. Scope and Mechanism

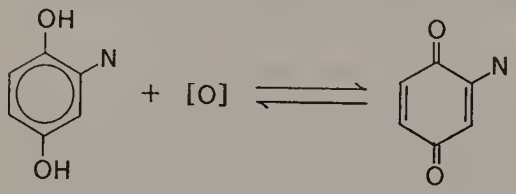
The vast majority of the reactions of quinones can be characterized as 1,4-reductive additions of the Michael type (equation 2). The initial hydroquinone product **1** is, of course, susceptible to oxidation by air,



(2)

(1)

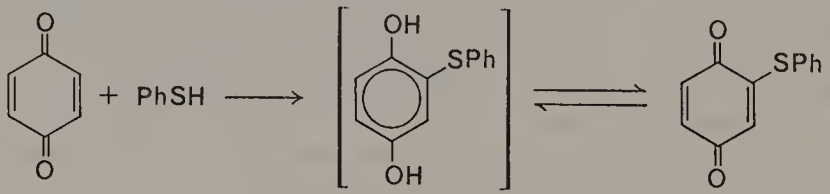
added oxidant, or (with electron-donating substituents) the quinone starting material (equation 3). The nature of the new substituent (N) introduced will determine, in large measure, the details of such subsequent



(3)

chemistry. The presence of the phenolic hydroxyl group (or the carbonyl group of the oxidation product, **2**) also leads to many important following reactions.

The addition of hydrogen chloride has already been cited as one of the earliest reported quinone addition reactions[1]. The addition of sulphur nucleophiles has been studied extensively and can lead either to oxidized (equation 4) or reduced (equation 5) product under appropriate circumstances[3,4]. The addition of amines and anilines to quinones usually



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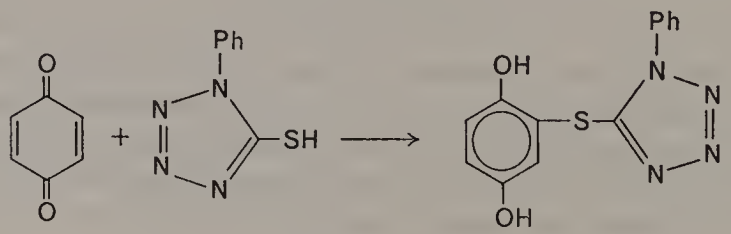
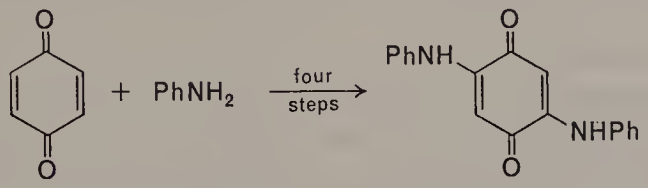


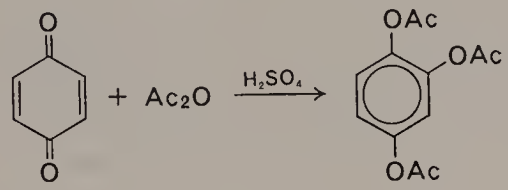
(5)

produces an easily oxidized substituted hydroquinone. In fact, the usual product is the result of a sequence of two additions each followed by oxidation (equation 6)[5]. Yet another widely used and extensively studied



(6)

addition reaction is the Thiele acetylation (equation 7)[6]. While the Thiele is an electrophilic reaction, it shows characteristics of the nucleophilic reactions rather than the diazonium arylations to be discussed in section VI.

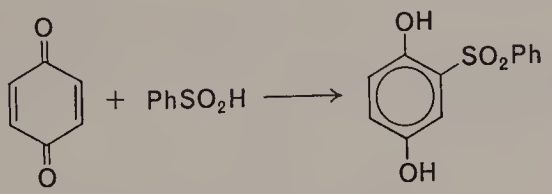


(7)

B. Sulphur Addition

1. Historical introduction

The earliest mention of a reaction between a sulphur compound and a quinone appears to be Bongartz's observation that in the absence of solvent 1,4-benzoquinone will oxidize thioglycolic acid and itself be reduced to hydroquinone[7]. Soon afterward examples of the addition of the two most common sulphur nucleophiles appeared in the literature; i.e. sulphinic acids (equation 8)[8–10] and thiols (equation 9)[11,12]. In the



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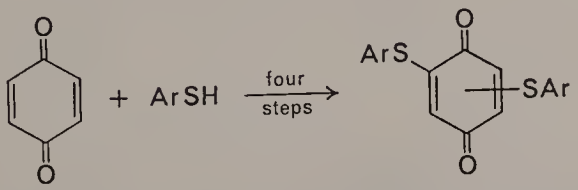


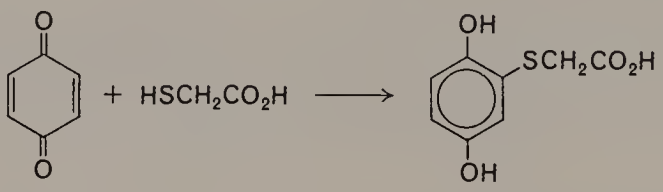
(9)

latter example a mixture of isomeric products was obtained; this situation will be discussed in some detail in connexion with the mechanism of the

reaction (see section II.B.2.b). The reaction between 1,4-benzoquinone and thiophenol (along with hydrogen chloride and aniline) played an important role in the early development of a clear picture of valence in organic molecules[12–16].

2. Mechanistic studies

There are relatively few mechanistic studies of the addition of sulphur nucleophiles to quinones, but those reported form a rather complete picture. The first really modern study with definite mechanistic implications is that of Snell and Weissberger[3]. By varying the relative proportions of quinone and thiol they were able to obtain either oxidation state of the product (equations 10 and 11). With other thiols it was not possible to stop



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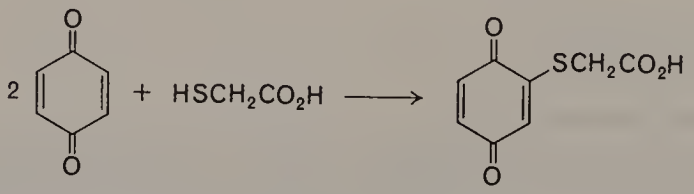
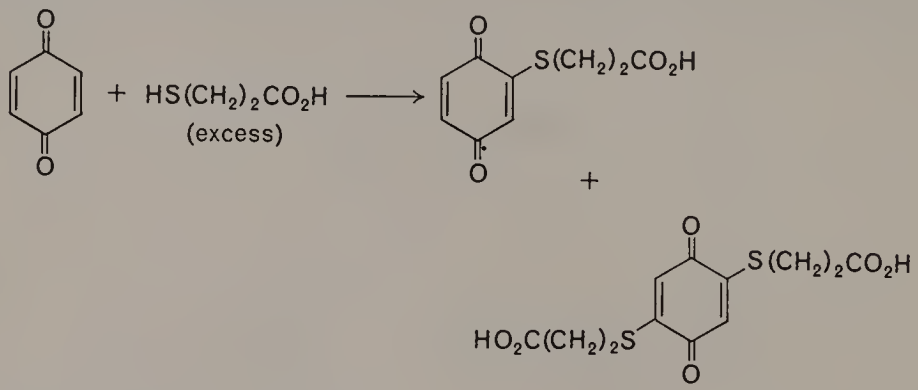


(11)

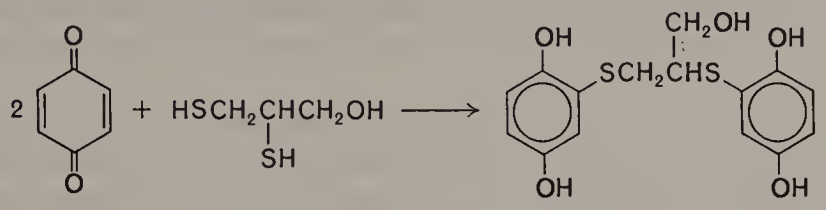
at the hydroquinone monosubstitution product, even with an excess of thiol (equation 12). All of these observations are consistent with the general mechanistic picture presented in section II.A (equations 3, 4 and 6) and the observations of Posner[12].



(12)

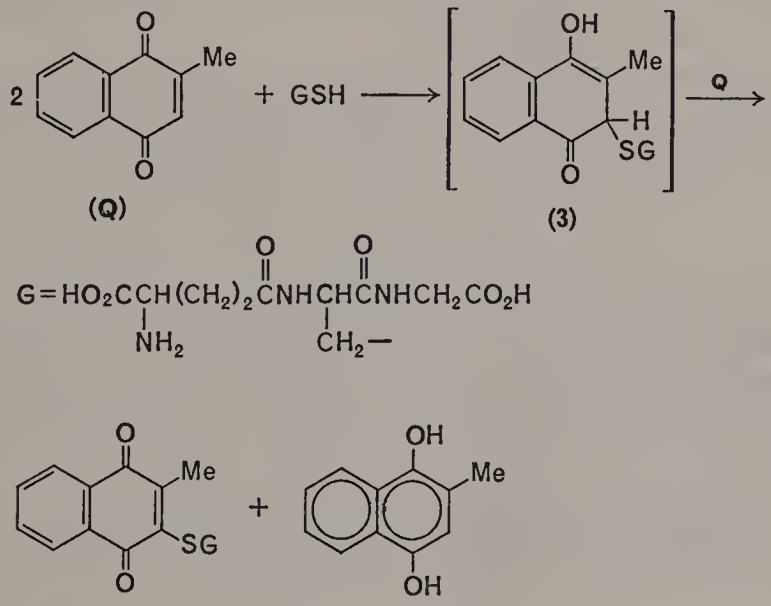
More recently, this generally accepted mechanism received some additional support from Zuman and Zumanová[17]. In a polarographic study of 2,3-dimercaptopropanol the formation of an insoluble mercury

salt produced an anodic wave useful for the study of several related reactions, including those with oxidants. When 1,4-benzoquinone was added no disulphide was formed and reaction with two moles of 1,4-benzoquinone (equation 13) was suggested to account for the disappearance of the wave.



(13)

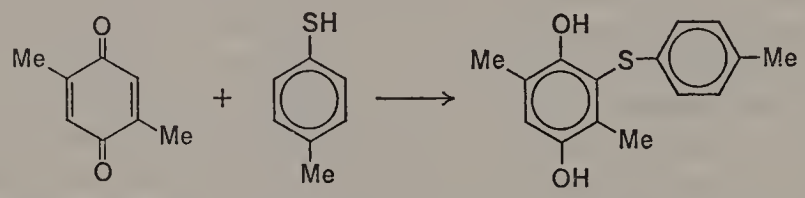
On the other hand, the reductive addition followed by cross-oxidation mechanism has been severely criticized in one instance[18]. The case presented in this paper states that in earlier work the substituted hydroquinone had not actually been isolated during the course of the reaction[3, 19, 20]. In fact, Snell and Weissberger present strong evidence of the formation of the substituted hydroquinone when equimolar amounts of 1,4-benzoquinone and thioglycolic acid are employed (i.e. loss of colour and formation of a lactone). When the reactant ratio was 2 : 1 (quinone : thiol) the substituted quinone was obtained as the product. Admittedly, the yields obtained by Snell and Weissberger were not high and the strength of their argument suffers from that deficiency. Also, it appears that the redox data presented by Nickerson and collaborators[18] argue for their proposed mechanism of substitution (equation 14). Since the products predicted by both groups are the same, the essential question is whether (i) the intermediate **3**



(14)

enolizes to a substituted naphthohydroquinone, or (ii) the intermediate **3** transfers hydrogen directly to a second molecule of 2-methyl-1,4-naphthoquinone. The observation of a small difference in redox potentials between the quinone starting material and the hydroquinone corresponding to the product, coupled with the lack of any appreciable cross-oxidation, is very important. It may well be that the bulky glutathionyl group (G) makes significant changes in the ability of the product to be reduced and to enolize.

In our own studies we have found that the addition of aryl thiols to 1,4-benzoquinones results in only small differences in redox values[21]. However, these differences are very important and lead to quite striking equilibrium results. The most significant results for the present discussion are, (i) a methyl group adjacent to the sulphide linkage severely inhibits the following cross-oxidation and (ii), so great is this inhibition that the postulated hydroquinone intermediate becomes the principal product (equation 15). We feel that this reaction, and those of the other methylated



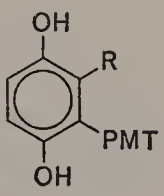
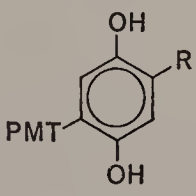
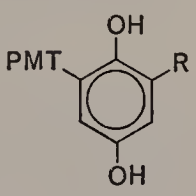
(15)

1,4-benzoquinones, is convincing evidence for the reductive addition mechanism; however, it does make the situation with 2-methyl-1,4-naphthoquinone all the more puzzling. The influence of the glutathionyl chain deserves more detailed study.

The first solid evidence of the correctness of the assumed ionic mode of addition of acidic thiols (see section IV.B) came from a study of 1-phenyl-5-mercaptotetrazole (HPMT). As indicated earlier (equation 5), very little cross-oxidation occurs and the substituted hydroquinone is isolated in good yield[4]. Our electrochemical results are also consistent with this synthetic observation[21]. When HPMT is added to monosubstituted 1,4-benzoquinones, the product distribution is consistent with a nucleophilic addition mechanism[22]. The original assignment of structure in disubstituted 1,4-benzoquinones was made by Posner on the basis of logical arguments[12]. The results of Gates and collaborators[22], using n.m.r., suggest that the earlier assignments are correct. The data presented in Table 1 offer some evidence for nucleophilic addition when compared with the predictions one makes from a consideration of the resonance possibilities of the ground state and intermediates for each of the three

possible orientations. We have recently re-examined Posner's original work, improved Gates' yields in some cases, and found general agreement with both reports[23].

TABLE 1. Product orientation in the addition of 1-phenyl-5-mercapto-tetrazole (HPMT) to monosubstituted 1,4-benzoquinones[22]

R	Yield (%)		
			
OMe		88	
4′-C_6H_4OMe		80	
Me		25	13
n-$C_{15}H_{31}$		48	12
4′-C_6H_4Me		10	30
Ph		10	46
PMT	28	20	26
4′-$C_6H_4NO_2$			82
4′-C_6H_4Ac [a]			36
Ac	74		8
CO_2Me	91		

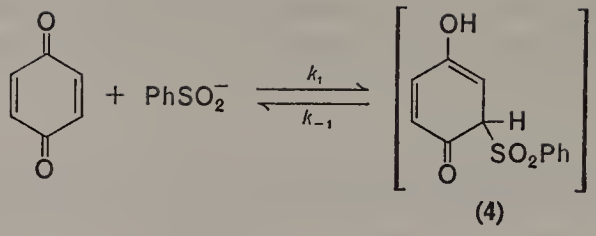
[a] A second minor product found but not identified.

The complete lack of kinetic studies in the thiol addition area is both notable and lamentable; however, two recent studies of sulphone formation (equation 8) are instructive[24, 25]. The rate law below pH 5·7 was shown to be:

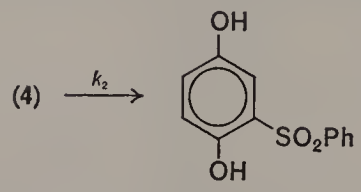
$$v = k[C_6H_4O_2]\,[PhSO_2^-]$$

At higher pH's, serious competing side-reactions made rate measurements difficult. The pH–rate profile shows a distinct change of slope at pH 3·5 to 4·0. The reactions below pH ca. 3·1 are subject to general-acid catalysis and show no kinetic isotope effect. At higher pH (ca. 4·0–5·7) the reactions are general-base-catalysed and exhibit an isotope effect that increases with pH.

The mechanism proposed involves two steps as shown in equations (16) and (17)[24]. At pH's below 3·1 the addition step (k_1) would be rate-determining; while above pH 4·0 the loss of a proton by the intermediate



(4) (16)



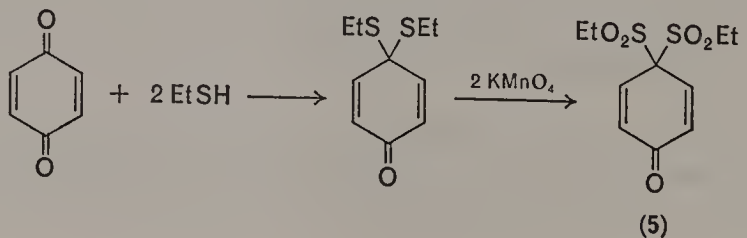
(17)

4 becomes kinetically significant. The observations reported for catalysis and isotope effect as well as the pH–rate profile all support these proposals. A later study extended these results to a series of 4-substituted arylsulphinic acids and showed an excellent Hammett correlation[25]. The negative ρ obtained ($-1{\cdot}55$ at pH 3·50) and the observation that it changes very little with pH are both consistent with the proposed mechanism. The essentially quantitative yields of reduced (i.e. substituted hydroquinone) product obtained in these reactions are quite expected from our electrochemical studies[21].

3. Synthetic survey

While detailed mechanistic studies of the addition of organic sulphur nucleophiles to quinones have been limited, a substantial number of significant synthetic reports are to be found. The intention in the present section (and analogous sections throughout the chapter) is to illustrate the breadth of past work and to furnish leading references to the type of synthesis under discussion.

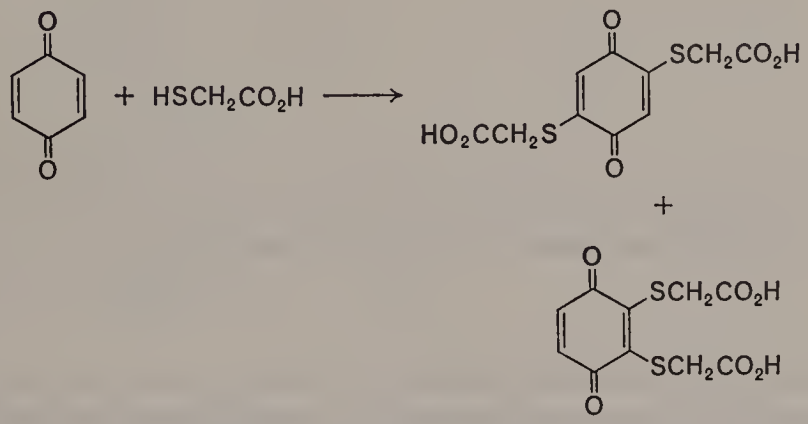
In 1927 Récsei reported some truly amazing addition and oxidation reactions of 1,4-benzo- and 1,4-naphthoquinone with ethyl mercaptan[26]. He maintained that carbonyl addition took place and that the adduct obtained could be oxidized to a disulphone with potassium permanganate (equation 18). The true course of these reactions has not been demonstrated,



(5) (18)

but Snell and Weissberger showed that a better yield of the alleged 'sulphone', **5**, could be obtained with ferric chloride and that the elemental analysis of **5** does not fit the proposed structure[3].

The addition of thioglycolic acid to 1,4-benzoquinone has already been mentioned[3,19]. The reaction first appeared in the chemical literature in 1930 when the formation of two isomeric disubstitution products was reported (equation 19)[27].

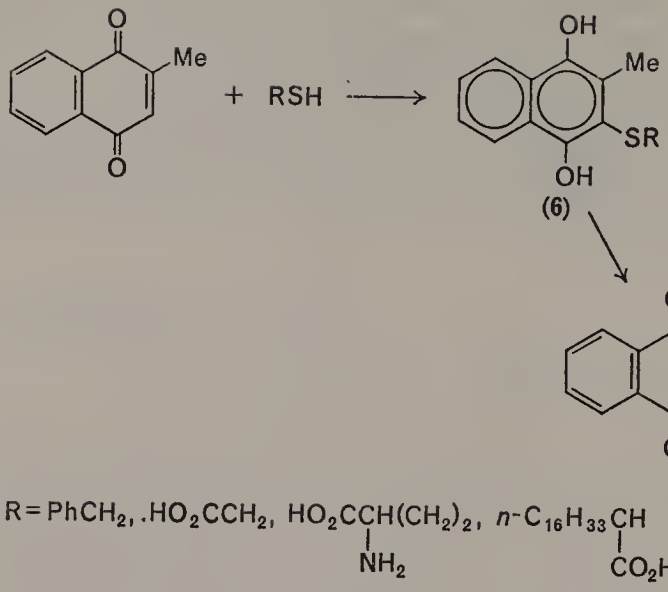


(19)

The addition of thiophenol to 1,4-benzoquinone has been considerably expanded and a number of *ortho*- and *para*-substituted phenylmercapto-1,4-benzoquinones prepared[28]. A few related 1,4-naphthoquinone and 1,4-dihydroxy-9,10-anthraquinone derivatives are included. The proposed structures are based on analogy with Posner's work[12], but are probably correct as suggested by Gates[22]. Some significant improvements in yields are reported under various modified reaction procedures.

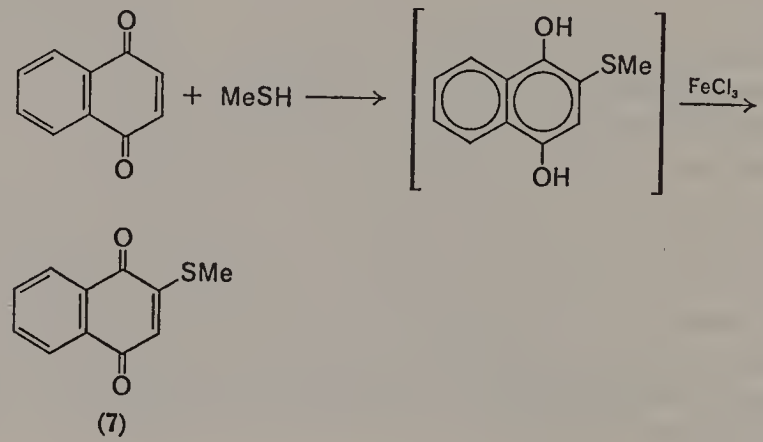
As one part of their continuing search for compounds of potential medicinal importance (specifically antihaemorrhagic or bacteriostatic activity) Fieser and Turner investigated the addition of a variety of thiols to 2-methyl-1,4-naphthoquinone (equation 20)[20]. It was not demonstrated that the substituted hydroquinone **6** is formed during the course of the reaction; a fact later pointed out by Nickerson and collaborators[18]. However, Fieser was surely confident of its presence, since he suggests the *in situ* oxidation of the products as the optimum synthetic method (see section II.B.2).

The obvious importance of alkyl and aryl sulphides of 1,4-naphthoquinones has led to the development of preferred synthetic routes. For example, Little, Sproston and Foote found that the yield of 2-methylmercapto-1,4-benzoquinone (**7**) could be doubled by adding ferric chloride when the first crystals of product appeared (equation 21)[29]. If the oxidant was added at the beginning of the reaction, no quinonoid product was



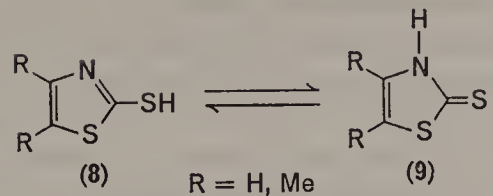
(20)

obtained. Fieser and Brown modified this method slightly and prepared a large number of mono- and disubstituted 1,4-naphthoquinone sulphides[30]. In this same study a very useful method of achieving either addition or substitution was found (see section VIII.D).

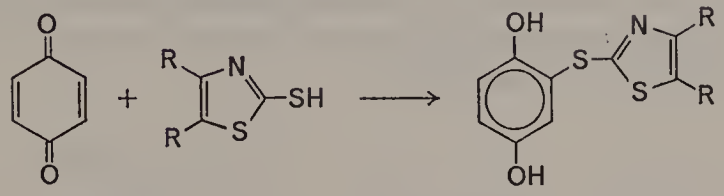


(21)

The addition of a heterocyclic mercaptan to 1,4-benzoquinone by Gates and his colleagues has been mentioned[4,22]. In an earlier study the question of sulphur versus nitrogen attack was answered for the related 2-mercapto-thiazoles[31]. These compounds can exist in either the mercapto (8) or the thione (9) form (equation 22). All three heterocycles added smoothly to give good yields of the hydroquinone sulphide (equations 5 and 23).

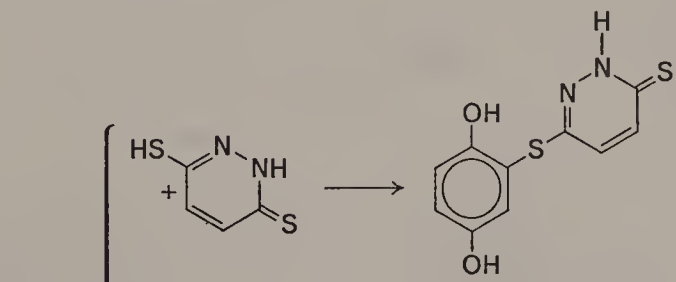


(8) R = H, Me (9) (22)



(23)

More recently a series of complex heterocycles were shown to add to 1,4-benzo- and 1,4-naphthoquinone in high yield (equations 24–26)[32]. The hydroquinone products can be oxidized with lead tetraacetate and a second addition carried out.



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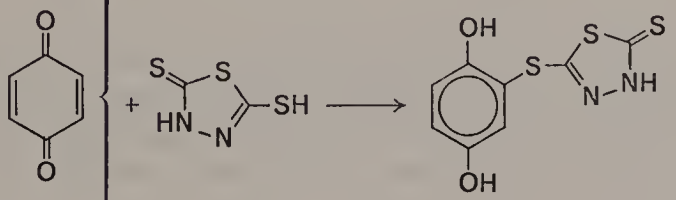

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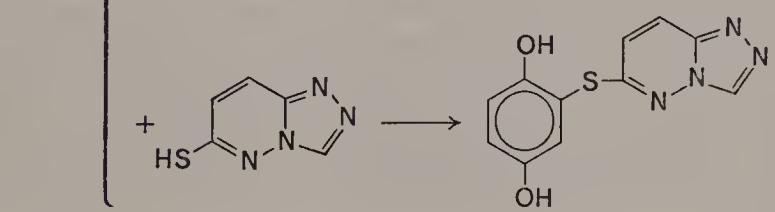
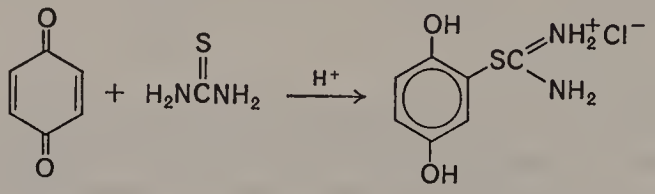


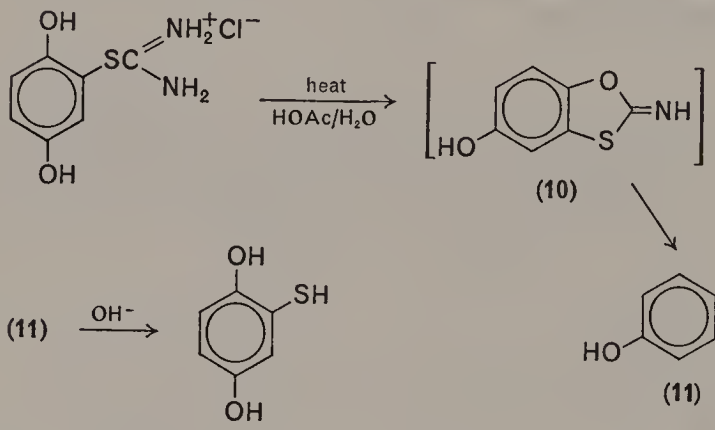
(26)

A related question of the mode of addition of ambident reactants is found in the cases of thiourea and cysteine. The first of these was mentioned by Schubert[19], who found it possible to isolate the hydrochloride salt at

moderate temperatures in acidic solution (equation 27). A more detailed study by Burton and David showed that the reaction could be achieved with several different quinones and that the product from 1,4-naphthoquinone is not as unstable as Schubert claimed[33]. They further found that the thiouronium salts can be cyclized to 5-hydroxy-1,3-benzoxathiol-2-ones* (**11**) and subsequently to 2-mercaptohydroquinone (equation 28). The presumed imino intermediate, **10**, was not isolated, nor was any definite evidence for it advanced.



(27)



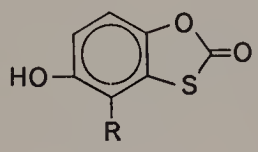
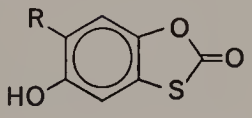
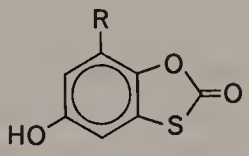
(28)

Definitive studies of the addition of thioureas to quinones have recently been published by Lau and collaborators[34,35]. They found that a large number of substituted 1,4-benzoquinones will add thiourea in excellent yield when an excess of the latter reagent and a strongly acidic medium are used. Examples of both the thiouronium salts (several cases) and the imino salts corresponding to **10** (a few cases) were isolated, purified and characterized. The decomposition problems reported by earlier workers occurred only from heating in weak acid solution or from failure to undergo cyclization (for example, with 1,4-naphthoquinone and 2,5-diacetyl-1,4-benzoquinone). Sterically very crowded molecules, like 2,5-di-*t*-butyl-1,4-benzoquinone, are simply reduced to the hydroquinone without addition.

* Incorrectly named 2′-hydroxy-4,5-benzothioxol-2-ones by Burton and David.

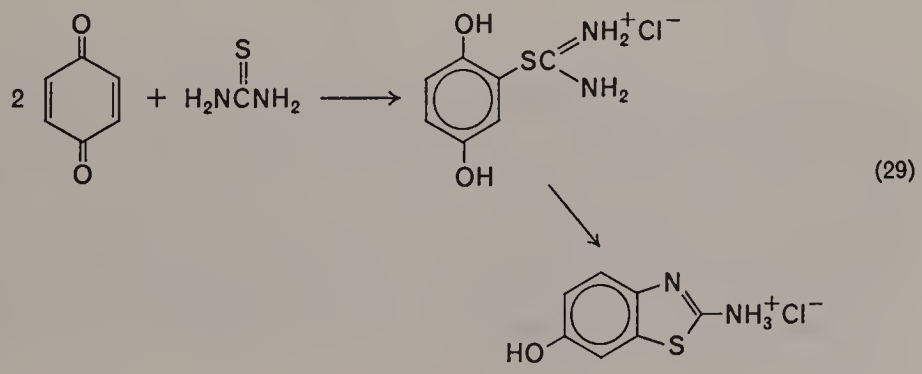
In addition to 1,4-benzoquinone and its di- and trisubstituted derivatives, a series of monosubstituted 1,4-benzoquinones were studied and the distribution of products determined. The data presented in Table 2 may

TABLE 2. Product orientation in the addition of thiourea to monosubstituted 1,4-benzoquinones[34]

R	Yield (%)		
			
Me		7	82
n-C_8H_{17}			99
n-$C_{18}H_{37}$			96
Ph		3	90
PhS		2	96
Cl	12	13	53
Ac	79		11

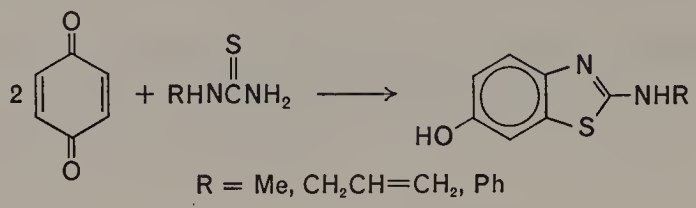
be compared with those of Gates (Table 1) presented earlier (see section II.B.2). The most striking point in the comparison is the shift of reactivity from 2,5- to 2,6-orientation for electron-releasing groups. This effect may be associated with the excellent hydrogen-bonding ability of the thiourea, but its impressive magnitude surely warrants further study. The overall reaction represents the preferred route to the 5-hydroxy-1,3-benzoxathiol-2-ones.

A later study by Lau and Gompf showed that the addition of thiourea to an excess of a quinone proceeds through the thiouronium salt to 2-amino-6-hydroxybenzothiazoles (equation 29)[35]. The yields, while not as high as in the benzoxathiol cases, are entirely satisfactory. With



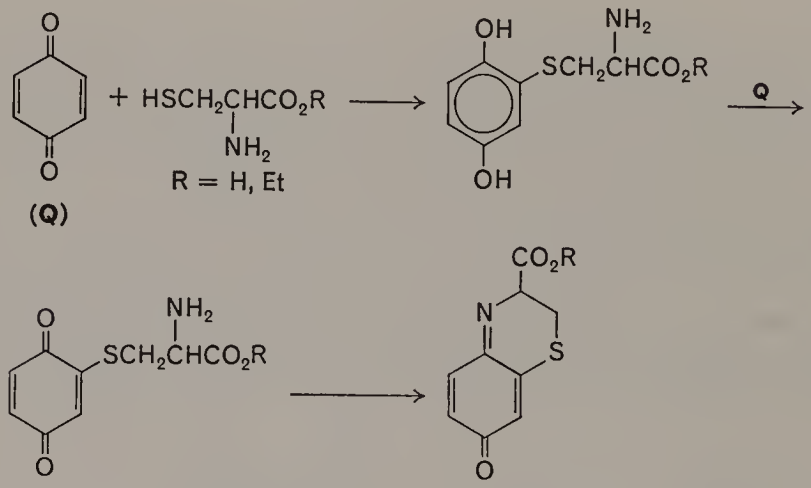
(29)

1,4-naphthoquinones only this second mode of cyclization is successful. The reaction has also been extended to some *N*-substituted thioureas (equation 30).



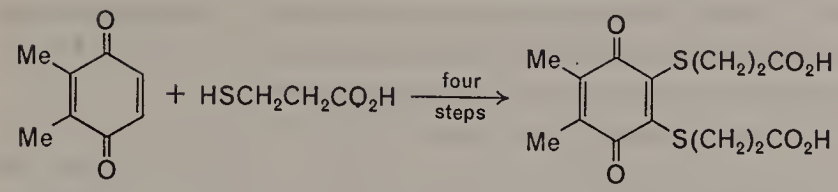
(30)

The naturally occurring α-amino acid cysteine presents orientation and reactivity problems similar to those of thiourea. Furthermore, the related structure present in certain enzymes makes such questions especially important (see section VIII.D). The reaction of cysteine involves initial addition of the thiol to the quinonoid ring[36]. This addition is followed by cross-oxidation and cyclization via dehydration (equation 31) and the yields reported are quite acceptable. Similar results were obtained with 2-methyl-, 2,5-dimethyl-1,4-benzoquinone and 1,4-naphthoquinone[37]. The addition reaction took place with 2-methyl-1,4-naphthoquinone, but the cyclization step was not reported[33].



(31)

In the process of establishing the structure of the active (antibiotic) component of gonyleptidine, Fieser and Ardao examined the addition of β-thiopropionic acid[38]. Sequential addition and oxidation should lead to completely substituted quinones which possess both increased chemical stability and molecular weight (for example, equation 32). In practice the yields were poor. The major component of gonyleptidine was shown to be 2,3-dimethyl-1,4-benzoquinone by alternate procedures (see sections II.D and V.A.3).

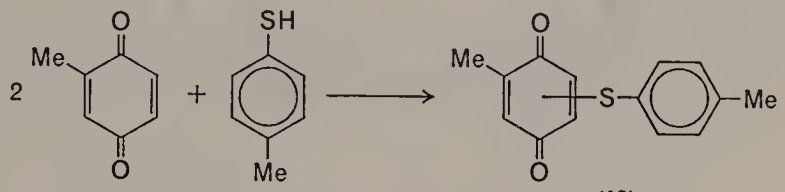


(32)

(and other simple quinones)

(and related products)

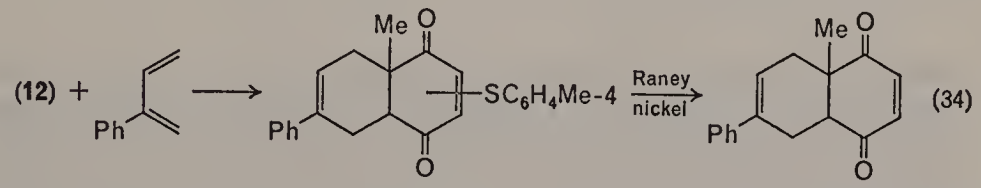
The synthesis of alicyclic compounds of rather complex structure has been accomplished using the Diels–Alder reaction (see section V.A.3) with quinones bearing an arylmercapto substituent for its protective and directive influence[39]. An addition reaction between *p*-toluenethiol and 2-methyl-1,4-benzoquinone was carried out with the usual results (equation 33). Following the Diels–Alder reaction of **12** with 2-phenylbutadiene,



(33)

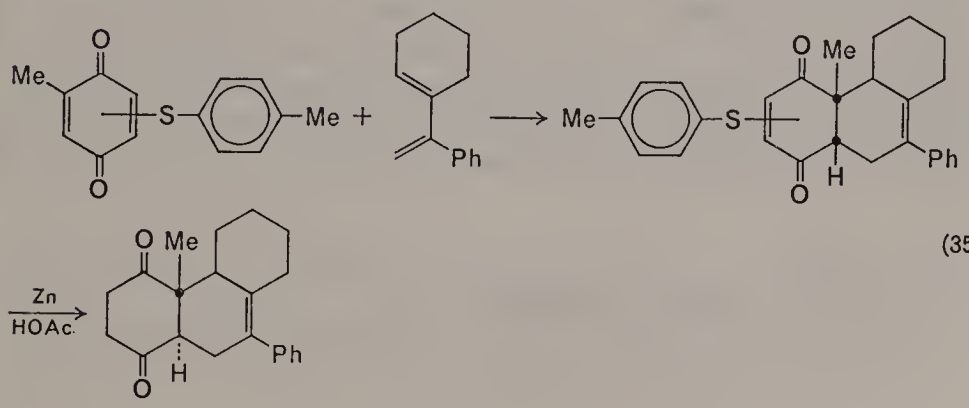
(12)

the sulphide substituent was removed with Raney nickel (equation 34). When zinc and acetic acid were the reactants in the desulphurization, the



(34)

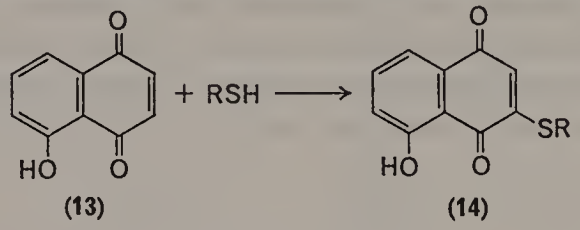
alkene linkage was also reduced and the *cis* ring-fusion product isomerized to the *trans* configuration (equation 35)[40]. The simpler methylmercapto group was also examined and found to be satisfactory for these functions.



(35)

The addition of excess methylmercaptan to 2-methyl-1,4-benzoquinone followed by ferric chloride produced a product distribution similar to our findings with thiophenol and excess 1,4-benzoquinone[23,41].

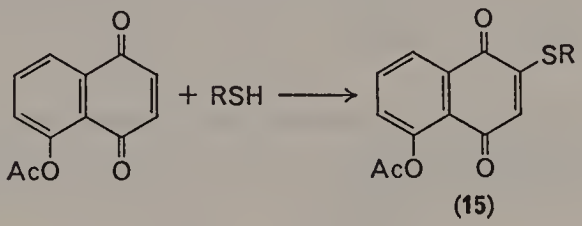
Not only has the addition of thiols been of interest in the synthesis and identification of natural products, but the study of thiol additions to quinonoid natural products has also received some attention. As part of his detailed study of the chemistry of juglone (**13**) Thomson added both thioglycolic acid and *p*-toluenethiol to the parent compound and its acetate, with very interesting results (equations 36 and 37)[42]. The complete



(36)

(13) (14)

R = HO_2CCH_2, 4-MeC_6H_4

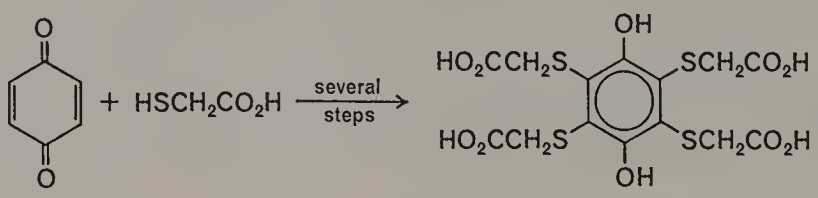


(37)

(15)

change of orientation (the yields were reasonably high in all four cases) was explained on the basis of radical addition to juglone acetate resulting in the 2-substituted mercapto product **15**. The 'normal' ionic addition to juglone itself produces the 3-substituted mercapto product **14**. There will be more to say about sulphur radical additions to quinones in section IV.B.

Thomson and Blackhall continued the study of thioglycolic acid addition using a series of simpler quinones[43]. They found this thiol, as had others earlier[3,19,20], to be very reactive in such additions. With the exception of 1,4-naphthoquinone and possibly 2-methyl-1,4-benzoquinone, sequential cross-oxidation and addition took place readily and only the completely substituted hydroquinone was obtained (e.g. equation 38).



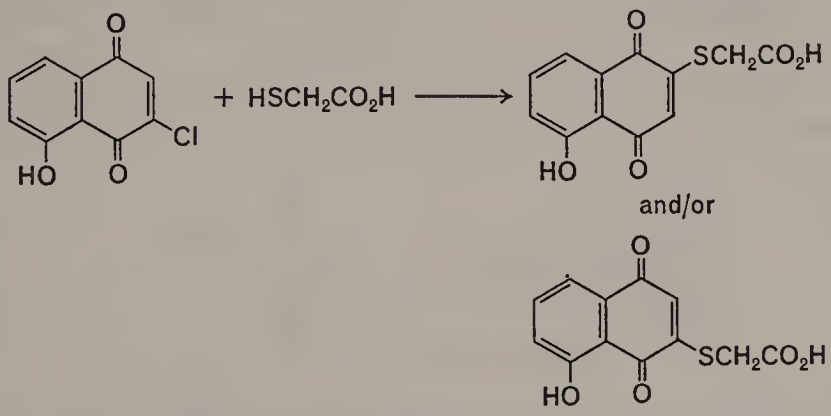
(38)

It was also found that 3-mercaptopropanoic acid behaves similarly, but 4-mercaptobutanoic acid is considerably less reactive. It was found that the reactivity of the thiols roughly paralleled their acidity; i.e.

$$HS(CH_2)_3CO_2H \approx PrSH < PhSH < HS(CH_2)_2CO_2H < HSCH_2CO_2H$$

The solvent employed also plays a significant, but only poorly defined role.

Rothman has also studied the reactions of juglone and juglone acetate with thioglycolic acid and questioned the suggested radical versus ionic pathway[44]. His chief concern was with the assignment of structure for the addition products claiming that displacement of halogen does not necessarily lead to product with the same structural arrangement (equation 39). His own structure proof led to exactly the opposite product orientations and eliminated the need for the proposed radical mechanism.

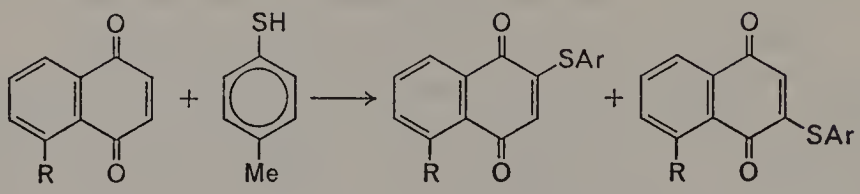


The third (and apparently the final) round in this controversy is Thomson's[45]. He and McLeod showed that for *p*-toluenethiol the original[42] structural assignments were correct. This was accomplished by basic hydrolysis to 2- and 3-hydroxyjuglones whose structures were established independently. Similar reactions with the thioglycolic acid adducts were not successful because of extensive decomposition and they admitted this extremely reactive thiol could be an exception. The study of the addition of *p*-toluenethiol was expanded to include a variety of 5-substituted-1,4-naphthoquinones (equation 40). The results shown in Table 3 clearly indicate the unusual character of juglone acetate. Thomson thus presents the first specific experimental evidence for competing ionic and radical addition of thiols to quinones[42, 45].

In the past few years, a number of interesting reactions involving sulphur nucleophiles and quinones have appeared. The following brief notes and equations will illustrate these observations:

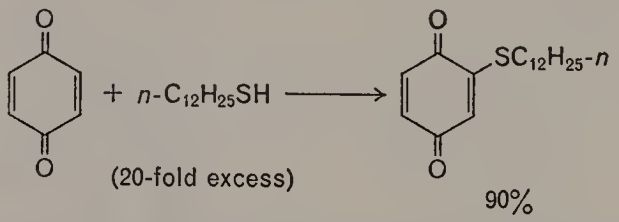
(1) The long alkyl chains (fattails), so useful in many technological applications, can be introduced in excellent yield (equation 41)[46].

TABLE 3. The addition of *p*-toluenethiol to 5-substituted 1,4-naphthoquinones[45]

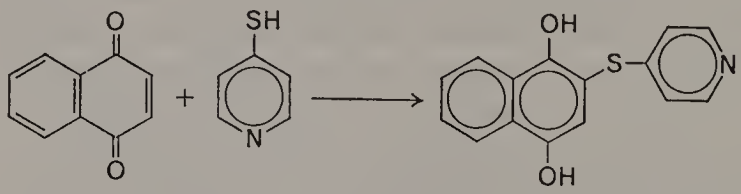


R	%	%
OH		90
AcO	80	80[a]
MeO		73
Me	10	75
AcNH		72
Cl	12	49

[a] See text.

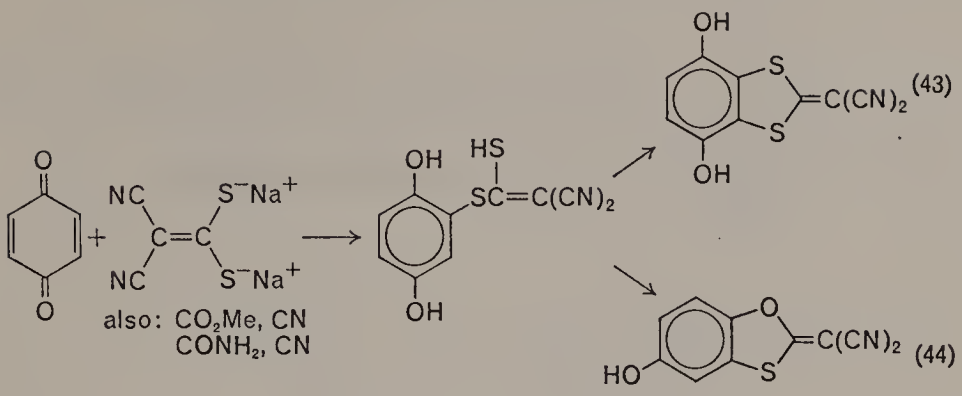


(2) The long list of important nitrogen–sulphur heterocyclic combinations has been expanded by addition of 2- and 4-mercaptopyridines to 1,4-naphthoquinones (equation 42)[47]. It was shown that, in most cases,

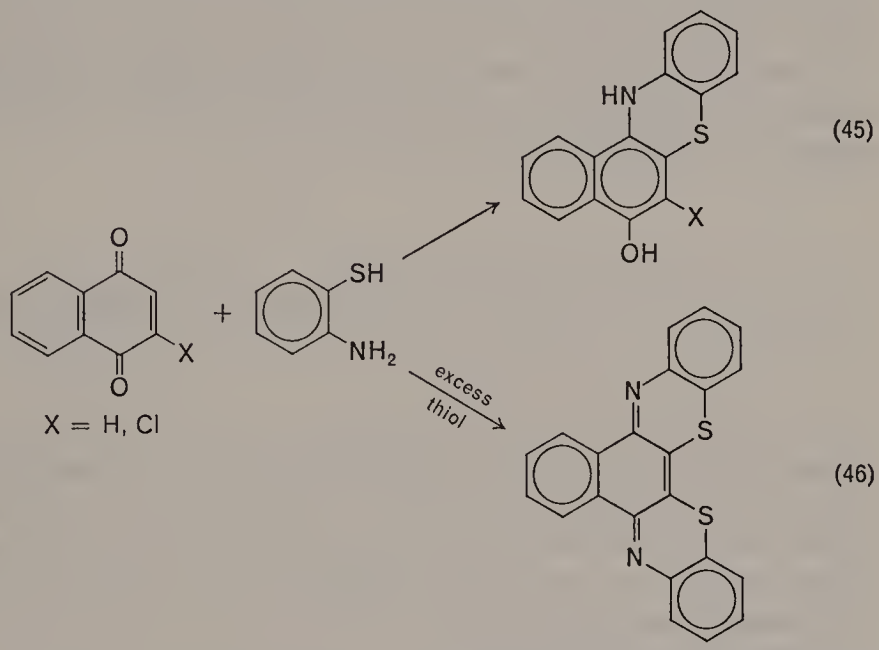


either the mono- or disubstituted product could be obtained under appropriate conditions.

(3) The addition of thioacetic acid enol salts bearing strong electron-withdrawing substituents in the α-position can lead to different heterocyclic products depending on the reaction conditions (equations 43 and 44)[48]. While no mechanistic detail is given, the displacement of sulphur by oxygen (equation 44) is noteworthy and resembles the thiourea examples given earlier[34,35].



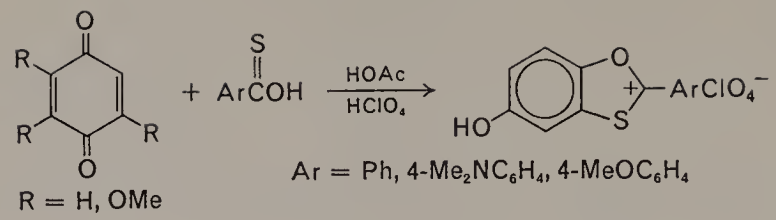
(4) The compound *o*-aminobenzenethiol, with its obvious similarities to many natural systems, will add to 1,4-naphthoquinone to form heterocyclic systems (equations 45 and 46)[49]. When the appropriate groups are



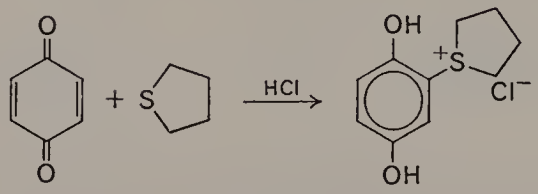
present substitution will take place (see section VIII.D) but, as indicated in equation (45), addition is the preferred route with either hydrogen or chlorine as the substituent.

(5) Nearly quantitative yields of heterocyclic perchlorate salts can be obtained from the addition of aryl monothioacetic acids to 1,4-benzo- and 1,4-naphthoquinones (equation 47)[50].

(6) For a wide variety of quinones and thioethers it has been shown that in acidic media the corresponding hydroquinone sulphonium salt can be obtained in high yield (e.g. equation 48)[51].

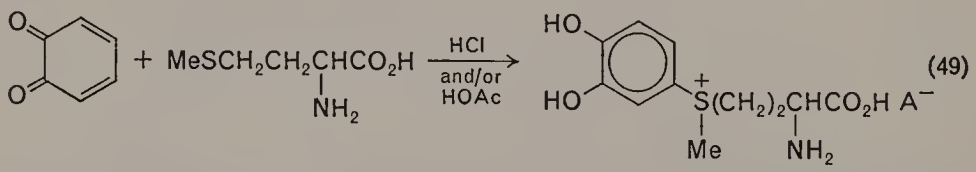


(47)



(48)

(7) The formation of sulphonium salts has also been studied with DL-methionine (as well as its *N*-acetyl derivative and methyl ester[52]). With 1,2-benzoquinone the structure of the product was established by the usual techniques: elemental analysis, spectral comparison, etc. (equation 49). The methionine residues of ribonuclease-A also showed this chemistry in acid solution.

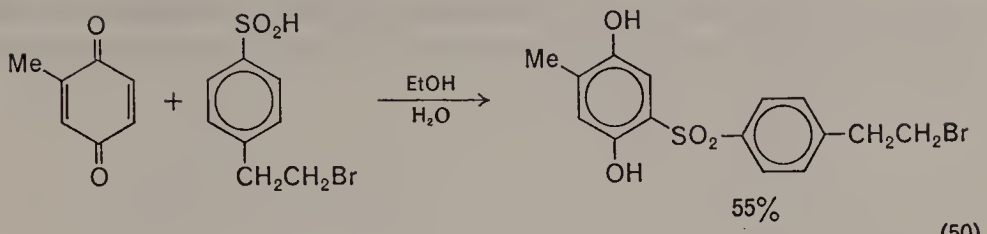


(49)

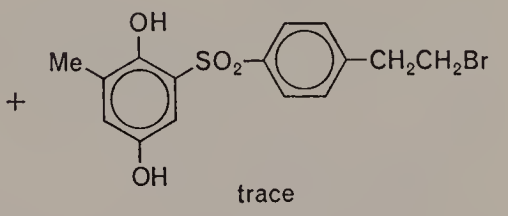
The second major area of synthetic interest in discussing sulphur nucleophiles and quinones is the addition of sulphinic acids (equation 8). After the initial work by Hinsberg[8–10], this field of quinone chemistry lay totally bare for over forty years. With the advent of the sulpha drugs an intense interest resumed and many compounds were prepared with little new chemistry being added[53–58].

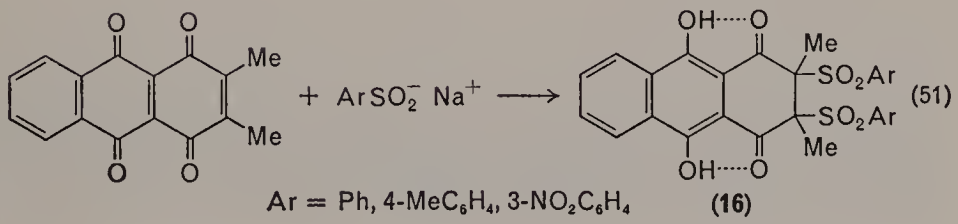
In 1963, as part of their studies of the synthesis and properties of redox polymers, Spinner and his collaborators reported an interesting orientation effect (equation 50)[59]. This situation seems strange since we have, in many attempts, found only the 3,4′-dimethyl isomer in the analogous addition of *p*-toluenesulphinic acid[21]. This problem is currently under active study.

A very interesting and unusual 2,3-addition of sulphinic acids to quinones has been reported (equation 51)[60]. Very strong intramolecular hydrogen bonding in the product, **16**, is assumed to explain the observed reaction.



(50)



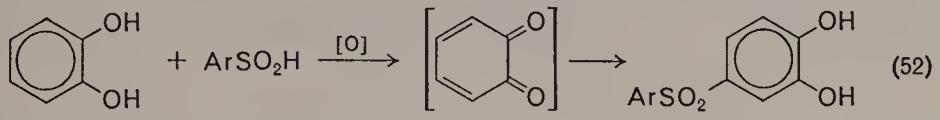


(51)

Ar = Ph, 4-MeC_6H_4, 3-$NO_2C_6H_4$ **(16)**

4. Nascent quinones

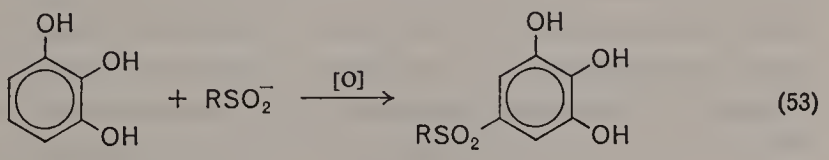
The pioneering work of Hinsberg and Himmelschein on the addition of sulphinic acids to quinones contained an example of synthesis via nascent quinones (equation 52)[10]. This technique of *in situ* preparation or



(52)

the nascent quinone has been applied most frequently to the less stable 1,2-quinones, but examples of 1,4-quinones are also be be found. The following examples of nascent quinones reacting with sulphur nucleophiles are drawn from a recent review[61].

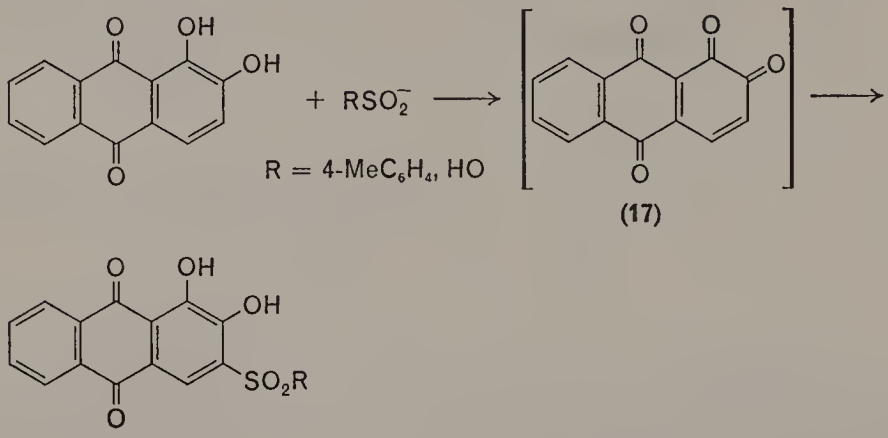
(1) Pyrogallol reacts with either benzenesulphinic acid or sulphite under oxidative conditions (equation 53)[62].



(53)

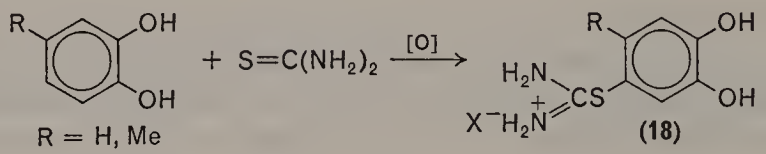
R = Ph, HO

(2) An unexpected product orientation results in the case of the diquinone formed from alizarin (equation 54)[61]. The intermediate quinone **17** is only known in solution[63].

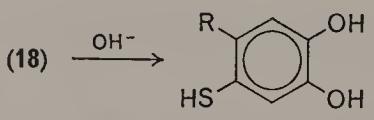


(54)

(3) The addition of thiourea to a nascent 1,2-benzoquinone has been reported to produce greater than a 90% yield (equation 55)[64,65]. It has also been shown that the product salt **18** can be hydrolysed by base to the corresponding mercaptan (equation 56)[65].



(55)



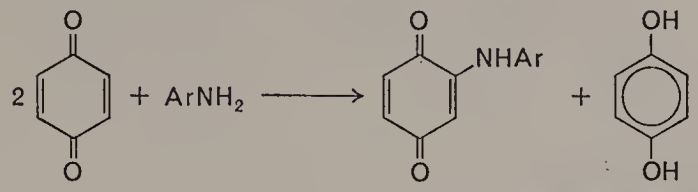
(56)

C. Nitrogen Addition

1. Historical introduction

The ability of compounds containing basic nitrogen to undergo Michael addition with a variety of quinones was observed and amply documented in the late 19th and early 20th centuries[66–80]. The culmination of these efforts is the synthetic *tour de force* of Suida and Suida[5]. In this single paper they reported the preparation and characterization of 50 addition products of 1,4-benzoquinone and various substituted anilines (equation 57). The study included some *N*-methylaniline derivatives and a brief look at 2-methyl-1,4-benzoquinone. Finally, the competition between

addition and substitution (see section VIII.B) was recognized in the case of several chloroquinones (e.g. equation 58).



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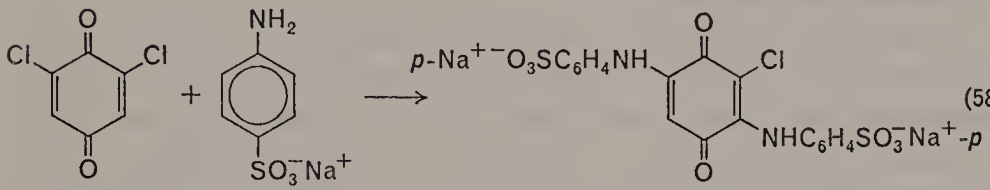
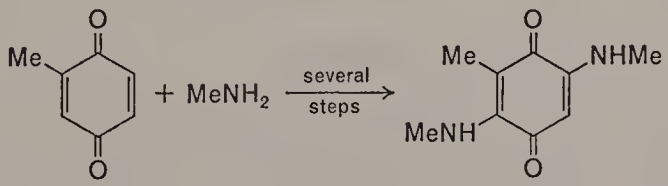


(58)

The possibility that nitrogen addition chemistry might be important in protein work was recognized. An early example deals with a very clinical concern—the bactericidal properties of quinones[82,83]. Cooper and Haines showed that a portion of the disinfectant activity of several quinones could be attributed to reaction with amino acids rather than with proteins. A rough set of kinetic experiments showed a strong positive salt effect for the reaction of 1,4-benzoquinone, but only a slight effect with 2-methyl-1,4-benzoquinone.

The method of choice for preparing dimethoxy quinones has also revealed structural detail of nitrogen addition products[84,85]. The method of synthesis does not demand the product structure shown in equation (59), but it was established by reliable methods. The structure of the product **19** is interesting in that the usual *para* orientation expected from a

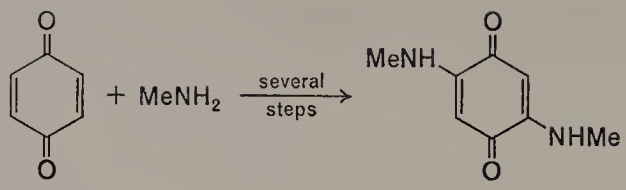


(59)

(19)

methyl group either does not occur or rearranges to allow the *para* arrangement for the two methylamino groups.

The interaction of alcoholic solutions of methylamine with methyl- and methoxy-substituted 1,4-benzoquinones has produced other unexpected chemistry[86]. The most interesting aspects of this study will be discussed in connexion with nitrogen substitution chemistry (see section VIII.B). The expected 2,5-bis(methylamino)-1,4-benzoquinone (**20**) is obtained in the simplest case (equation 60).



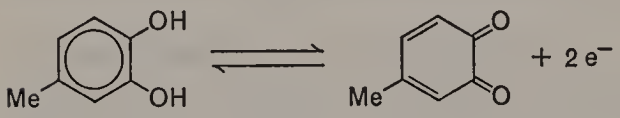
(60)

(20)

2. Mechanistic studies

In spite of the rather large amount of synthetic effort that has been expended on the addition of amines to quinones, relatively few purely mechanistic studies have been reported. The analytical difficulties in such studies are real and account, in part at least, for their scarcity. It should be noted that many of the reports cited in sections II.C.3 and 4 make important contributions to our understanding of the reaction mechanism.

The first study of the detailed mechanistic path for the addition of amines to quinones involved the electrochemical study of 1,2-benzoquinone generated *in situ*[87]. Using chronoamperometry, cyclic voltammetry and chronopotentiometry it was possible to obtain rate and equilibrium data that are consistent with the following reaction sequence (equations 61–64).



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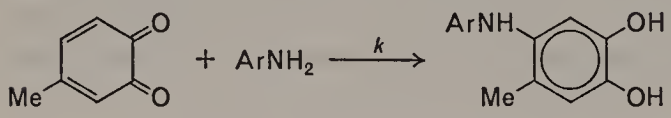
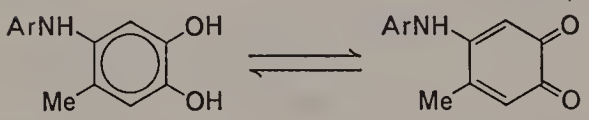


(62)

Ar = Ph, 2-$HO_2CC_6H_4$



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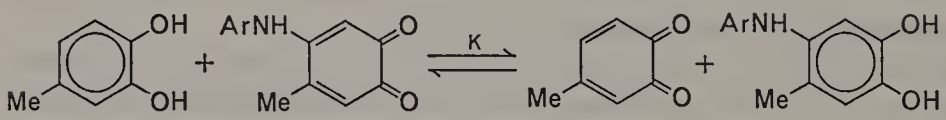
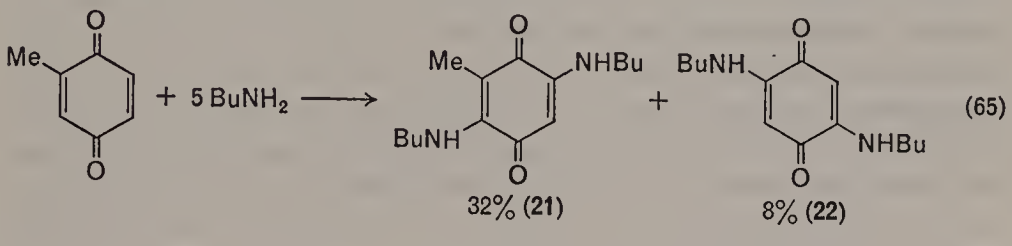


(64)

Second-order rate constants $k = 7{\cdot}8 \times 10^4$ and $5{\cdot}5 \times 10^3$ ($s^{-1}M^{-1}$), for aniline and *o*-aminobenzoic acid respectively, were obtained and the equilibrium constant K was found to be very small ($\approx 10^{-4}$) for both

anilines. The curve-fitting procedures used leave no doubt that the equilibrium constant is very significant and that for aniline addition the nitrogen-substituted catechol is practically non-existent.

The combination of thin-layer chromatography and polarography has proved to be of value in these studies[88]. The system 2-methyl-1,4-benzoquinone and *n*-butylamine was chosen because the reaction rates are suitable for study by standard kinetic techniques. The products found, both with excess amine (equation 65) and excess quinone (equation 66), are consistent with earlier experience. The product analyses for the



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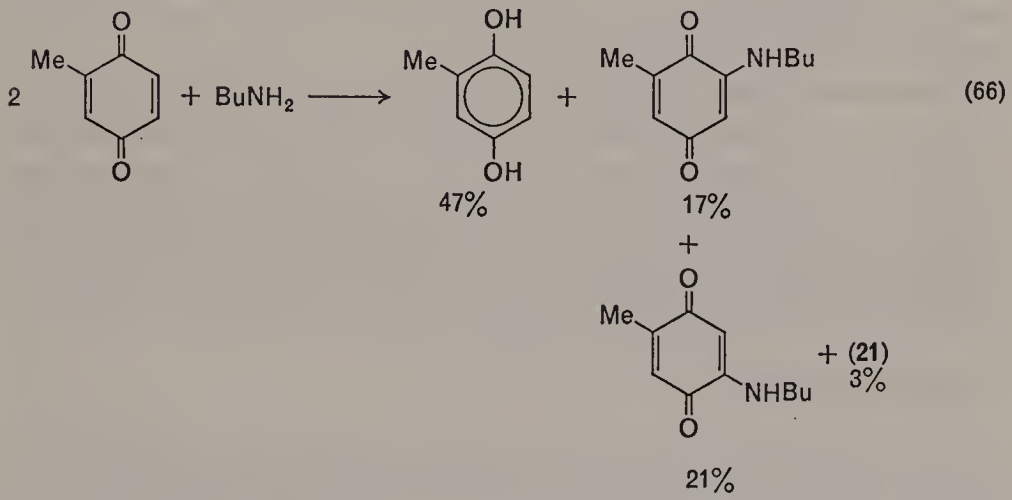
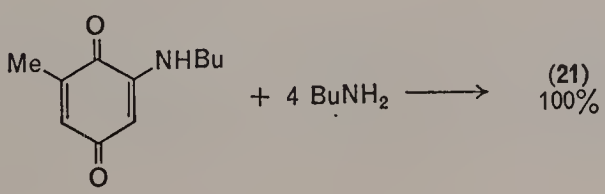
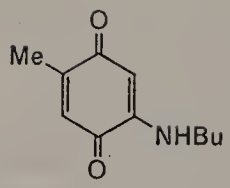


(66)

reactions of 3- and 4-butylamino-2-methyl-1,4-benzoquinone (equations 67 and 68) are also of interest. In both reactions a significant amount of methyl group displacement was observed (see section VIII.B.2) and a large amount of unidentified by-product was obtained. Excellent material balance was found over the course of these reactions and reactivity index calculations (superdelocalizability by the ω-technique[88a]) were used to discuss the observed reactivity.



(67)



$$+ \ 4\ BuNH_2 \longrightarrow \underset{34\%}{(22)} + \underset{1\%}{(21)} \qquad (68)$$

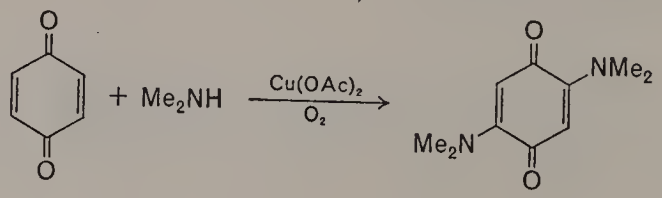
The techniques developed in the study just cited have continued to be employed: for example, the ω-technique calculations have been used for a more detailed analysis of the reactivity of 1,4-benzoquinones with amines[89]. The first step is the addition of the amine; both reactivity indices and resonance energy calculations indicate that this involves nucleophilic 1,4-attack.

The effect of alkyl groups in the amine on the rate of reaction is important[90]. With 1,4-benzoquinone the primary amines Me, Et, Pr, *i*-Pr, Bu, *s*-Bu and *t*-Bu all gave bis(alkylamino)-1,4-benzoquinones. The secondary amines Me_2, Et_2, Pr_2 and Bu_2 gave only mono-dialkylamino-1,4-benzoquinones. In the latter case the reaction rate decreased with increasing size of the alkyl groups.

The most recent mechanistic study of the addition of amines to quinones made use of rapid-scan spectrophotometry[91]. The work presented by Yamaoka and Nagakura deals mostly with substitution chemistry (see section VIII.B.1), but they did show that an electron transfer from the amine to the quinone occurs prior to the formation of the final product, 2,5-bis(butylamino)-1,4-benzoquinone. They were unable to observe a spectrum for 2-butylamino-1,4-benzoquinone.

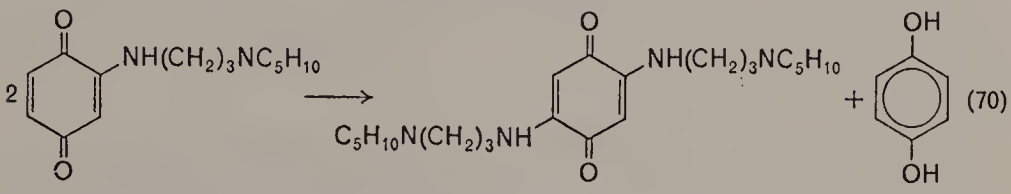
3. Synthetic survey

Some of the post World War II work was simply routine syntheses in an effort to explore and exploit physiological properties of the nitrogen-substituted quinones[92,93], but some useful synthetic and mechanistic information was also obtained. First, it was found that in cases where the 2,5-disubstituted product is desired, the use of an added oxidant greatly improves the conversion of the starting quinone and simplifies the purification (equation 69)[94]. The technique, while useful, appears to be quite limited as it was unsuccessful with methylamine, aniline and ammonia.



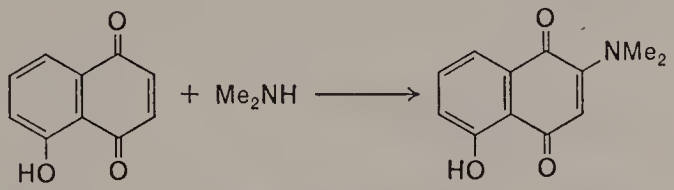
(69)

In a synthetic study, where both the mono- and the 2,5-dialkylamino-1,4-benzoquinones were isolated, it was found that the former can undergo disproportionation to the latter (equation 70)[95]. This observation could bear on the unusual orientation cited earlier.



(70)

The reactions of quinonoid natural products with amines have been studied and have contributed to our understanding of addition chemistry. Thomson's work with juglone sulphur chemistry has already been described[42] (see section II.B.3). Less success was achieved with direct nitrogen addition and dimethylamine gave only a 34% yield (equation 71).

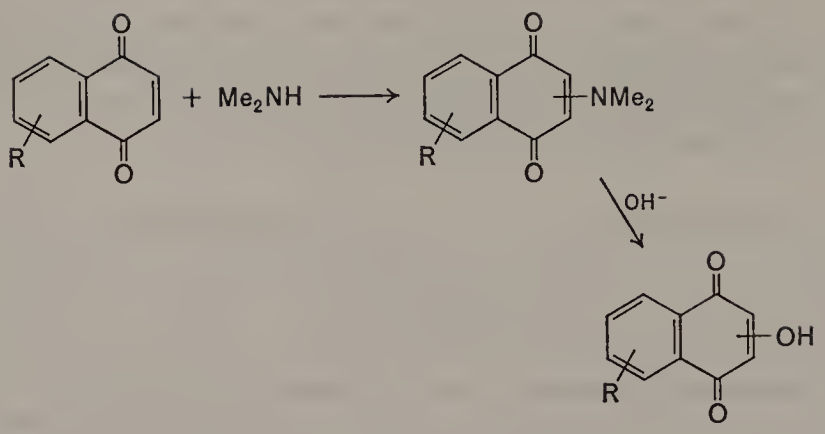


(71)

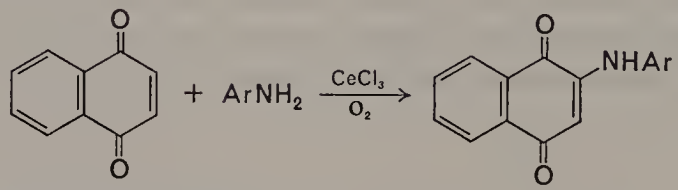
The 3-isomer was also prepared, but only by substitution (see section VIII.B.2). When aniline was added to juglone acetate the yield was somewhat better (66%) and the expected 3-anilino product was obtained. Unlike *p*-toluenethiol, aniline reacts with various 5-substituted 1,4-naphth o quinones to give only the 3-anilino product[45]. The reaction with 5-acetamido-1,4-naphthoquinone, like juglone, gave only black amorphous material.

The addition of dimethylamine to juglone (equation 71) has been expanded to a series of 1,4-naphthoquinones with substituents in the aromatic ring[96]. The product distribution was determined after hydrolysis to the corresponding hydroxy quinone (equation 72). The results shown in Table 4 are interesting, especially the very strong methyl effect, but the most significant questions are still not answered because of the low overall yields.

In the course of preparing compounds for biological testing, an added oxidant, cerium(III) chloride, has been used[97] (equation 73). Several of the substituted 2-naphthylamines reacted very poorly and sulphuric acid proved a good catalyst, but no detailed study of the effect was made. The general observations of the substituent effect on reactivity were consistent with nucleophilic addition; i.e. 6-bromo > 8-nitro > 1-bromo ≈ 1,6-dibromo > 1-nitro.



(72)



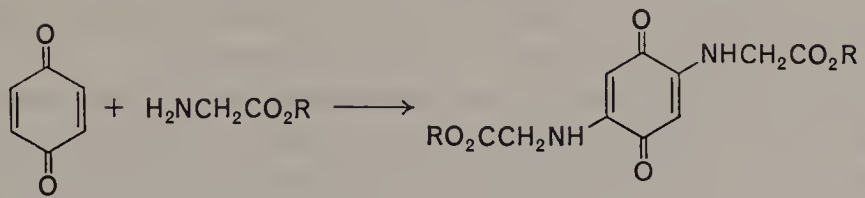
(73)

Ar = various halo and nitro substituted 2-naphthyls

TABLE 4. Product distribution in the addition of dimethylamine to 5- and 6-substituted 1,4-naphthoquinones (equation 72)[42, 96]

Substituent (R)		Product (%)		Total yield (%)
5	6	2	3	
OH	—	100	0	34
AcO	—	0	0	0
MeO	—	50	50	42
Me	—	Trace	~100	Not given
—	Me	~100	Trace	55

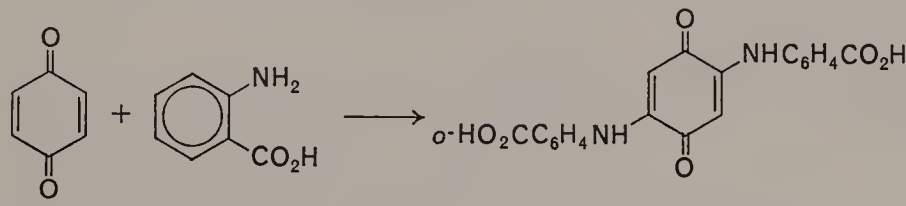
The application of polarographic methods to the study of quinones and their reactions has been very productive. In the field of nitrogen addition, amino acids and peptides have been shown to undergo reversible redox reactions at the dropping mercury electrode[98]. The earlier work on the interaction of amino acids and quinones[82, 83] has been followed by the synthesis of some peptide-like derivatives of 1,4-benzoquinone (equation 74)[99]. Three other amino acid esters were used and the product obtained in reasonable yield.



(74)

R = H, Me, Et, $PhCH_2$

The addition of anthranilic acid to 1,4-benzoquinones is interesting in that a recent study failed to agree with a number of earlier reports[100]. Only in the case of 2,3-dimethoxy-1,4-benzoquinone was the mono-addition product obtained and several previously reported reactions did not produce useful products. The observed reaction is the normal one shown in equation (75). Reaction with 2-methyl-1,4-benzoquinone did



(75)

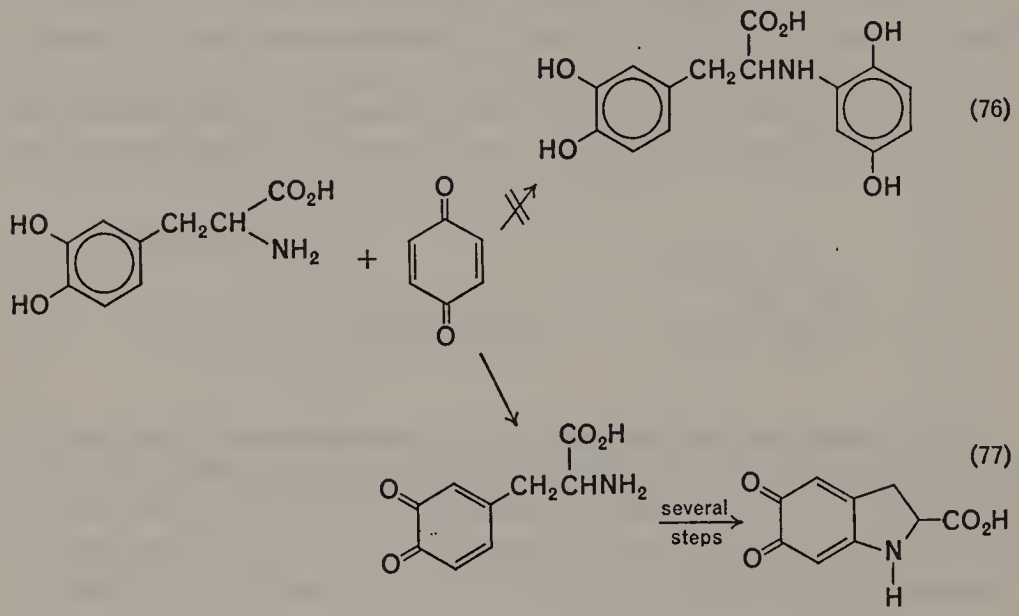
not give crystalline products, nor did *N*-ethylanthranilic acid. The example of 2,3-dimethoxy-1,4-benzoquinone is also limited in that neither the methyl ester nor the *N*-methyl derivative of anthranilic acid reacted. These observations deserve closer attention in view of the heterocyclic compounds for which they might serve as precursors and their relationship to the natural amino acids.

More recently, the important problem of model systems for the fixation of nitrogen in soils and the formation of humic acids has been studied polarographically[101]. Earlier studies suggested the formation of 2-hydroxy-1,4-benzoquinone as a key intermediate in aqueous-ammonia solutions. The experimental results of Lindbeck and Young make it clear that, depending on pH and ammonia concentration, 2-amino- and/or 2,5-diamino-1,4-benzoquinone must be considered significant intermediates in any proposed mechanism. The stability of organic nitrogen in soils has also been studied by examining the acid hydrolysis of quinone–α-aminoacid adducts[102]. The nature of these reactions led to the suggestion that such compounds play an important role in stability considerations.

Interest in the chemistry of amino acids and quinones continues and a recent report contained some important rate studies[103]. The optimum pH for the reaction of 1,4-benzoquinone and glycine was determined. A wide range of amino acids was studied and the rates of addition are

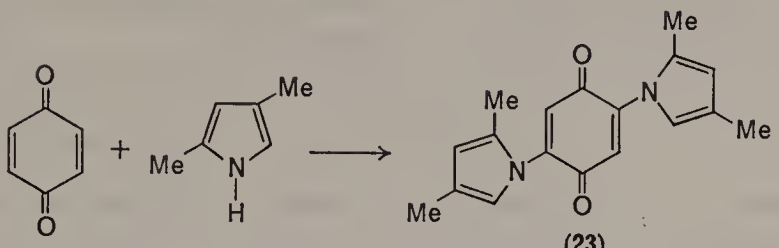
quite similar. However, the ability of the *N*-substituted quinone products to catalyse ascorbic acid oxidation varied with substituent.

Of particular significance to the future direction of the chemistry just described is the question of what actually happens to quinones and amino acids under physiological conditions. A first effort in this area has been made in the study of 3,4-dihydroxyphenylalanine (dopa)[104]. The rate of addition (equation 76) is not fast enough to be significant, but oxidation followed by intramolecular cyclization does occur (equation 77).



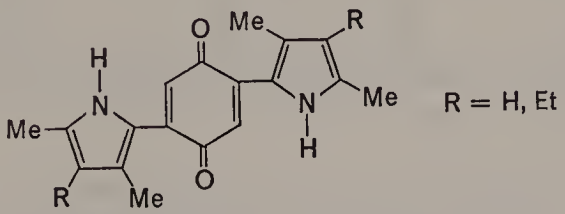
A more detailed synthetic study of the use of added inorganic oxidant for 2,5-diamino-1,4-benzoquinones further revealed the nature of the reaction[105]. The failure of the reaction with diisopropyamine is of significance and was explored to some extent. Other fairly bulky secondary amines produce quite good yields of product (e.g. di-*n*-propyl-, methyl-isopropyl- and benzylmethylamine). This steric hindrance is very clearly demonstrated in substitutions (see section VIII.B.1). The weakest base in the series, morpholine, gave the highest yield (96%). Finally, while 1,4-naphthoquinone gave an excellent yield of 2-(1-piperidyl)-1,4-naphthoquinone with piperidine, 1,2-naphthoquinone did not react.

The reaction of substituted pyrroles with 1,4-benzoquinones is especially interesting in that it leads to carbon–carbon bond formation! An early report suggested the expected nitrogen addition product (equation 78)[106]. A study of the i.r. spectra of the product thought to be **23**, and its 3-ethyl analogue, showed N—H vibrations that clearly indicate the bonding



(78)

(23)

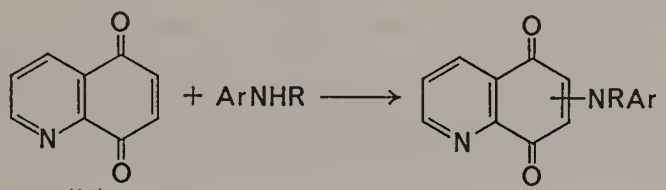


R = H, Et

(24)

cannot be with nitrogen[107]. The alternative structure, **24**, offers an explanation of the compound's colour and behaviour with acid. Finally, this understanding has been applied to provide a better picture of the important pyrrole–quinone dyes[108].

The two interesting research lines of substituent effects and added oxidants have received detailed attention in the chemistry of 5,8-quinoline-quinone (**25**)[109]. The addition of aniline to this quinone and its alkyl derivatives had been studied some years before[110]. Several substituted anilines were added to this quinone and the relative amounts of the 6- and 7-isomers determined (equation 79). As expected, the 6-isomer is the



(79)

(25)

Ar = 4-Me, 4-ClC$_6$H$_4$
R = H, Me

major product in all experiments. Table 5 shows the very significant improvement in yield obtained with cerous chloride as the oxygen carrier. While the yield should be higher with the quinone starting material not being used up as an oxidant, the change in several cases is greater than can be expected on this basis alone. An impressive example of this effect is the reaction of *p*-nitroaniline with 1,4-naphthoquinone, where the product yields are 1% and 81% in the absence and presence of cerous chloride (0·1 mole) respectively. Furthermore, the relative amount of

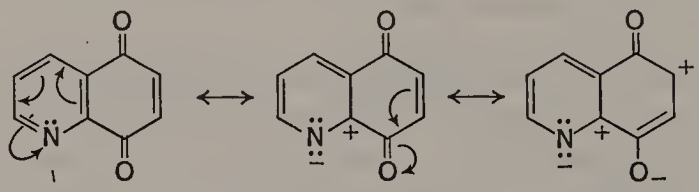
TABLE 5. Product distribution in the addition of anilines to 5,8-quinolinequinone (equation 79)[109]

Aniline	Yield, % (without $CeCl_3$)		Yield, % (with equivalent $CeCl_3$)	
	6-isomer	7-isomer	6-isomer	7-isomer
p-Toluidine	30	24	68	Trace
p-Chloroaniline	19	13	68	Trace
N-Methylaniline[a]	28	5	62	0

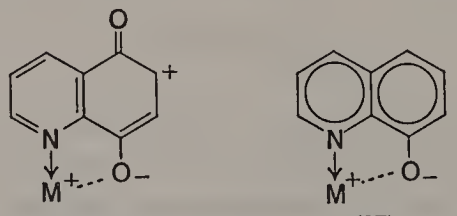
[a] Quinone : aniline = 1 : 10.

the 6-isomer increases dramatically in the presence of the metallic salt, suggesting that cerous chloride enhances the reactivity of the 6-position.

The observed isomer distributions with 5,8-quinolinequinone can be understood in terms of the 8-carbonyl group being bound to the α-position of the pyridine ring and hence more electron-deficient than the 5-carbonyl group in the β-position. The lower electron density is then transferred to



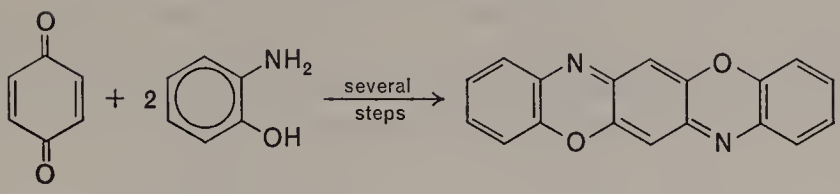
the 6,7-double bond as shown and leads to electron deficiency and observed preferential attack at the 6-carbon. The catalysis by the positive cerous ion is understood as involving structure **26**; its relationship to chelated 8-quinolinol (**27**) is noteworthy. Experiments dealing with the relationship between addition and substitution in this system are also discussed and will be treated later (see section VIII.B).



(26) **(27)**

A number of relatively limited studies involving the addition of amines to quinones have appeared in recent years.

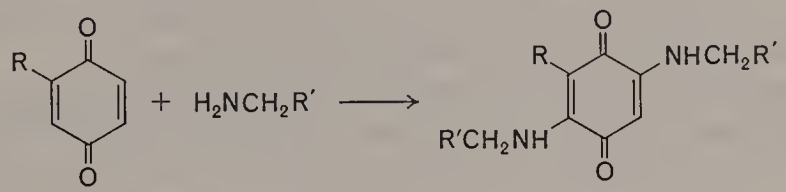
(1) Valuable heterocyclic systems can be prepared by condensing quinones with *o*-aminophenol (equation 80). The use of ^{13}C-labelled



(80)

1,4-benzoquinone allowed demonstration that the first step is addition of the amino group to the quinone ring rather than to the carbonyl group or cross-oxidation followed by condensation[111].

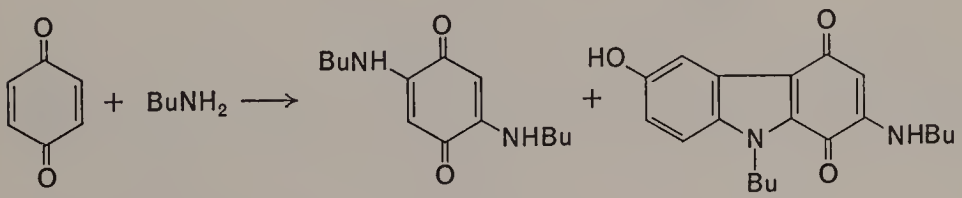
(2) Amino alcohols have been reported to add to quinones if care is taken to prevent polymerization (equation 81)[112]. More limited success was achieved with 2-methyl-1,4-benzoquinone and 1,4-naphthoquinone.



(81)

R = H, Me R′ = CH_2OH, CH_2CH_2OH, CH(Me)OH

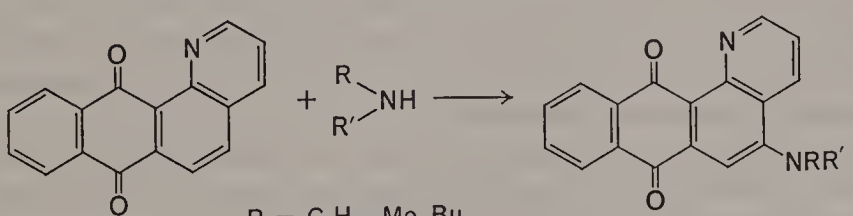
(3) An interesting new compound has recently been obtained from the addition of butylamine to 1,4-benzoquinone (equation 82)[113].



(82)

27% 8·6%

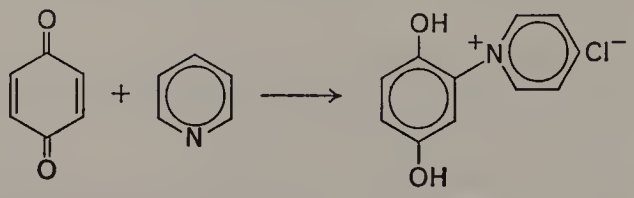
(4) For obvious reasons the anthraquinones do not usually undergo addition reactions of the type under discussion. An interesting exception was found in naphtho[2,3-*h*]quinoline-7,12-dione (equation 83)[114]. Thiophenol also added at the 5-carbon atom.



(83)

R = C_6H_{11}, Me, Bu
R′ = H, Me
R and R′ = $(CH_2CH_2)_2O$

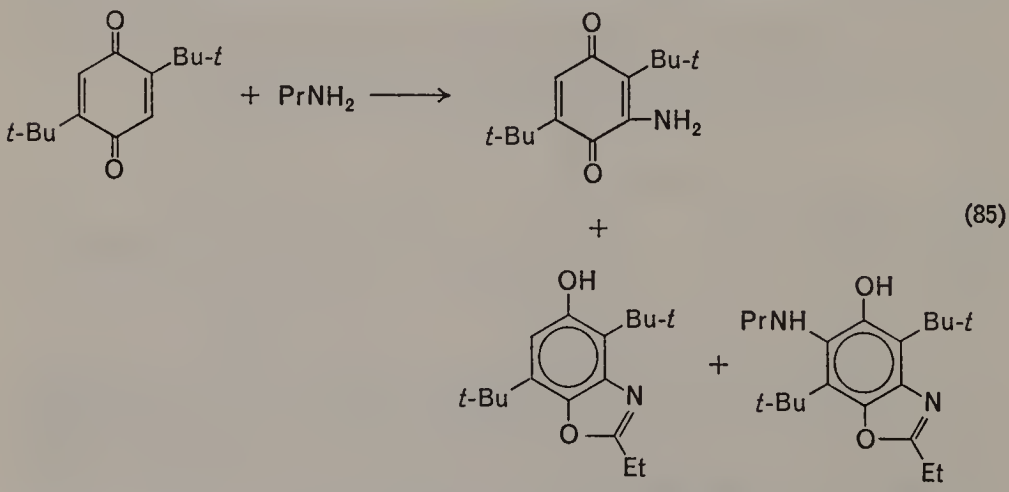
(5) The addition of pyridine to 1,4-benzoquinone leads to the pyridinium salt in moderate yield (equation 84)[115]. A variety of solvents is useful and a small amount of water seems to favour the reaction. The catalyst of choice is hexachlorocyclotriphosphazatriene.



(84)

(6) Methods have been worked out in which 1,4-benzoquinone is useful as a qualitative and quantitative chromatographic reagent for both primary and secondary amines, including amino acids. Applications in thin-layer[116] and paper[117] chromatography are presented.

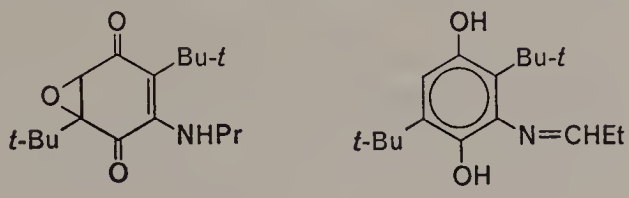
(7) The reaction between 2,5-di-*t*-butyl-1,4-benzoquinone and propylamine has been shown to lead to some unexpected products[118]. When the reaction is carried out in the dark, under nitrogen and with the amine as solvent, the products shown in equation (85) are found. Air was passed



(85)

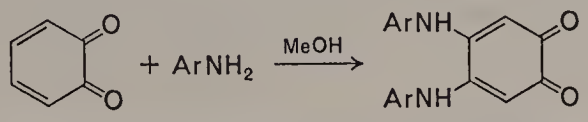
through the reaction just prior to work-up and a large amount of unreacted starting quinone was recovered. The same reaction carried out in the presence of air gave the products shown along with a 20% yield of the following epoxide. The enamine **28** was suggested as an intermediate in the anaerobic reaction (equation 85).

Because of the rather unstable nature of 1,2-benzoquinone the usual method for studying its chemistry is *in situ* oxidation or the nascent quinone technique (see section II.C.4). Recently an effort was made to verify the usefulness of this method by starting with the quinone itself[119].



(28)

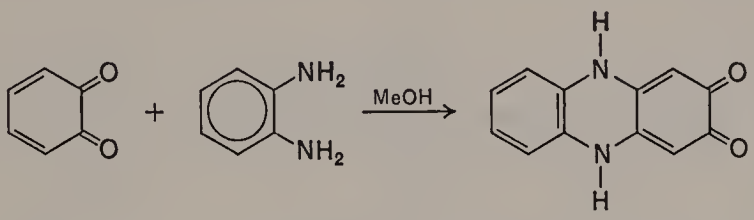
The reaction with various anilines gave the expected product (equation 86). No reaction was observed with 4-nitroaniline and *o*-phenylenediamine



(86)

Ar = 2-$AcOC_6H_4$, 4-$MeOC_6H_4$, 4-BrC_6H_4, 4-ClC_6H_4

gave cycloaddition (equation 87). The failure of this latter reaction to



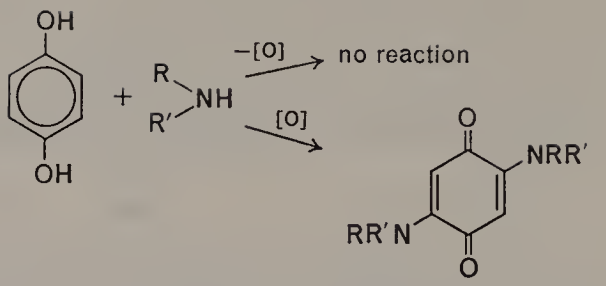
(87)

produce phenazine was attributed to the formation of hemiacetals by methanol and the quinone carbonyl groups. In ether solution phenazine was obtained, although in poor yield.

4. Nascent quinones

The idea of *in situ* preparation of quinones for nitrogen addition does not appear to have as long a history as in the case of sulphur. However, Harger observed in 1924 that hydroquinone reacted with a variety of primary and secondary amines only under aerobic conditions (equations 88 and 89)[120]. Even earlier Kehrmann and Cordone had shown that the oxidation of catechol in the presence of aniline leads to 4,5-dianilino-1,2-benzoquinone (equation 90)[75].

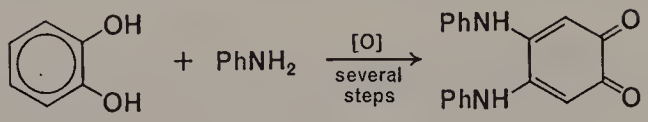
More recently, the addition of secondary amines to nascent quinones has been examined quite successfully[121]. The addition of dimethylamine and ethyleneimine produced reasonable yields of 4,5-disubstituted 1,2-benzoquinone product, but *N*-methylaniline gave an excellent yield of 4-*N*-methylanilino-1,2-benzoquinone.



(88)

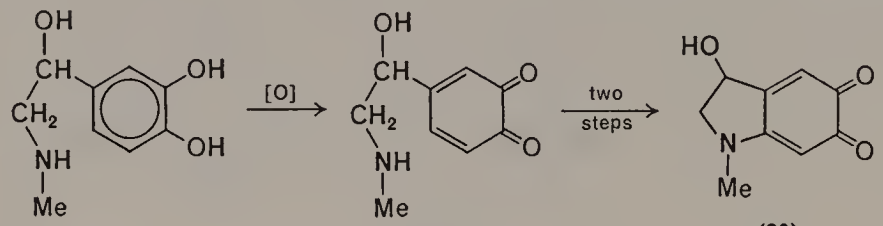
(89)

R or R′ = H, Me, Et, *i*-Bu, *s*-Bu, Am, allyl, $PhCH_2$



(90)

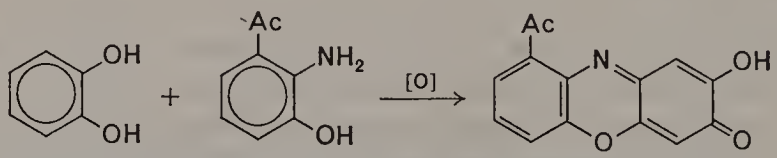
An interesting example of intramolecular addition of amines to quinones has been studied in the formation of adrenochrome (**30** in equation 91)[122]. The intermediate (**29**) can be detected in the early stages of the reaction[61].



(91)

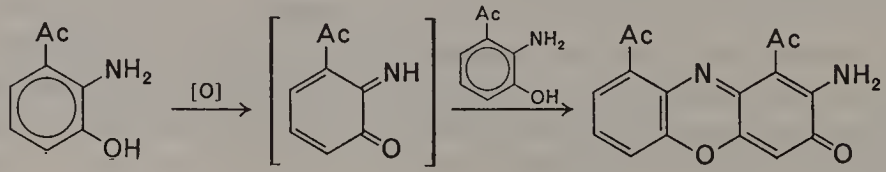
(29) (30)

A bifunctional reagent of the *o*-aminophenol type can undergo condensation with either catechol or itself under oxidative conditions. The former path has been important in the study of insect pigments and leads to 2-hydroxy-3-phenoxazones (equation 92)[123]. The latter leads to 2-amino-



(92)

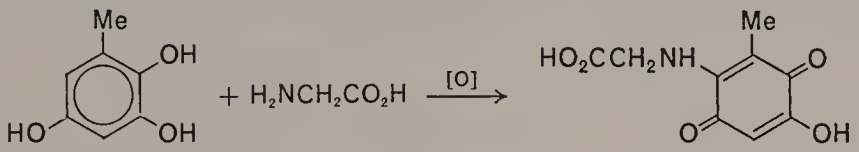
3-phenoxazones (equation 93) and has been important in several natural product syntheses[124]. The earlier literature of this field has been reviewed[125].



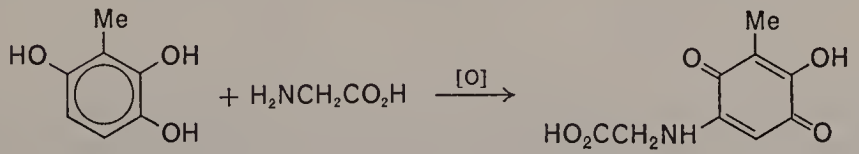
(93)

An effort has been made to evaluate the reactivity of protein towards nascent quinones[126]. Of the compounds studied, 3-*n*-pentadecyl-1,2-benzoquinone, formed by silver oxide oxidation, was found most reactive toward γ-globulin, bovine fraction II. The three isomeric methyl derivatives of this quinone were only slightly less reactive, while the 4,5-dimethyl and 4,5,6-trimethyl derivatives were completely unreactive.

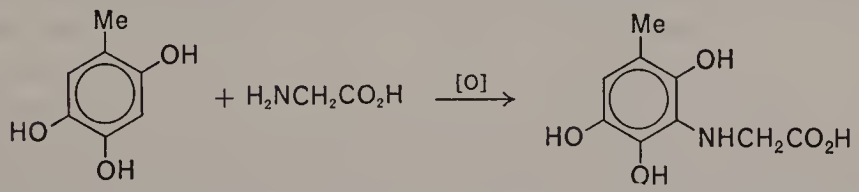
In a related study, conducted polarographically, glycine was allowed to react with the quinones that result from the oxidation of 2,3,5-, 2,3,6- and 2,4,5-trihydroxytoluene[127]. The pattern of addition and subsequent reaction was shown to be influenced rather strongly by the substitution in the starting material (equations 94–96).



(94)

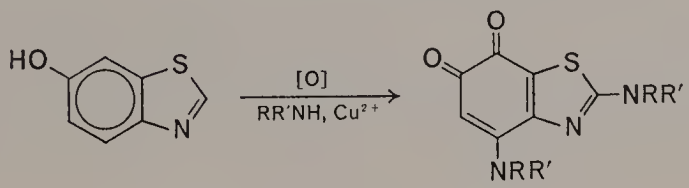


(95)



(96)

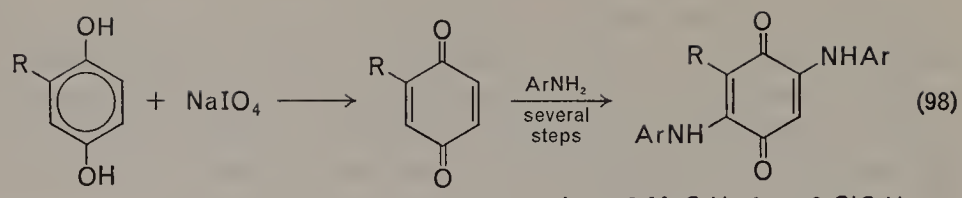
A very unusual and interesting modification of the nascent quinone route involves the oxidation of 6-hydroxybenzothiazole followed by amine addition and re-oxidation (equation 97)[128]. Clearly, a great many questions remain to be answered about these reactions.



(97)

R, R' = Me, C_5H_{10}, $(CH_2CH_2)_2O$

The experiments described earlier involving an added oxidant are, of course, examples of nascent quinone syntheses[94, 95, 97, 105, 109]. Recently, sodium periodate has been found to be an excellent reagent for such reactions (equation 98)[129]. Yields of 80–90% were found.



(98)

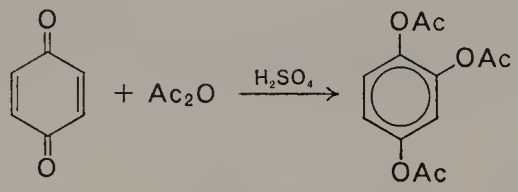
R = Ac, CO_2Me, Me, Br, $CONMe_2$

Ar = 2-MeC_6H_4, 2- or 3-ClC_6H_4, 4-$MeOC_6H_4$, 3-pyridyl

D. Thiele Acetylation

1. Historical introduction

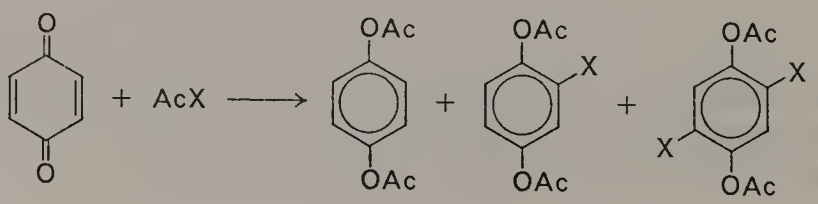
The treatment of quinones with acetic anhydride under acidic conditions produces a combination of addition and esterification (equation 99)[130].



(99)

The reaction has been very widely used for the synthesis of new quinones and hydroquinones, the proof of structure of quinonoid materials, and to facilitate the isolation and purification of natural products. The reaction is usually known as the Thiele acetylation. Our interest is chiefly concerned with mechanistic questions and because of the simplicity and generality of the reaction a reasonably clear picture has been formed. This state of affairs is very fortunate because the Thiele reaction, while properly considered electrophilic, is closely related to the reductive, nucleophilic reactions of quinones. Why the acetylium ion and monosubstituted 1,4-benzoquinones lead to a product orientation predicted by nucleophilic considerations deserves some serious study.

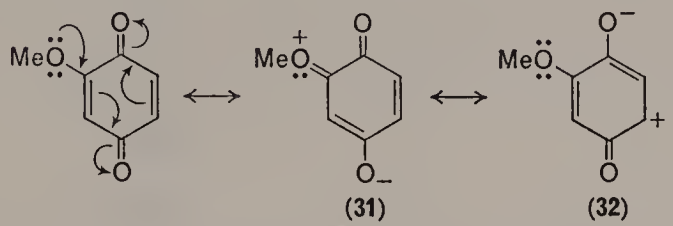
A reaction closely related to the Thiele acetylation is that of quinones with carboxylic acid halides. The reaction was observed and reported long before Thiele's first publication (equation 100)[131,132]. It was recognized that both mono- and dihalogenated hydroquinone diacetates are formed, although the proposed sequence of steps does not appear to be correct in view of later studies.

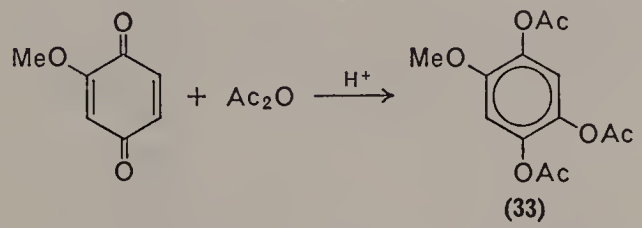


(100)

2. Mechanistic studies

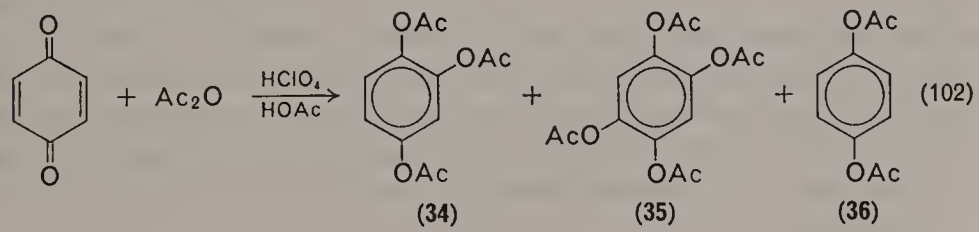
The mechanistic study of the Thiele reaction began very early in the development of physical organic chemistry. In an effort to apply the new electronic theory to quinonoid systems, Erdtman presented the relative reactivities and product orientation for several alkyl- and methoxyl-substituted 1,4-benzoquinones[133]. His general observations and conclusions for electron-donating substituents have been verified in later studies. For example, 2-methoxy-1,4-benzoquinone would be expected to have structures **31** and **32** as principal resonance contributors and thus to react as indicated in equation (101). In fact, 2,4,5-triacetoxyanisole (**33**) is obtained in quantitative yield under very mild conditions.





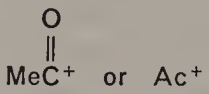
(101)

A series of papers giving a kinetic picture of the Thiele acetylation of 1,4-benzoquinone and 2-methyl-1,4-benzoquinone has appeared[134]. From these studies it is clear that the mechanism of the reaction is more complicated than that employed by Erdtman, although he suggested that this was likely to be the case. The limitations of the earlier proposal are obvious from the change in products with the composition of the reaction medium. In nearly pure acetic anhydride the 1,2,4-triacetoxybenzene (**34**) obtained by Thiele is the sole product, but in 50 vol. % acetic acid : acetic anhydride, two additional significant products (**35** and **36**) are found (equation 102). These additional products, the kinetics, the



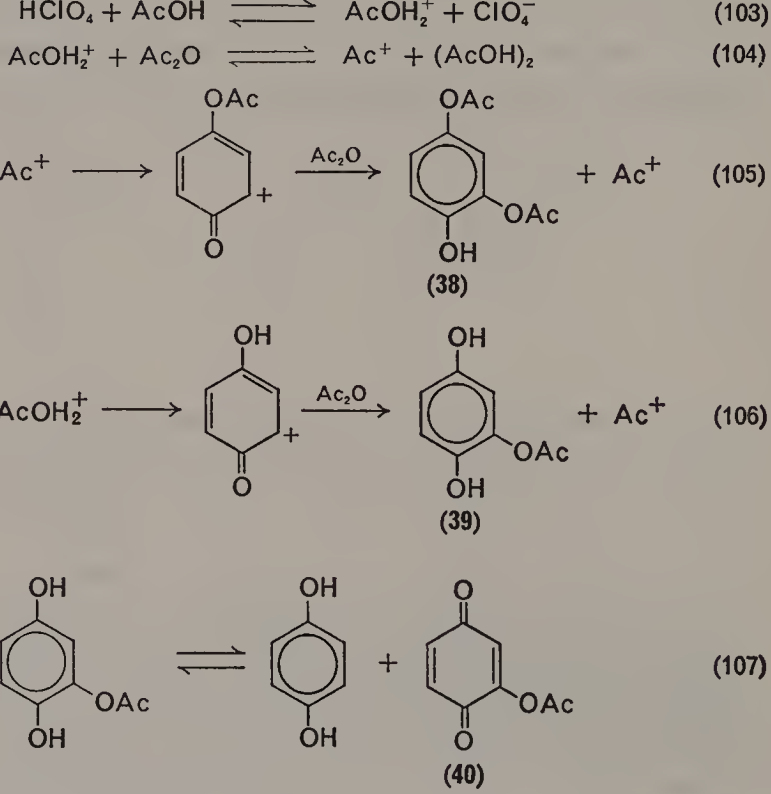
(102)

thermodynamics and the behaviour of the solvent system all contribute evidence for the presence of the acetylium ion **37**.

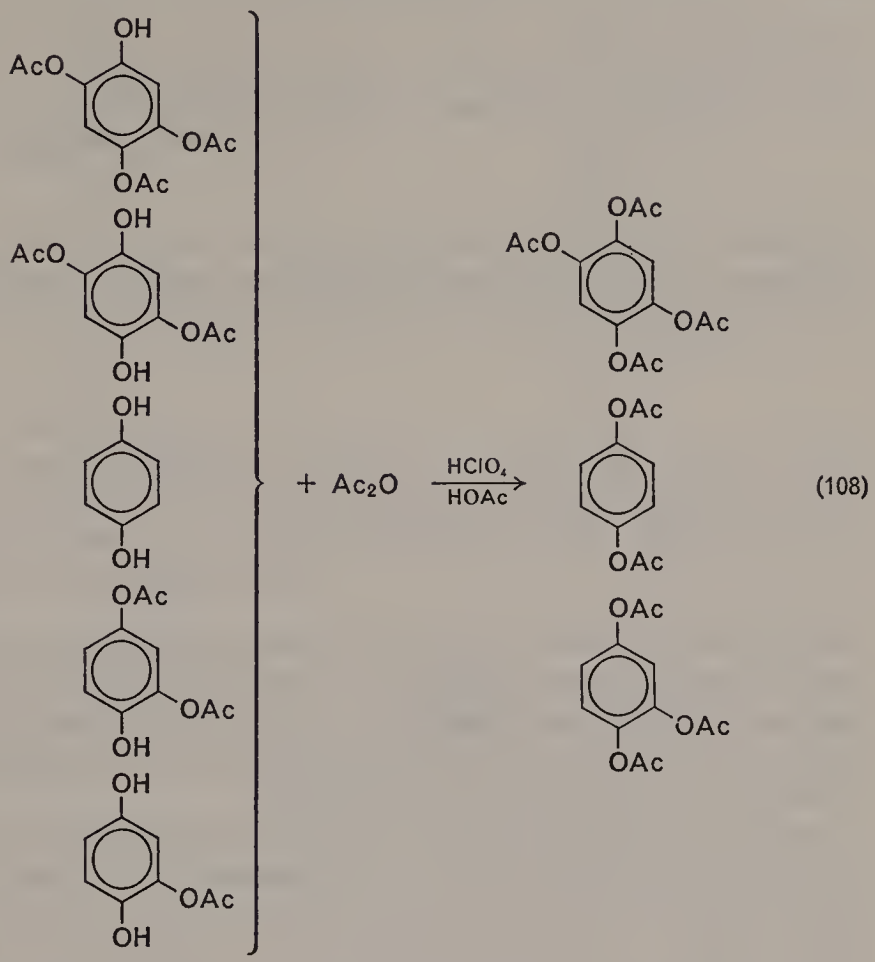


(37)

The suggested mechanism (equations 103–107) is capable of accounting for all of these observations. The quinonoid cross-oxidation product **40**



can now react similarly to the original quinone. When the initial products of this second generation Thiele acetylation (hydroquinone, **38** and **39**) have all hydroxyl groups acetylated, the observed products are obtained (equation 108). An analogous, but somewhat more complicated, scheme was worked out for the Thiele acetylation of 2-methyl-1,4-benzoquinone. The presence of any significant concentration of 2-acetoxyhydroquinone in the reaction mixture has been questioned[135]. Burton and Praill do not offer any explanation for the presence of 1,2,4,5-tetraacetoxybenzene (**35**) and 1,4-diacetoxybenzene (**36**). The observation of analogous multiple addition products in other very rapid reactions (see sections II.B and II.C) suggests that the cross-oxidation reaction is able to compete, even with aggressive reagents.

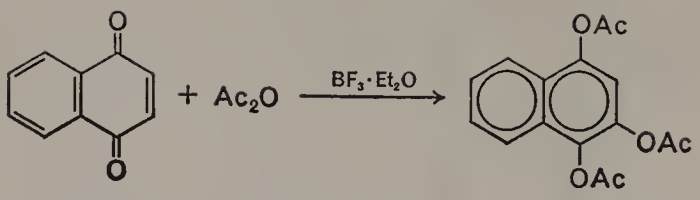


(108)

A rather detailed theoretical treatment of the reactivity of quinones has been published[136]. Standard methods of calculating localization energies were employed and the influence of both resonance and Coulomb integrals was evaluated. The agreement between prediction and observed experimental results is quite good, but many more data are needed. The discussion of various examples of addition mechanisms is excellent and especially informative in the case of the Thiele acetylation.

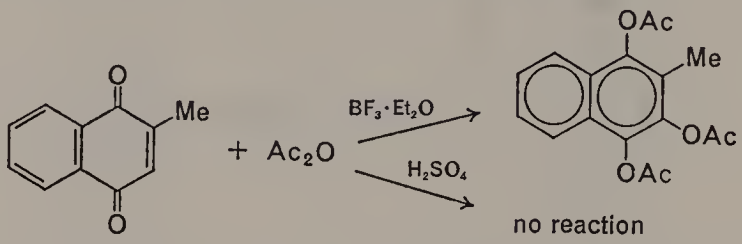
3. Synthetic survey

In the past 25 years the synthetic literature of the Thiele acetylation has provided a good preparative route to hydroxyquinones and a number of isolated, but intriguing reactions. As one aspect of an enormous synthetic study of potential antimalarial drugs, Fieser and his collaborators introduced the use of boron trifluoride etherate as the acidic catalyst (equation 109)[137–139]. The Thiele acetylation of naphthoquinone, using



(109)

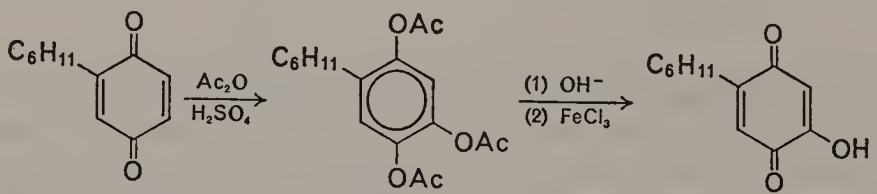
sulphuric acid, had been successfully carried out by Thiele himself[140]. Of greater interest is the ability of BF_3 to catalyse the acetylation of 2-methyl-1,4-naphthoquinone (equation 110); with sulphuric acid the



(110)

reaction does not occur[141]. It has also been shown that perchloric acid, used earlier for kinetic studies, is a very fine catalyst for preparative applications. Burton and Praill go so far as to claim: 'there appears little doubt that for preparative purposes perchloric acid is probably the most efficient catalyst for the Thiele acetylation'[142].

McLamore applied the Thiele acetylation with sulphuric acid to the synthesis of hydroxy alkyl-1,4-benzoquinones (e.g. equation 111)[143].

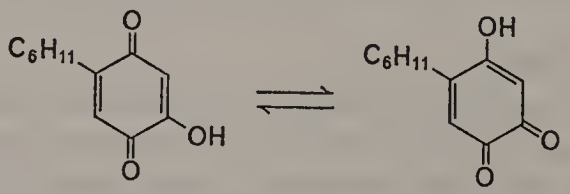


(111)

C_6H_{11} = cyclohexyl

(41)

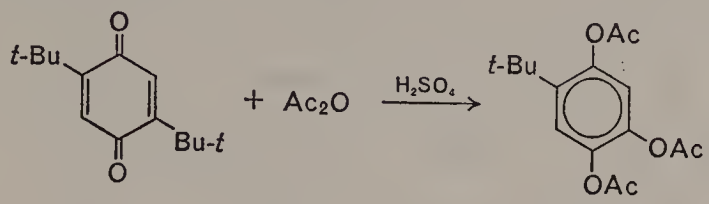
The structure of the product **41** was demonstrated by two independent syntheses, but the question of tautomerism (equation 112) was not treated.



(112)

The use of BF_3 was not reported in this study and comparison is made with the 2-alkylnaphthoquinones that are said not to undergo the Thiele reaction: nevertheless, some hindered benzoquinones were acetylated.

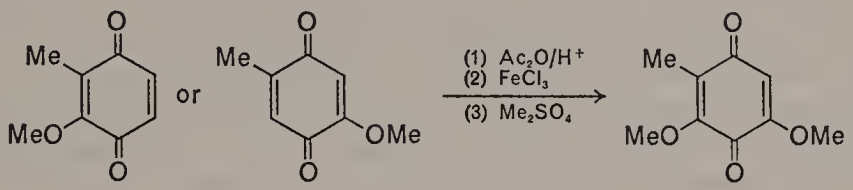
The most interesting of the reactions is that of 2,5-di-*t*-butyl-1,4-benzoquinone (equation 113). The structure of product **42** was simply deduced from the elemental analysis, but it is reminiscent of some nitrogen dealkylations (see section VIII.B).



(113)

(42)

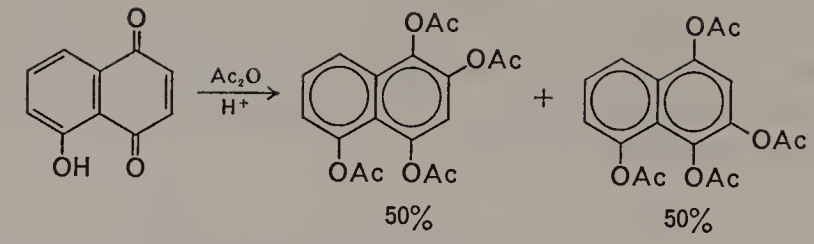
The Thiele reaction has been used in conjunction with dimethyl sulphate for the synthesis of methoxy quinones[85]. Both 2-methyl-3-methoxy- and 2-methyl-5-methoxy-1,4-benzoquinone react to produce the same product (equation 114).



(114)

The structure of the antibiotic gonyleptidine, and associated minor companions, was demonstrated in part, using the Thiele reaction[38]. From several lines of evidence, gonyleptidine proved to be chiefly 2,3-dimethyl-1,4-benzoquinone accompanied by smaller amounts of 2,5-dimethyl- and 2,3,5-trimethyl-1,4-benzoquinone. As expected, the 2,3-dimethyl isomer underwent the Thiele reaction very rapidly and nearly quantitatively, while the 2,3,5-trimethyl homologue was recovered from the reaction mixture unchanged. Fieser was interested in the fact that 2,5-dimethyl-1,4-benzoquinone, unlike 2,5-dimethoxy-1,4-benzoquinone, produces a very high yield of 1,3,4-triacetoxy-2,5-dimethylbenzene with BF_3 as the catalyst. It was known from earlier work that sulphuric acid produces an even higher yield of product.

The large number of studies and the variety of applications of the Thiele acetylation have provided a good deal of understanding of the scope and mechanism of the reaction. However, the same studies have provided a number of conflicting reports; for example, regarding the question of orientation in unsymmetrically substituted quinones. In 1967 only two examples of more than one isomeric product had been reported (equations 115 and 116)[96,133]. Questions of the most suitable catalyst,



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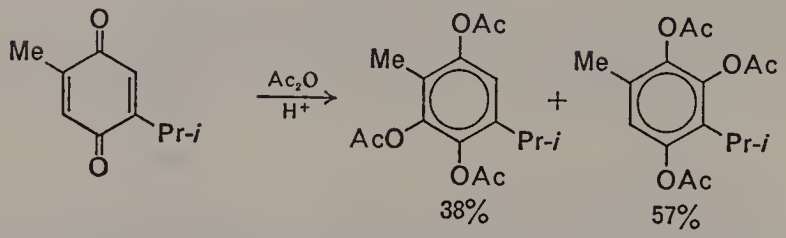


(116)

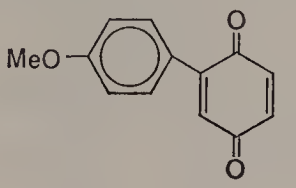
optimum yields and conflicting reports of 'unreactive' quinones led Wilgus and Gates to summarize the literature and attempt some definitive experiments[144].

Probably the most significant result of this study was the extension of the Thiele reaction to quinones having electron-withdrawing substituents. Both 2-acetyl- and 2-carbomethoxy-1,4-benzoquinone gave only the 1,3,4-triacetoxy product: the latter in poor yield. Only 2-(4′-nitrophenyl)-1,4-benzoquinone gave significant amounts of all three isomeric products. The minor isomeric product was isolated in the cases of 2-methyl- and 2-phenyl-1,4-benzoquinone and the yields determined. In general, the orientation pattern as a function of quinone substituent shown in Table 6 is similar to that found in thiol addition (see section II.B.2). The isomer distribution does not appear to be strongly influenced by the catalyst

Table 6. Isomeric yields for the Thiele reaction of monosubstituted 1,4-benzoquinones[144]

Substituent	Acetoxy group position (%)			Catalyst
	3	5	6	
Ac	92			H_2SO_4
Ac	78			BF_3
CO_2Me	34			H_2SO_4
Me		78	15	H_2SO_4
Me		89	11	BF_3
4′-$NO_2C_6H_4$	18	56	19	H_2SO_4
4′-MeO-3′,5′-$Cl_2C_6H_2$		65	35	H_2SO_4
Ph	21	52		H_2SO_4
Ph	31	62		BF_3

employed (perchloric acid was not examined), but the overall yields and ease of isolation are probably improved with $BF_3 \cdot Et_2O$. It is very likely that the milder the catalyst the better; however, note the complete failure of the reaction with 2-(4′-methoxyphenyl)-1,4-benzoquinone (see also reference 145) and the outstanding success with 2-(4′-methoxy-3′,5′-dichlorophenyl)-1,4-benzoquinone (equations 117 and 118). It seems clear that competing Friedel–Crafts reactions are important.



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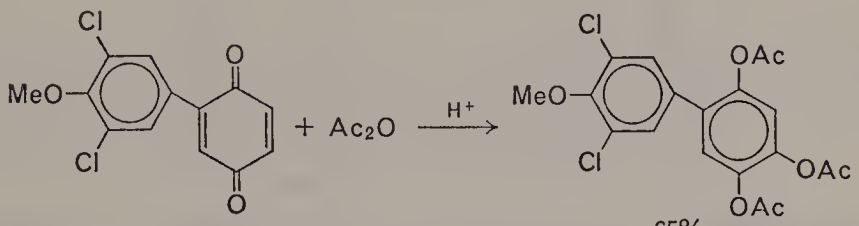

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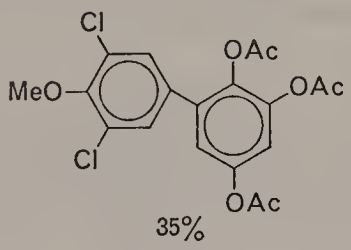
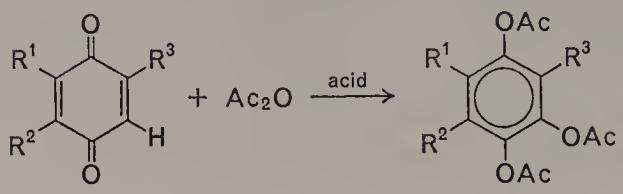


The scope of the Thiele reaction is still under active investigation with much emphasis on halo- and alkoxyquinones (equation 119). It was found sometime ago that 2,6-dichloro- and 2-bromo-3,5-dimethoxy-1,4-benzoquinone fail to undergo the Thiele acetylation. Recently, detailed studies of the Thiele acetylation of haloquinones produced the results in Table 7[146]. It is apparent that steric effects are important and may overbalance the activating electronic effect of the electron-withdrawing substituent.

The strong electronic deactivating influence of the methoxy group makes it an interesting substituent for detailed study. The earlier reports that 2,5- and 2,6-dimethoxy-1,4-benzoquinone fail to react with acetic anhydride in the presence of sulphuric acid have been confirmed[147]. The more powerful catalyst, perchloric acid, also fails to cause either these two compounds or 2,3,5-trimethoxy-1,4-benzoquinone to undergo Thiele acetylation. The

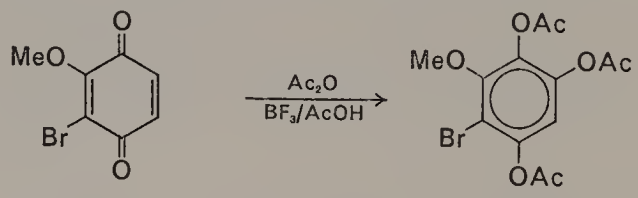
TABLE 7. Thiele acetylation of various halo-1,4-benzoquinones[146]



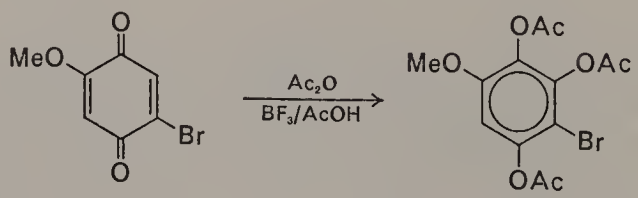
(119)

Substituent(s)			Yield (%)	
R^1	R^2	R^3	BF_3	$HClO_4$
Br	H	H	42	28
I	H	H	35	—
Cl	H	Cl	60	60
Br	Br	H	47	—
Br	H	Br	33	40
H	Br	Br	49	12
I	H	I	10	23
Br	Br	Br	4	0

various combinations of bromo and methoxy groups and their effect on the Thiele reaction sheds some light on the general mechanistic picture (equations 120–122). The six trisubstituted (bromo, methoxy) 1,4-benzo-



(120)



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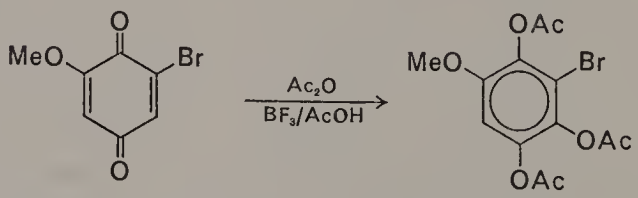
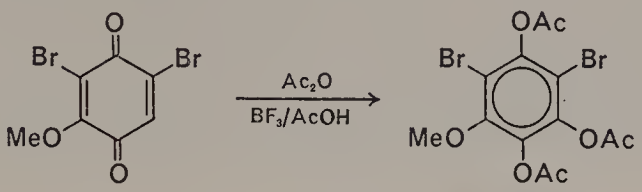


(122)

quinones were also prepared and subjected to Thiele conditions. Only the two shown in equations (123) and (124) underwent reductive acetylation. The other four compounds also failed to react with perchloric acid as the catalyst. This evidence seems to confirm completely the hypothesis that

Thiele acetylation, and presumably the other nucleophilic quinone addition reactions, does not occur *ortho* to an alkoxy group (for an extreme case resulting in an exception, see section V.A).



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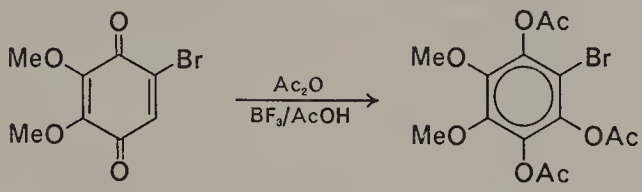
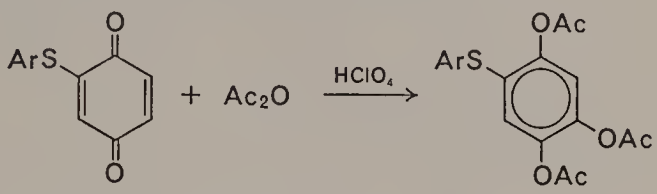


(124)

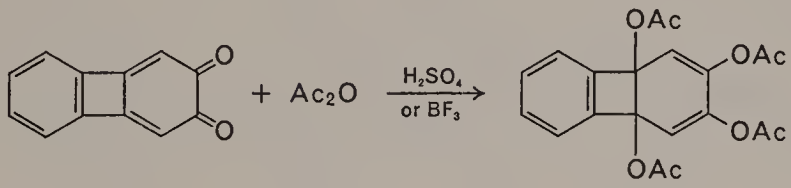
One study of the analogous alkylthio groups has been made and only starting material or resinous product was found[148]. However, the arylthio groups did lead to the expected triacetates (equation 125).



(125)

Ar = Ph, 4-MeC_6H_4 and 4-ClC_6H_4

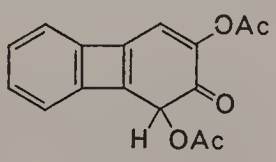
Very little has been written about the Thiele acetylation of 1,2-quinones. An exceptional case and an unexpected product have been reported for a biphenylene quinone[149]. The structure of the tetraacetate, **43**, is supported by chemical and physical data. This unusual structure is rationalized on



(126)

(43)

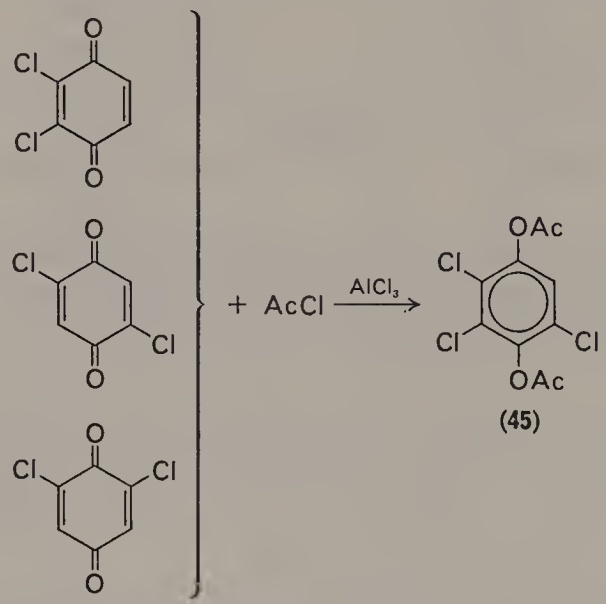
the basis that normal Thiele acetylation would have to involve an intermediate like **44** with an unstable benzocyclobutadiene structure.



(44)

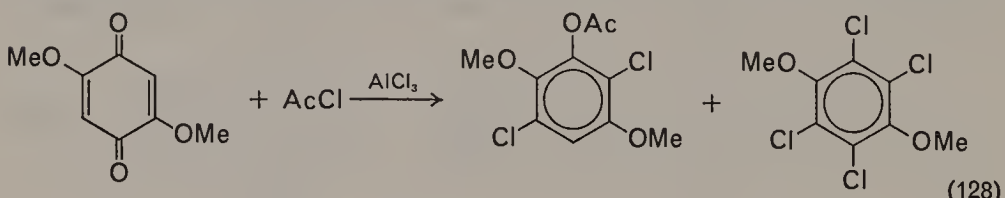
4. Reactions of acetyl halides

This reaction, which bears some resemblance to the Thiele acetylation, does not appear to be very general since the dimethoxy- and dichloro-1,4-benzoquinones fail to react with acetyl chloride, even on boiling[150]. When aluminium chloride is added, in much greater than catalytic amount, the three dichloro isomers studied do react (equation 127). The three reactions lead to a common, but non-Thiele product (**45**). Similar reactions



(45) (127)

of 2,5-dimethoxy- and 2,5-diethoxy-1,4-benzoquinone lead to products even further removed from simple addition (equations 128 and 129)[151,152].



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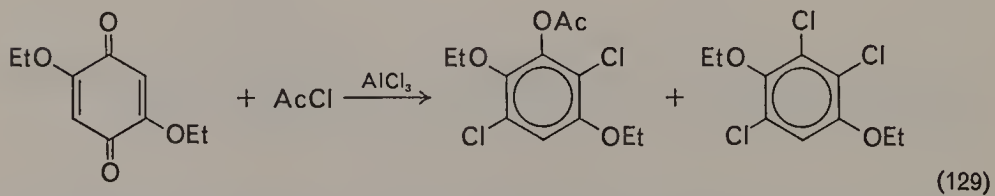
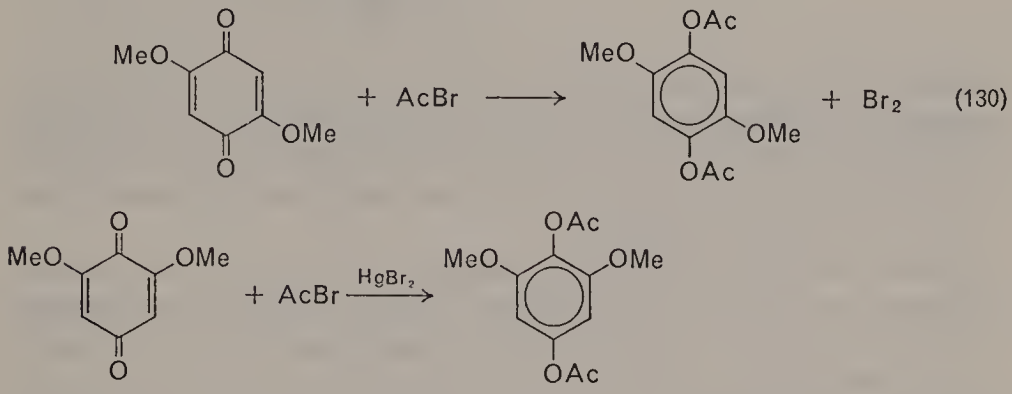
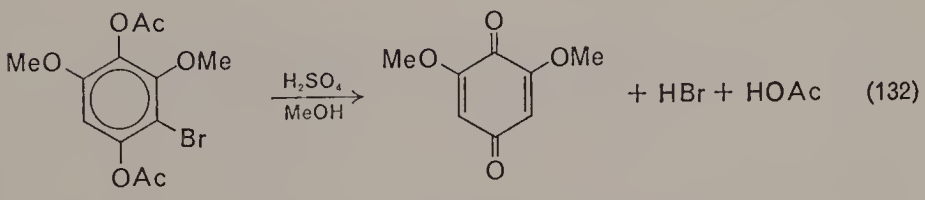


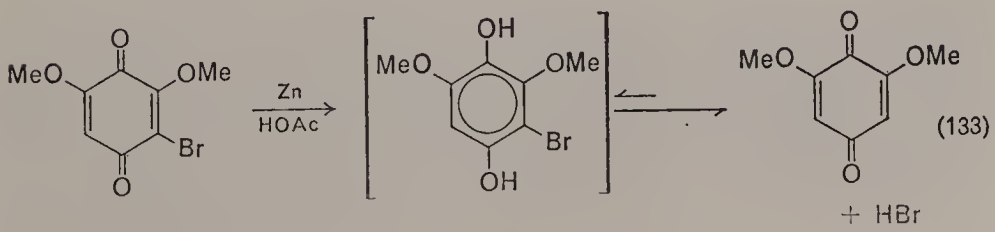
(129)

No reaction was observed with 2,6-dimethoxy-1,4-benzoquinone. Thiele himself used the Lewis acid zinc chloride to a limited extent, but this has been shown to be a poor synthetic system by later workers.

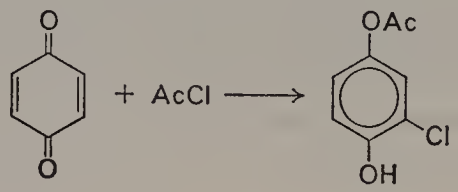
Quinones with certain substituents can undergo reversible addition reactions and an investigation of this process bears on the mechanism of the reactions of quinones and acid halides. Asp and Lindberg were able to verify nearly all the observations of Oliverio and collaborator[150,151], and they extended the study to the reactions of acetyl bromide (equations 130 and 131)[153]. When the hydrolysis of the monobromo addition product **46** was attempted, it lost hydrogen bromide and regenerated the starting quinone (equation 132). The expected 3-bromo-2,6-dimethoxyhydroquinone could be obtained in ether solution (equation 133) but decomposed when concentration under reduced pressure was attempted.







In an effort to find a more useful preparative route to the haloquinones, Cason and collaborators found some very significant facts concerning the addition of acetyl chloride[154]. They reasoned that simple addition, leading to 2-chloro-4-acetoxyphenol (**47**), might be observed under carefully controlled conditions (equation 134). Such a reaction should not lead to a

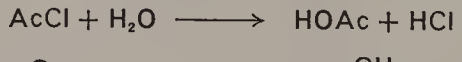


(134)

(47)

dichloro product and thus represents an ideal route to pure monochloroquinones or hydroquinones. Actually, with purified acetyl chloride and dry equipment, no reaction took place. Upon addition of a small amount of acetic acid, a vigorous reaction took place and formed the usual mixture of mono- and dichloro products.

Cason's conclusion, that the simple addition of hydrogen chloride and subsequent acetylation is the probable reaction mechanism, has received substantial support[155]. The products originally described by Schulz[132] were verified (equation 100) as was the extremely slow rate under anhydrous conditions. The suggested mechanism is shown in equations (135) through (138); followed by the acetylation of the phenolic products (**48–50**). Additional evidence for this hypothesis includes: (1) The isolation of 2-chlorohydroquinone under certain conditions, and (2) The chlorine content of the mixed products corresponds to that calculated for a quantitative yield of monochloro product. The mechanism for reaction-



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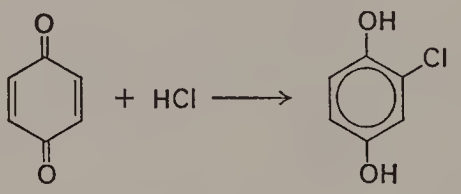
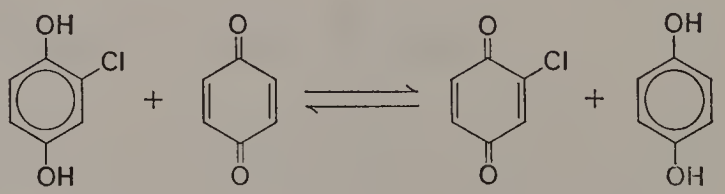


(136)

(48)



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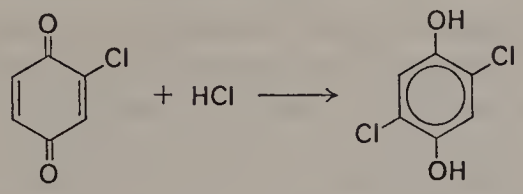


(138)

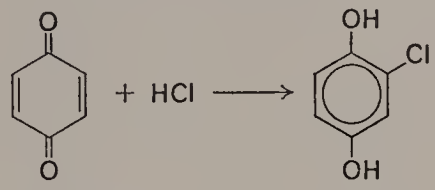
(50)

with 2-methyl-1,4-benzoquinone is probably similar, but the role of the acid is clouded by the observation of a different isomeric product with water from that found earlier with zinc chloride.

E. Addition of Inorganic Substances

1. Halogen and hydrogen halides

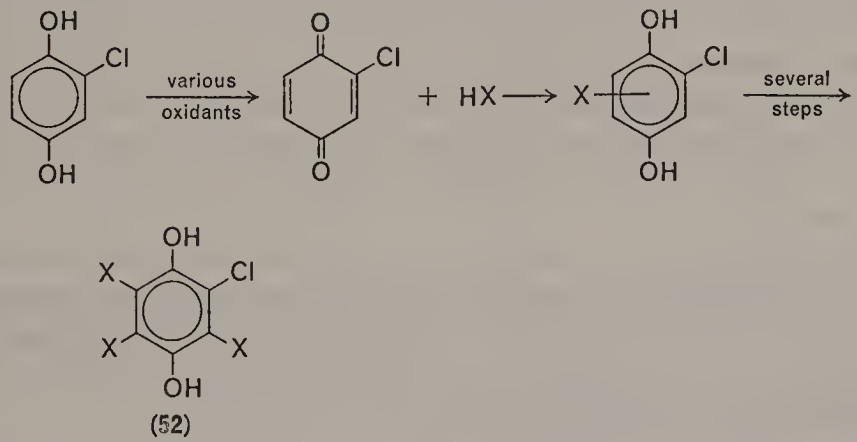
a. Historical introduction. Interest in the interaction of hydrochloric acid and 1,4-benzoquinone (equation 139) dates from the very beginning of modern organic chemistry[1]. A later and thorough synthetic study



(139)

(51)

showed that the initial reductive addition product **51** could be oxidized and subjected to successive additions of either HCl or HBr (equation 140)

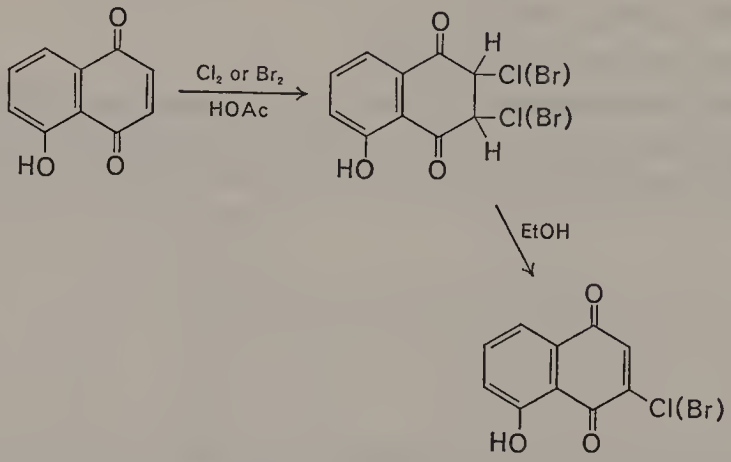


(140)

(52)

to produce eventually the tetrahalo-1,4-benzoquinone (**52**); for example, chloranil (X = Cl). Levy and Schultz also attempted the reductive addition of HF, HI and HCN to 1,4-benzoquinone[156]. Hydrogen iodide in chloroform solution caused the reduction of the quinone to hydroquinone; hydrogen fluoride and hydrogen cyanide in the same solvent produced no identifiable addition products.

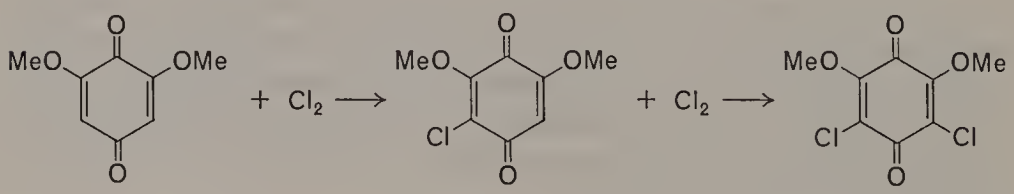
A substantial number of papers concerned with the synthesis of halogenated quinones appeared in the late 19th century and the results have been carefully reviewed[157–164]. During the first half of the 20th century little of synthetic significance was achieved, although there were reports (some conflicting) of the application of these reactions for the preparation of specific halogenated quinones[165–168]. One exception to this undistinguished record comes from the field of natural products. Thomson showed that juglone can be halogenated, followed by dehydrohalogenation to produce 3-halojuglone (equation 141)[169]. One should be warned of a



(141)

number of earlier papers where this reaction was said to lead to the 2-halojuglones[170]. The dihalojuglones can be obtained by treating the 3-halo compounds with additional halogen in acetic acid. When juglone acetate is halogenated and then treated with anhydrous sodium acetate, the 2-halojuglone product is obtained[42]. These substituent effects are clearly related to those described for thiols and anilines (see sections II.B.3 and C.3).

When this route was attempted on 2-methyl-5-hydroxy-1,4-naphthoquinone (plumbagin) the reactions were slow and produced mixtures[96]. On the other hand, Huisman has used the direct halogenation of substituted 1,4-benzoquinones for the preparation of useful synthetic intermediates (for example, equation 142)[171].

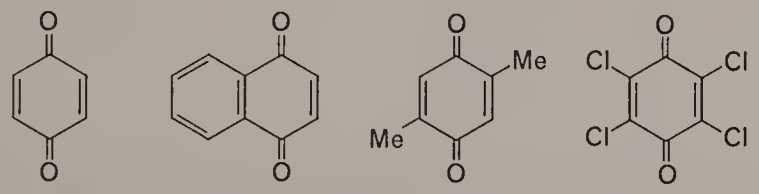


(142)

The varying reports and uncertain results led Cason and his students to make a careful study of the synthesis and especially the isolation and purification of chlorinated 1,4-benzoquinones[154]. The study included 2-methyl-1,4-benzoquinone and its 3-, 5- and 6-chloro derivatives (the latter with HBr or HCl) as well as 1,4-benzoquinone. With the exception of the preparation of 5-chloro-2-methyl-1,4-benzoquinone reported previously[172], the direct addition of hydrogen halides proved to be an entirely unacceptable method for obtaining pure haloquinones.

b. Mechanistic studies. Like the synthetic studies, mechanistic work on the quinone–hydrogen chloride reaction began very early. Clark suggested a mechanism that seems unnecessarily complicated[173] and Michael argued against 2-halohydroquinone as the initial product[174]. The troublesome presence of higher halogenated quinone products makes simple reductive 1,4-addition followed by a cross-oxidation equilibrium attractive. A rather detailed study of the kinetics of HCl addition in methanol is also convincing evidence for the current mechanism[175].

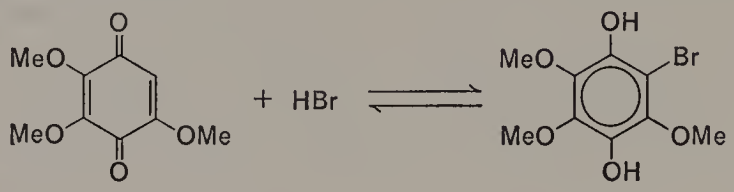
The kinetics of the addition of bromine to 1,4-quinones have been described and the not unexpected very slow electrophilic and very fast acid-catalysed reactions were found[176]. For example, 2-methyl-5-isopropyl-1,4-benzoquinone shows the following rate values in acetic acid: $k(\text{NaOAc}) < 0{\cdot}01$, $k(H_2SO_4)$ ca. 100. The rate of the second addition of bromine is extremely slow, even in the presence of sulphuric acid ($k < 5 \times 10^{-4}$). The following comparative rates (with added H_2SO_4) for various quinones were given:



All of these rate data were rationalized on the basis of significant resonance contributors to the quinone nucleus.

The interesting anomalous behaviour of certain methoxy quinones has been mentioned before (see section II.D.3). Neither 2,5- nor 2,6-dimethoxy-1,4-benzoquinone is reactive toward hydrogen chloride or bromide[153]. However, once prepared indirectly, the 2-halo-3,6-dimethoxyhydroquinones are quite stable, while the 3,5-dimethoxy isomers decompose readily[177]. In an effort to understand this strange effect, Lindberg studied the reaction of hydrogen bromide with 2,3,5-trimethoxy-1,4-benzoquinone[178]. He found what appears to be the first example of a reversible

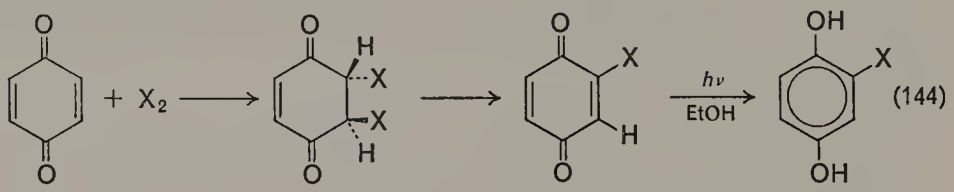
hydrogen halide addition to a quinone (equation 143). The product **53** is formed and can be converted to a diacetate known from independent synthesis. The chlorinated monomethoxy-1,4-benzoquinones are also known to be sensitive[179].



(143)

(53)

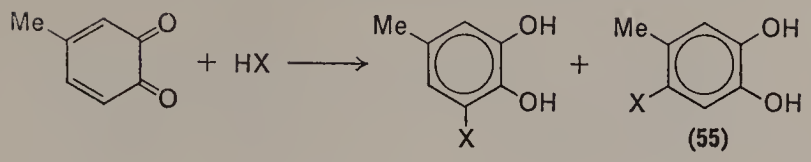
There has been some conflict in the literature concerning the configuration of the dichloride produced by addition of chlorine to 1,4-benzoquinone[180,181]. In the most recent study of this particular question, the spectral evidence earlier employed to suggest a *cis* product that isomerizes to the *trans* product was re-examined[182]. It was possible to isolate and characterize the intermediate and end products of the reactions of dichlorides that occur in alcohol. On the basis of this evidence it has been concluded that only the *trans*-dichloride (or dibromide) is formed in these additions, but elimination to the monohaloquinone can occur. This is then followed by photochemical reduction to the observed monohalohydroquinone (equation 144).



(144)

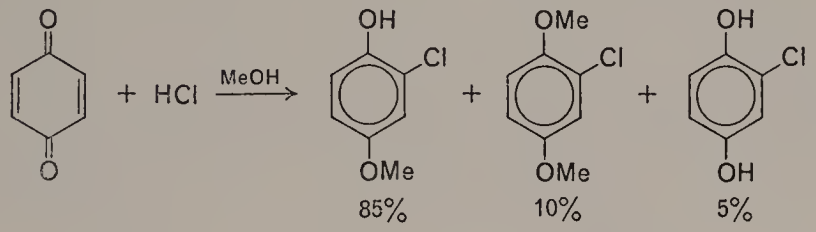
If there were any doubts concerning the detailed mechanism of hydrogen chloride addition to quinonoid systems, they were put to rest by the recent elegant kinetic study of Adams, Hawley and Feldberg[87]. Using chronoamperometry, cyclic voltammetry and chronopotentiometry it was possible to show that the addition of HCl to 4-methyl-1,2-benzoquinone (generated electrochemically) is dependent on both the rate of addition and the equilibrium constant for the subsequent cross-oxidation.

This same *ortho* quinone was the substrate for a study with HCl or HBr in a series of solvents[183]. A combination of thin-layer chromatography and u.v.–visible spectroscopy allowed the determination of the amounts of the two isomeric products (equation 145). An excellent correlation was found with the more polar solvents favouring 1,4- over 1,6-addition (i.e. **54** ≪ **55**).



(145)

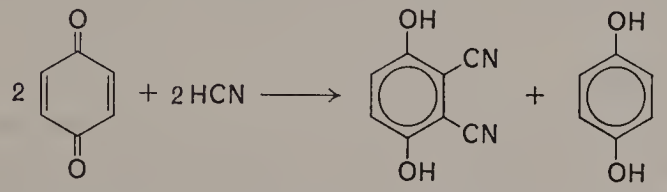
It has been found quite recently that when HCl addition is carried out in methanol this solvent enters into the reaction to a very significant extent (equation 146). Moderately sophisticated theoretical calculations (e.g. extended Hückel) gave a good interpretation of the observed results.



(146)

2. Hydrogen cyanide

Thiele and Meisenheimer made the interesting observation that, unlike the apparently similar hydrogen halides, hydrogen cyanide yields only a diaddition product with 1,4-benzoquinone—that being the 2,3-isomer (equation 147)[184]. No monoaddition product could be isolated. A

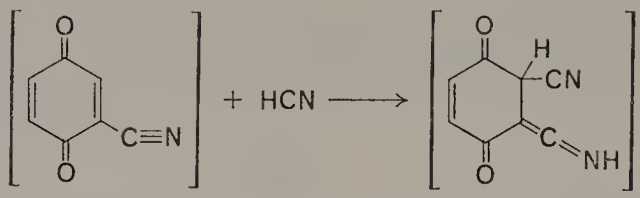


(147)

reasonable explanation of this experimental fact is the presence, in the first-step product, of a strong electron-withdrawing group which also offers an attractive conjugated system for 1,4-addition (equation 148). Allen and Wilson pointed out that this reaction is very sensitive to temperature and only succeeds in a very narrow range (20–30°C)[185].

In some cases it is possible to add sodium cyanide to quinones (equation 149)[186]. The best results were obtained with 2-(*p*-nitrophenyl)-1,4-naphthoquinone. No cyanohydroquinones were obtained from 1,4-benzo-, 1,4-naphtho- or 2-methyl-1,4-naphthoquinone.

The reaction of 1,4-benzoquinone with cyanide forms the basis for an extremely sensitive quantitative determination of that anion[187]. The reaction is very rapid at a concentration of as little as 0·2 μg/ml. The



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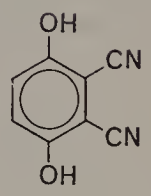
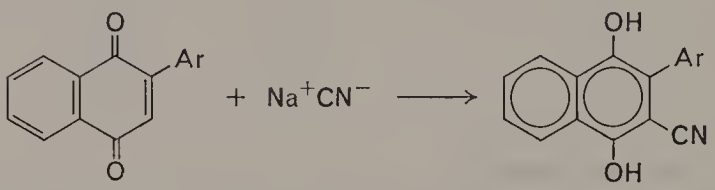




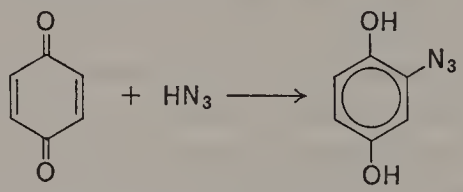
(149)

Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$

fluorescence of the 2,3-dicyanohydroquinone, presumed to be produced, is proportional to cyanide concentration over the range 0·2 to 50 μg/ml. A wide variety of other quinone derivatives was tested, but all gave inferior results.

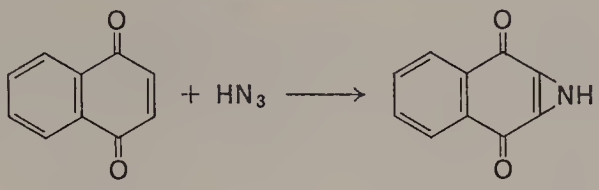
3. Hydrazoic acid

In 1915 Oliveri-Mandalá and Calderaro disproved the earlier report that hydrazoic acid reacts with 1,4-benzoquinone to produce only nitrogen-free product[188,189]. In fact, the addition takes place in a manner very similar to HCl addition (equation 150); the nitrogen-free product reported previously is quinhydrone.



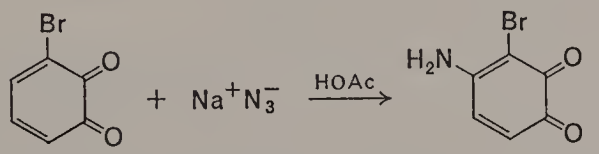
(150)

In the naphthoquinone series a similar situation occurred when an early report suggested an especially interesting structure for the addition product (equation 151)[190]. Fieser and Hartwell re-examined the reaction and showed that the product was actually 2-amino-1,4-benzoquinone[191]. The



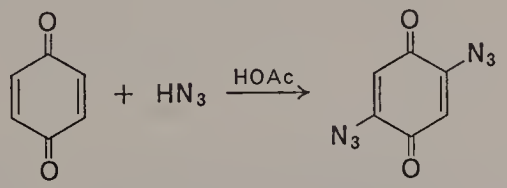
(151)

suggested mechanism was simply 1,4-addition followed by a redox reaction between the azido group and the quinone. The difference in oxidation potential between 1,4-naphthoquinone and 1,4-benzoquinone can explain the observed difference in product. Efforts to test this hypothesis by isolating the expected intermediate, 2-azido-1,4-naphthoquinone, failed, but the scope of the reaction was examined. It was found that 1,2-naphthoquinone gave the 4-amino derivative, but both 2-methyl-1,4- and 4-methyl-1,2-naphthoquinone were unreactive toward HN_3. With 3-bromo-1,2-benzoquinone, only addition at the 4-position is observed (equation 152).



(152)

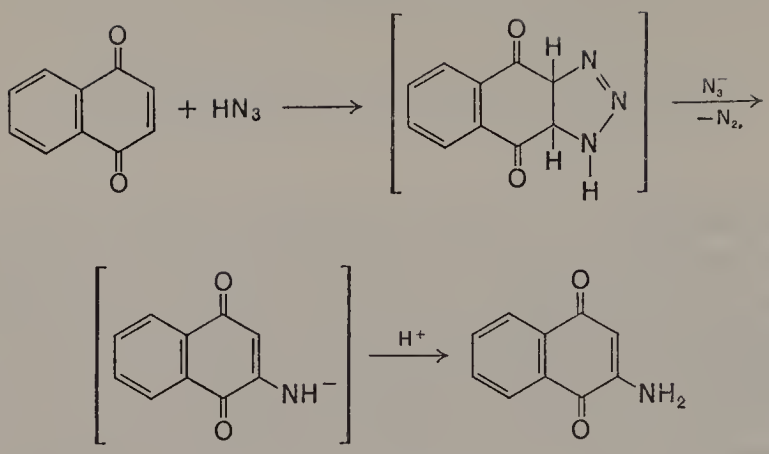
Fieser and Hartwell also carried out the addition of sodium azide and 1,4-benzoquinone in acetic acid[191] and agreed with Oliveri-Mandalá[189]. Recent work has shown that the product is actually 2,5-diazido-1,4-benzoquinone (equation 153) and that the original work in benzene does produce 2-azidohydroquinone (equation 150)[192].



(153)

The mechanism of these reactions has also been discussed briefly by Dean and collaborators[193]. They favour initial triazole formation followed by proton abstraction by azide with loss of nitrogen, which leaves the amide anion to take up a proton to form a product (equation 154). It would seem that this is a much more attractive explanation of the failure of 2-methyl-1,4-naphthoquinone to react.

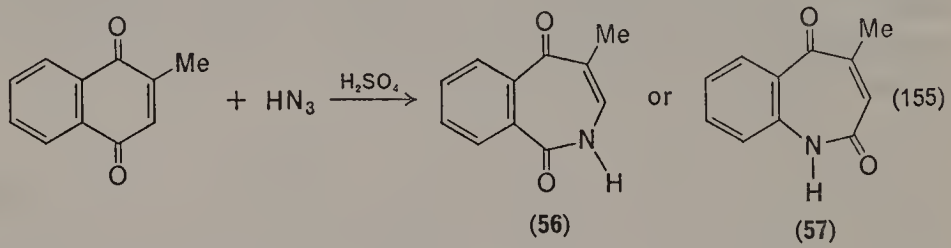
The reaction between hydrazoic acid and quinones in sulphuric acid solution has been studied and the simple quinones led only to decomposition products[194]. With 2,5-dimethyl- and 2-methyl-5-isopropyl-1,4-benzoquinone, however, it was possible to isolate pure products with



(154)

analyses consistent with the addition of HN[195]. The products did not show the properties of amines and evidence of imide structure was sought. The ease of hydrolysis of the compounds is consistent with an imide structure, but no compelling evidence was presented.

In more recent work it has been demonstrated that quinones undergo the Schmidt reaction upon treatment with hydrazoic acid and sulphuric acid (equation 155)[196]. This reaction presents a very valuable synthetic entry to the 2,5- H-2,5-azepindiones and thus the structure of the product (**56** or **57**) is of special importance. The spectroscopic character of N—H



(155)

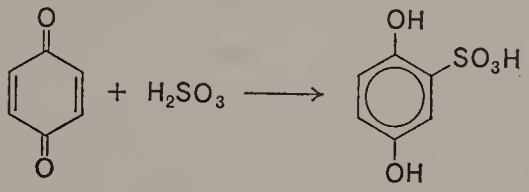
(56) (57)

and C—H protons led Folkers and collaborators to suggest **56** as the correct structure; i.e. preferential migration of the least hindered end of the quinone. This assignment has been re-examined and the alternate structure, **57**, found to be in better agreement with the spectra and a chemical rearrangement product of known structure[197].

4. Sulphur anions

The reactions of sulphite and related anions with quinones have been of practical importance in photography for a long time and fundamental research on the subject has accompanied this interest[198,199]. These first experiments verified the general assumption that the quinone formed in

the developing process oxidized aqueous sulphur dioxide to sulphuric acid. Dodgson also found strong evidence for a second reaction: i.e. the addition of sulphite to the quinone (equation 156)[198]. The hydroquinone



(156)

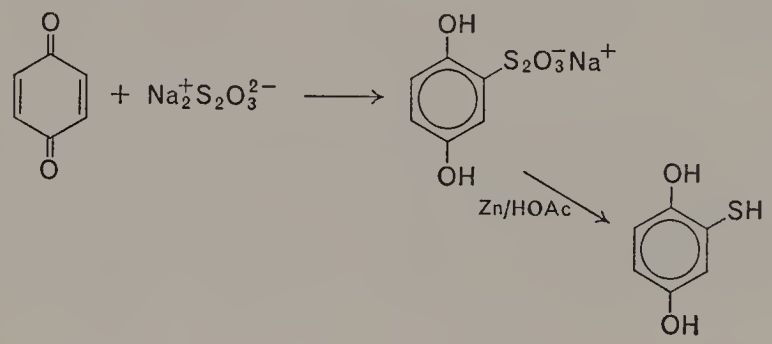
(58)

sulphonic acid **58** was isolated and characterized. The amounts of sulphate and sulphonic acid were shown to provide a reasonable material balance for the quinone employed. The expected effect of increased hydroxide concentration, i.e. increased base leads to increased sulphonic acid formation, was substantiated with experimental evidence. It was also observed that above an equivalent amount of base, sulphate production remained constant while less and less sulphonic acid was found. This was attributed to the destruction of quinone by base. Similar results were obtained with a series of substituted 1,4-benzoquinones. Again the effect of hydroxide ion was found, although it generally required more excess base than in the case of 1,4-benzoquinone. The more highly substituted quinones were also somewhat more resistant to attack by base. Substitution as well as addition was observed with chlorinated quinones.

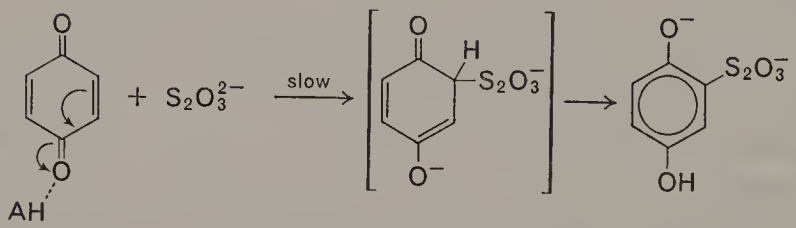
A kinetic study of the inhibition of the autoxidation of several hydroquinones by sulphite has shown that the oxidation of hydroquinone by oxygen is most consistent with the rate data and the product distribution[200]. The hydrogen peroxide formed in the first step appears to be responsible for the oxidation of sulphite to sulphate. The rate laws are not first-order, but to a good approximation the assumption that sulphite acts to remove quinone by one or two additions fits the observations. Of special interest to organic chemists is the observation that thiols (e.g. cysteine, thioglycolic acid, thiocresol, etc.) act in a manner very similar to sulphite; the products of their reaction with quinones have been discussed (see section II.B.3). An elaborate spectrophotometric study of the reactions of various quinones with sulphite has been published[201]. Apart from showing that the system is exceedingly complex little of interest to the organic chemist is presented. The addition of sulphite to nascent quinones was mentioned in section II.B.4.

The addition of sodium thiosulphate to 1,4-benzoquinones has been used as a preparative route to mercaptohydroquinones (equation 157)[202].

The first report that 2-methyl-1,4-benzoquinone gave only the 2,5-addition product was later corrected; in fact, the 2,6-isomer is the major product[203]. A careful kinetic study of this reaction has been conducted[204]. The yield of product in the pH range 1–5 in aqueous solution was quantitative and the rate law is: $v = k$[quinone][thiosulphate]. The data at various acidities show general-acid catalysis and a linear relationship between the rate constant and the redox potential. The fact that the addition is very dependent upon the redox potential is reasonable in view of the reductive nature of the addition. The energy and entropy of activation (4·0 kcal/mole and −39 e.u. at pH 3·19) are certainly reasonable when compared with the values for additions to other α,β-unsaturated carbonyl compounds. The picture obtained is quite consistent with the widely held mechanistic view of such additions (equation 158). A marked increase in rate was found with



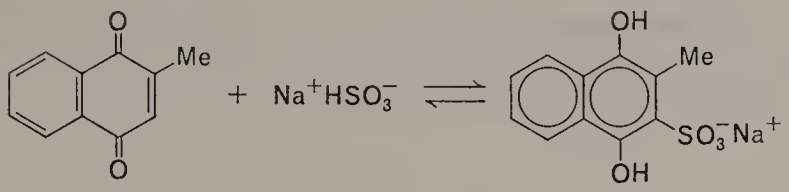
(157)



(158)

increasing fraction of ethanol in the aqueous solvent. This observation is also consistent with the mechanism presented. As the polarity of the solvent decreases the increased opportunity for hydrogen bonding enhances the catalytic effect of acetic acid buffer.

It was found that 2-methyl-1,4-naphthoquinone readily dissolves in aqueous bisulphite and that such a solution possesses excellent anti-haemorrhagic activity[205]. The reaction was considered an example of normal 1,4-addition (equation 159). It was found that the quinone itself is very much less active, as are other 2-methyl-1,4-naphthoquinones with substituents in the 3-position.

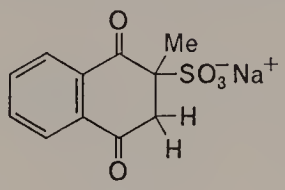


(159)

(59)

The usefulness of the sulphonate led at once to an active effort to establish its structure with certainty[206]. When 2-methyl-1,4-naphthoquinone was added to concentrated aqueous potassium bisulphite, two different salts were obtained. One showed the remarkable activity desired and the other showed less than one-tenth as much. Through a series of chemical interconversions and an independent synthesis, the inactive salt was shown to be the expected product **59**. The active isomeric salt is converted to **59** by heat.

The most likely structure for the active salt **60** was proposed on the basis of comparison of its u.v. spectrum with model compounds[207]. The



(60)

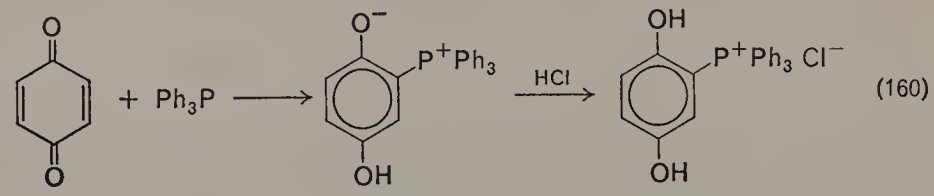
similarity of the spectrum of **60** with that of 2-methyl-1,4-naphthoquinone-2,3-oxide is very impressive. The chemical facts concerning the active salt are also best understood in terms of this structure.

Unsubstituted 1,4-naphthoquinone and 1,4-anthraquinone have also been studied in bisulphite solution[208–210]. In addition to the 2-sulphonate salt, two distinct complexes were also observed and in some cases isolated. On the basis of i.r. spectral data and the characteristics of their reactions with various nitrogen-containing carbonyl reagents, these complexes are described as 1,2- and 1,4-adducts in equilibrium. Their stability is attributed to their resonance possibilities.

5. Aryl phosphorus compounds

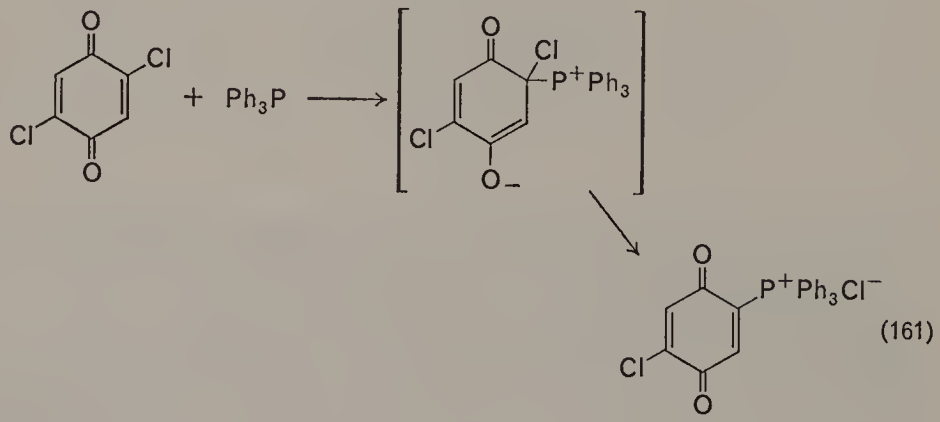
Much of the chemistry of quinones and phosphorus compounds has involved carbonyl addition (see section III), but examples of nuclear addition have also been presented. While ruling out a carbon-to-phosphorus bond in the reaction of chloranil with triphenylphosphine, Ramirez and Dershowitz offer convincing evidence for such a bond in the case of

1,4-benzoquinone (equation 160)[211]. The u.v. spectra of these phosphonium salts, as well as a substantial number of chemical transformation, are all best understood in terms of these structures.



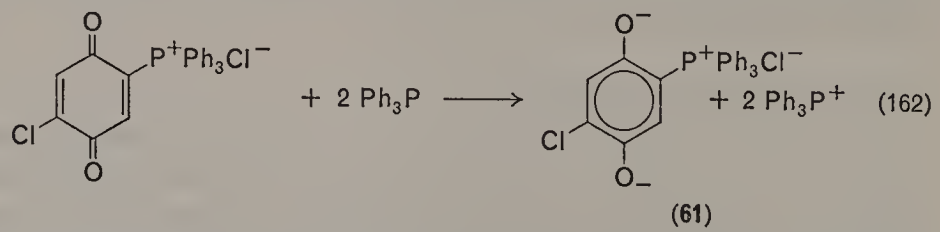
(160)

The intermediate case of 2,5-dichloro-1,4-benzoquinone is of special interest. Two points came to light immediately: (i) pure adduct formed quantitatively only when a 3 : 2 ratio of phosphine to quinone was employed, and (ii) the adduct had a chloride ion associated with it. Like chloranil, reaction with this quinone resulted in the oxidation of two moles of triphenylphosphine and the formation of oxygen-to-phosphorus bonds. Like 1,4-benzoquinone, ring attachment also occurred. In this instance it also results in the displacement of a chloride ion (equation 161).



(161)

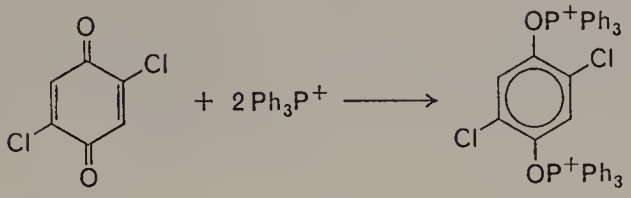
This new quinone (one of the observed products) with its positively charged group should have a high oxidation potential and thus accomplish the next required step (equation 162). Finally, the reduction of the second



(162)

(61)

mole of quinone and the formation of the other observed product (equation 163) occurs. The two products (**61** and **62**) behave as a single material

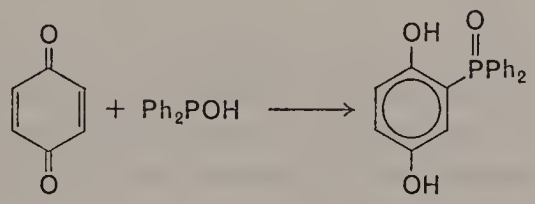


(163)

(62)

until they are hydrolysed in aqueous methanol. Again, the chemical and spectral evidence for these structures is impressive. On the basis of a detailed study of the i.r. spectra of the adducts of different quinones with several tertiary phosphines, the conclusion that there must be substitution on the quinone ring and quaternarization of the phosphorus atom was reached[212].

A report of a very similar addition of a secondary phosphine oxide to 1,4-benzoquinone has appeared (equation 164)[213]. The yield of adduct is high and the authors see no reason to suspect other than a simple addition.

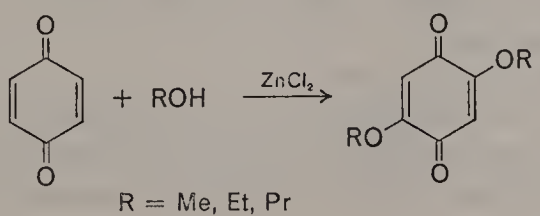


(164)

F. Oxygen Addition

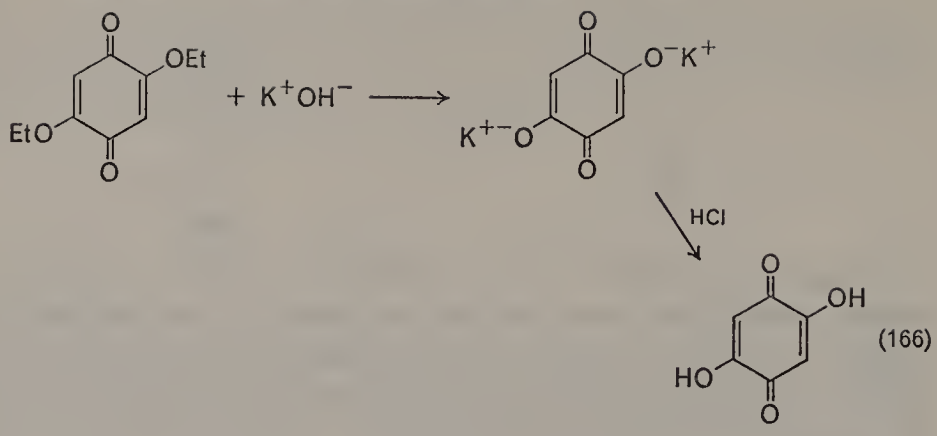
1. Alkoxyquinones and related compounds

The importance of quinonoid materials in aqueous and sometimes basic solutions (for example, physiological and photographic) has created an interest in their reactions with oxygen nucleophiles. It was recognized very early that the direct treatment of quinones, having little substitution, with strong bases led to extensive decomposition. Thus, it was of some significance when an indirect preparation of such compounds was found (equations 165 and 166)[214]. The first reaction for the preparation of alkoxy derivatives is also of value. In an attempt to apply this method to 2-methyl-1,4-benzoquinone a modest yield of the 5-methoxy derivative and none of the desired 3,6-dimethoxy product was obtained (equation 167)[215].

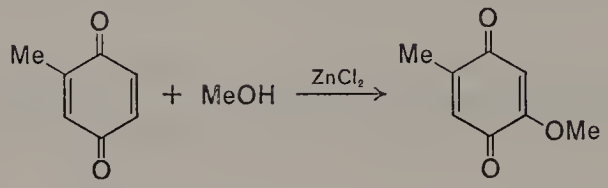


R = Me, Et, Pr

(165)

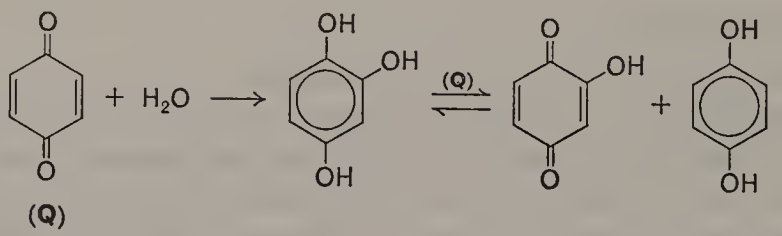


(166)



(167)

The direct reactions of quinones with water are of great interest and generally very difficult to study. The products from the aqueous decomposition of 1,4-benzoquinone and 1,2-naphthoquinone have been shown to be the corresponding hydroxy quinone and hydroquinone (equation 168)[216, 217]. A similar mechanism has been proposed for the decomposition



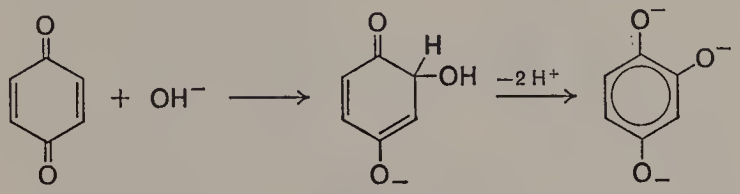
(Q)

(168)

of 1,2-benzoquinone[218] and a polarographic study of this quinone has shown that two molecules of 1,2-benzoquinone do produce one of catechol and one of some new substance[219]. However, the second product is not the required hydroxylated quinone; furthermore it is polarographically inactive and other means of characterizing it had to be found. A kinetic study of the decomposition showed that it is autocatalytic. The mechanism of decomposition of 4-methyl-1,2-benzoquinone appears to be the same, but it is considerably slower.

The most convincing evidence concerning the course of the alkaline decomposition of 1,4-benzoquinone was the isolation of 2-hydroxy-1,4-benzoquinone[220]. However, the mechanism was still better understood when Eigen and Matthies published their kinetic studies[221]. Their analysis

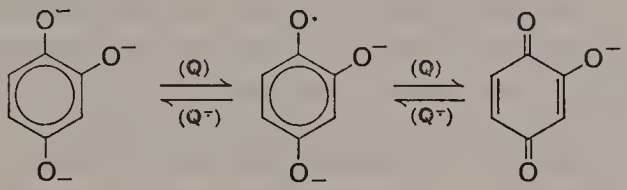
of the reactions takes into account the intermediate semiquinone. It is the characteristic spectrum of that species that allowed the flow determination of kinetic and equilibrium data. On the basis of these data the following reaction scheme was defended. First, the addition reaction (equation 169).



(169)

(Q)

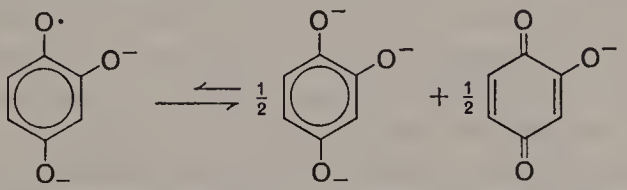
Second, the oxidation equilibria (equation 170).



(170)

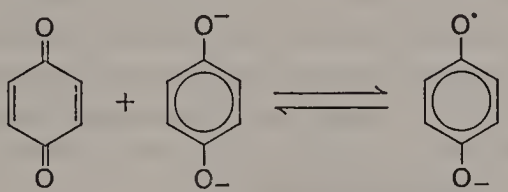
$(Q^{\cdot-})$

Third, the disproportionation (equation 171).



(171)

Two other studies of the semiquinone equilibrium and the mechanism of hydroxide attack have appeared. The first of these reports an extensive study of the factors that affect the equilibrium between quinone–hydroquinone and semiquinone (e.g. equations 172 and 173)[222]. The effect of various nuclear substituents, the effect of pH and the effect of reversible 1,2-carbonyl addition are all discussed.

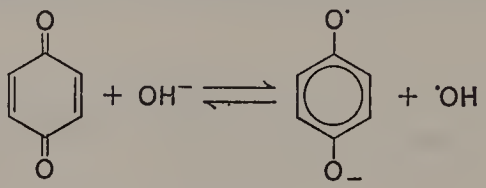


(172)

(T) (R^{2-}) (S)

$$K' = \frac{[S]^2}{[T][R^{2-}]} \qquad (173)$$

In the second paper, two of the current pictures of the hydroxide decomposition of 1,4-benzoquinone are examined[223]. One of these mechanisms is that of Eigen and Matthies already discussed[221]; the other is a more recent suggestion[223a] (equations 174 and 175). A careful selection



(174)

$$2\cdot OH \longrightarrow H_2O_2 \qquad (175)$$

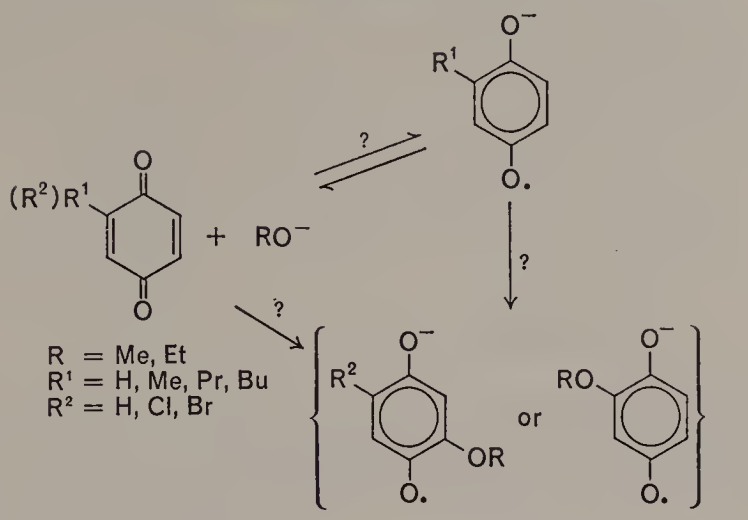
was made of experimental conditions for the detection of hydrogen peroxide. The complete failure to find any in such systems is taken as evidence against this later scheme. The failure of tetrasubstituted quinones to produce semiquinone anions as required by the above proposal is also presented as an argument in favour of Eigen's proposal.

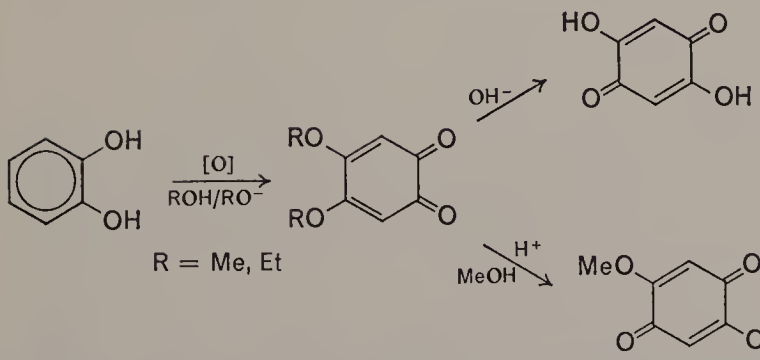
Interest in the reactions of quinones with hydroxide and alkoxide ions continues. A variety of 1,4-benzoquinones, with hydroxide and alkoxide ions, have been shown to be first-order in base and quinone[224]. The rates were measured both by following the loss of base (potentiometrically) and the increase of radical (e.s.r.): good agreement was found. When a similar study was conducted in the presence of various proteins, a catalytic effect was found[225]. A higher mobility of hydroxide ion at the water–protein interface was suggested as the explanation.

A recent study of the kinetics of alkoxide reactions with 1,4-benzoquinone, and several alkyl and halo derivatives, centred on the formation of the semiquinone[226]. It was not possible either to detect the expected monoalkoxy semiquinone intermediates or to decide whether the first semiquinone is an intermediate or the product of a concurrent reaction (equations 176 and 177). Stopped-flow spectrophotometry was used to follow the semiquinone formation. In the short reaction times studied, alkyl 1,4-benzoquinones showed only semiquinone formation, but hydrogen or halogen substitution produced dialkoxy semiquinone.

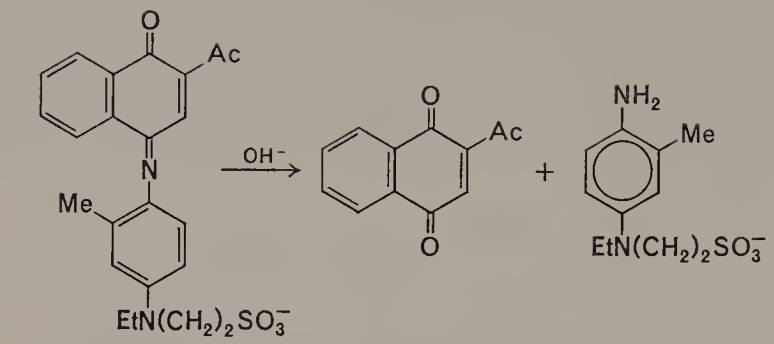
A recent report of the use of nascent 1,2-benzoquinone is interesting for the product structure and subsequent conversion to substituted 1,4-benzoquinones (equations 178 and 179)[227]. Similar chemistry is observed with 4-methylcatechol.

As a part of a study of the bleaching of imine dyes, Reeves and Tong found it necessary to study the decomposition of 2-acetyl-1,4-naphthoquinone in basic aqueous solution[228]. This quinone is one product of the

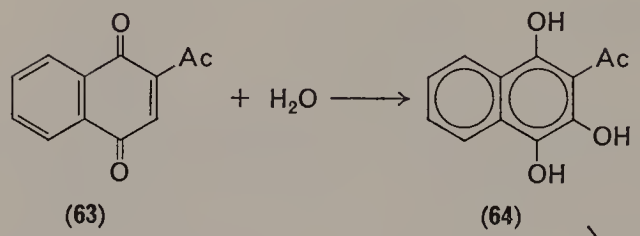




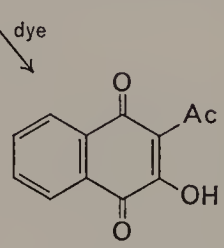
hydrolysis of the dyes studied (equation 180). The product of its reaction with water can cause a serious side-reaction with the original dye (equation 181). The most significant observation for our present concern was that **63** alone in pH 9·2 buffer does not decompose in the simple fashion suggested as the first step of equation (181). Compounds **63** and **64** would be expected to establish the cross-oxidation equilibrium shown in equation (182). Compound **63** has completely disappeared within 30 seconds. However, the yields of compounds **65** and **66** are 42% and 28% respectively rather than the expected equal amounts and they appear over a period of



(180)

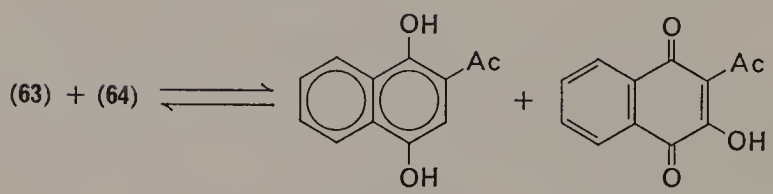


(63) (64)



(181)

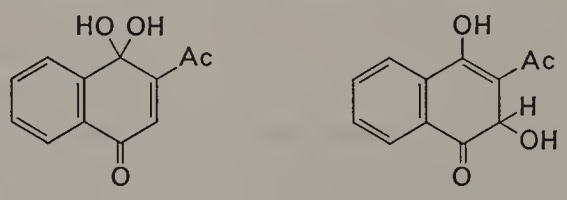
+ leuco dye



(65) (66)

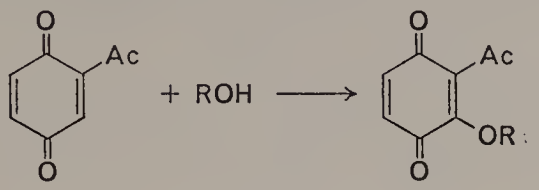
(182)

about 10 minutes. Spectral evidence indicates that at least two intermediates must intervene between reactants (**63** and **64**) and products (**65** and **66**). The following intermediates are suggested. The conversion of the latter intermediate (**67**) could well be the slow product-forming step.



(67)

The addition of alcohols to 2-acetyl-1,4-benzoquinone has been studied and the expected 2,3-orientation observed (equation 183)[229]. Excellent



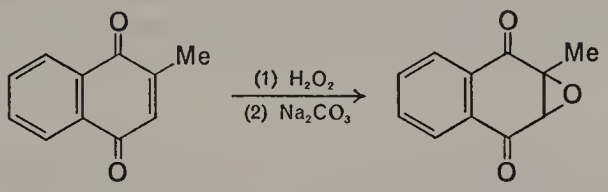
(183)

R = Me, Et, *i*-Pr, Bu, allyl, C_6H_{11}, CH_2Ph

yields were obtained for a broad range of alcohols when equimolar reactants were used in dry benzene. Poor yields of the initial hydroquinone adduct were obtained when the alcohol was used as solvent. No reaction was found with *t*-butyl alcohol.

2. Epoxyquinones and their chemistry

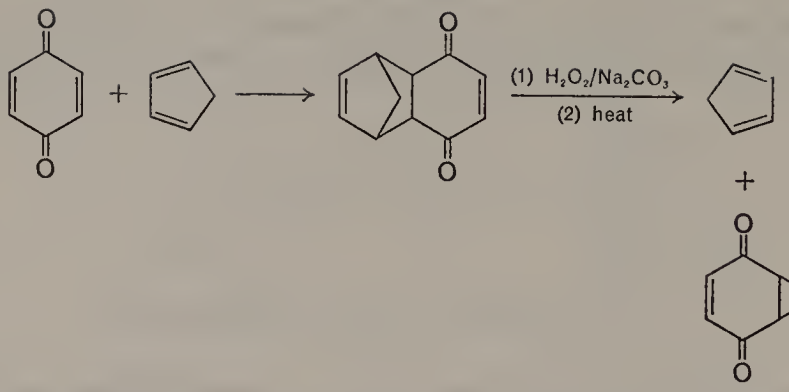
It has been known for a long time that the double bonds of quinonoid nuclei can be epoxidized. The method most widely used was worked out by Fieser and his students (equation 184)[230]. This preparative method has



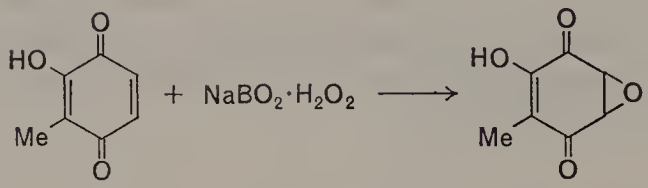
(184)

been applied to a great many quinones including 5,8-quinolinequinone and its 6-alkyl derivatives and excellent yields are obtained[110]. A promising alternate route to quinone epoxides is sodium hypochlorite in aqueous dioxan[231]. The yields of product appear quite satisfactory and the reagent is faster, safer and cheaper than 30% peroxide.

The synthesis of 1,4-benzoquinone epoxides is a good deal more difficult. An indirect method devised by Alder and collaborators involves the formation of the mono- adduct with cyclopentadiene and thermal reversal of that reaction after epoxidation (equation 185)[232]. The generality of this method suffers from the orientation of the Diels–Alder adducts and the thermal instability of some quinone epoxides. In an effort to find a milder epoxidation reagent Rashid and Read found sodium perborate to be excellent[233]. They were particularly interested in the synthesis of terreic acid (**68** in equation 186). A number of other sensitive quinone epoxides were prepared in low yield; e.g. 1,4-benzoquinone and juglone.



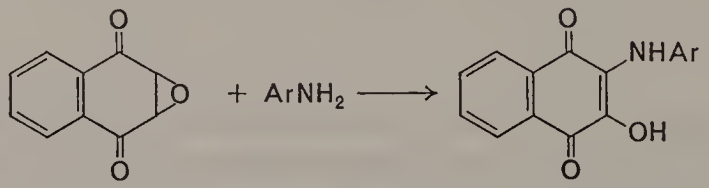
(185)



(186)

(68)

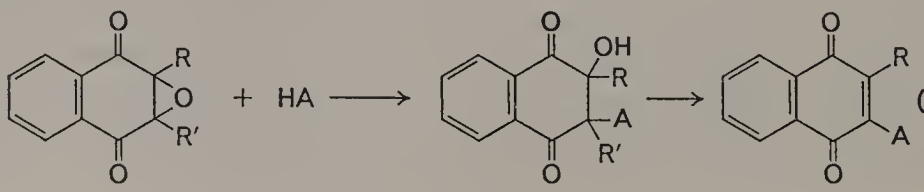
The quinone epoxides have proved to be useful intermediates for the synthesis of 2,3-disubstituted quinones in which one of the substituents is a hydroxy or alkoxy group. For example, a series of 2-anilino-3-hydroxy-1,4-naphthoquinones have been prepared by this route (equation 187)[234]. The yields are only fair and in the nitro cases poor (3-NO_2 = 4-NO_2 = 5%, 2-NO_2 = 0).



(187)

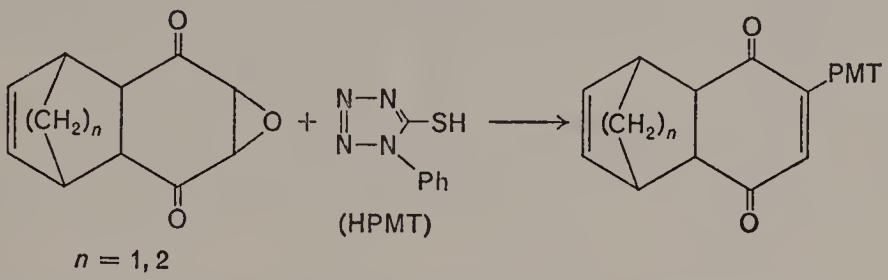
Ar = 2-ClC_6H_4, 4-ClC_6H_4, 2,4-$Cl_2C_6H_3$, 2-$MeOC_6H_4$, 4-$MeOC_6H_4$, 4-$HO_2CC_6H_4$, 4-$H_2NO_2SC_6H_4$, 3-$O_2NC_6H_4$, 4-$O_2NC_6H_4$

As part of a synthetic search for bacterial growth inhibitors various substituted 1,4-naphthoquinone epoxides were treated with aniline, *n*-butanethiol and hydrogen halides (equation 188)[235]. When either R or R′ is hydrogen, the yield of quinone product is satisfactory, but when both groups are alkyl the second step does not occur.



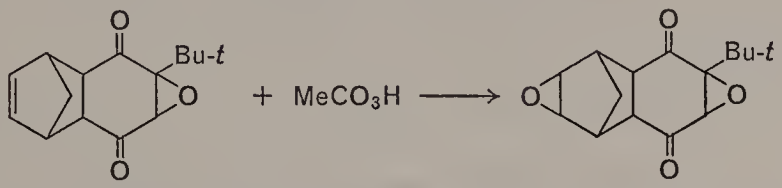
(188)

The chemistry of epoxides of quinone Diels–Alder adducts has been studied by Gates and colleagues. Through an n.m.r. study of the cyclopentadiene adducts of various 1,4-benzoquinones and their epoxides the *cis–endo* configuration of the Diels–Alder product was confirmed[236]. Similar results were found with 1,3-cyclohexadiene adducts. The configuration of the epoxide was shown to be *exo*. The ring-opening reaction with 1-phenyl-5-mercaptotetrazole (HPMT) was carried out (equation 189). The configuration of the 2-thioether enediones corresponds to the



(189)

Diels–Alder adduct. Finally, it was found that peracetic acid is a useful reagent for preparing diepoxides (equation 190).

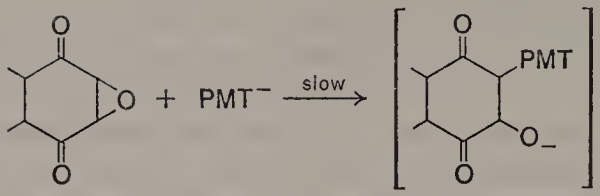


(190)

A kinetic study of the reaction of the epoxides described above with HPMT has been carried out in basic buffered ethanol solution[237]. The following reaction mechanism is consistent with the observations (equations 191–194). The effect of substitution on the rate of ring opening is similar to that found in halide displacement and large negative entropies of activation were found (−28 to −32 e.u.). Both of these effects could arise from participation of the carbonyl groups in the reaction, but comparison of the rate of ring opening of cyclohexene oxide by HPMT and data for other similar nucleophilic reactions argue against such participation.

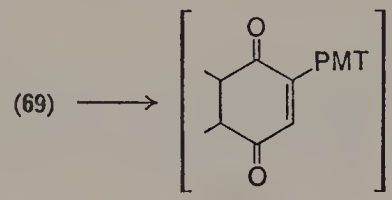
A rather interesting ring-contraction reaction occurs when cyclopentadiene quinone adduct epoxides bearing aryl substituents are treated with acids (equation 195)[238]. Analogous reactions occur with strong proton acids and with the double bond reduced and with 1,3-cyclohexadiene adducts. The structures of the products were convincingly demonstrated with spectral and chemical evidence and the yields were fair to excellent with the choice of acid apparently very important.

$$HPMT + B: \rightleftharpoons PMT^- + BH^+ \quad (191)$$



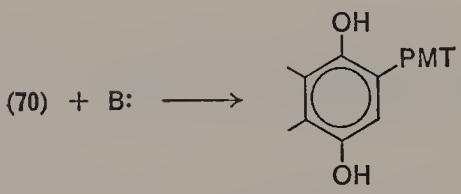
(192)

(69)



(193)

(70)



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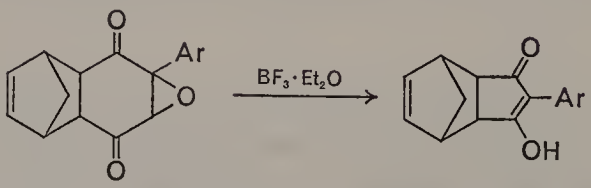


(195)

Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$

III. THE CARBONYL CHEMISTRY OF QUINONES

A. Introduction

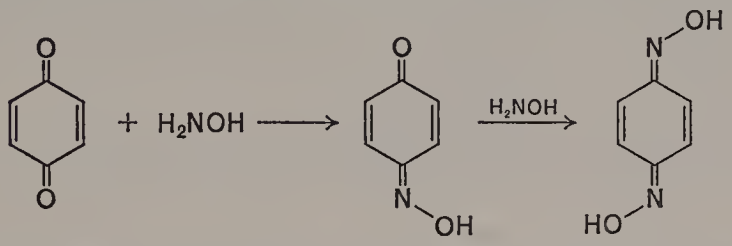
As might be expected, the carbonyl group plays a significant role in quinone chemistry. However, some aspects of this chemistry are rather closely related to another quinone addition reaction and have been treated in that section; for example

Thiele acetylation, section II.D.
Radical addition, section IV.B.
Hydroboration alkylation, section IV.C.4.
1,2-Quinone cycloaddition, section V.A.4.
Diazo cycloaddition, section V.B.

Enamine addition, section V.C.1.
Active methylene compounds, section VII.
Substitution chemistry, section VIII.D.

The present section is designed to discuss those features of quinone chemistry that relate chiefly to the carbon–oxygen double bonds.

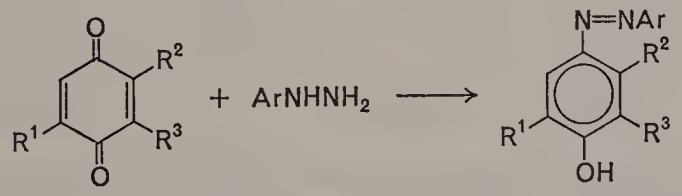
The earliest studies that deal exclusively with the chemistry of the quinonoid carbonyl group are those of Kehrmann and collaborators who examined the formation of oxides (equation 196)[239–242]. Either the mono- or the dioxime can be obtained with monosubstituted or 2,5-disubstituted



(196)

1,4-benzoquinones. The monooximes of the less hindered carbonyl group are obtained in the monosubstituted case and are the only product with 2,6-disubstituted and trisubstituted 1,4-benzoquinones. A review of the earlier literature is included[239]. Tetrasubstituted 1,4-benzoquinones did not form oximes under these conditions. The large number of nitrogen-containing carbonyl reagents provide additional examples[243–247] and a very early kinetic study is available[248].

The work of Borsche[245,246] was developed by Smith and Irwin as an important tool in demonstrating the structure of substituted quinones[249]. They realized that the addition of an arylhydrazine to a quinone and the addition of an aryldiazonium salt to a phenol may lead to isomeric products if the other substituents are the same (equations 197 and 198)*.



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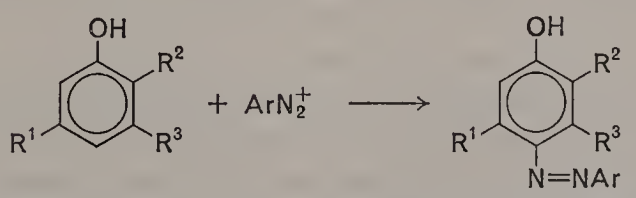
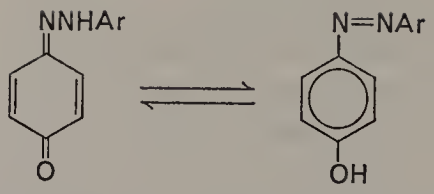


(198)

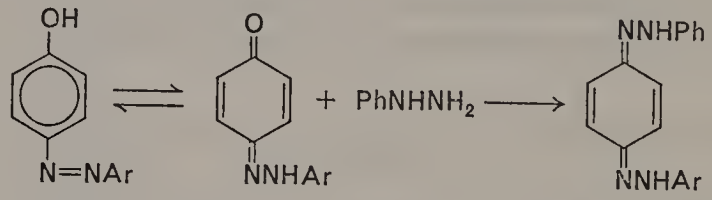
* This argument assumes that the quinone monohydrazone exists in the azo form (equation 199). Some recent studies of this equilibrium and the factors that influence it have appeared[250, 251].



(199)

The scheme worked very well with *p*-nitrophenylhydrazine and *p*-nitroaniline. In most cases the yields were excellent and the conversions to isomeric *p*-aminophenols and then to identical 1,4-benzoquinones were smooth. Formation of the monohydrazone derivatives with 2,4-dinitrophenylhydrazine was satisfactory, but the subsequent cleavage was not. It was found that duroquinone reacted very satisfactorily, unlike the earlier reports of attempted oximation.

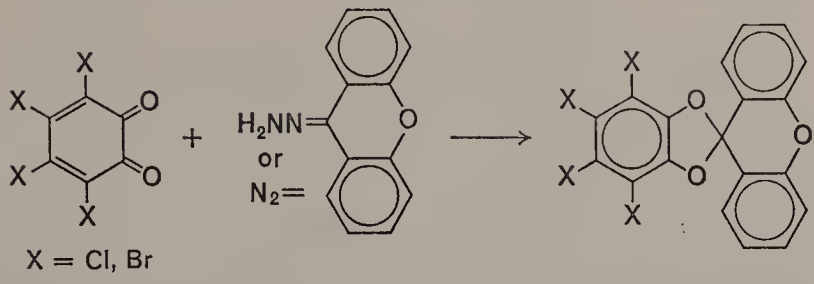
In the process of examining the question of azo–hydrazone tautomerism, a more detailed picture of the steric requirements for quinone carbonyl addition reactions was obtained[252]. A series of nine arylhydrazines, with a variety of halo and nitro substituents, reacted smoothly with 1,4-benzoquinone, 2-methyl-1,4-benzoquinone and 2-methyl-5-isopropyl-1,4-benzoquinone. Chloranil, anthraquinone and β-methylanthraquinone reacted only with those hydrazines substituted in neither or one *ortho* position. When one *ortho* position is substituted, the hydrazones show chemical and physical properties quite unlike those resulting from the less substituted quinones. Typical of this difference is the interesting reaction between phenylhydrazine and *p*-arylazophenol (equation 200). The highly hindered quinones and hydrazines failed to undergo this reaction, which incidentally clearly demonstrates the tautomerism of the starting material.



(200)

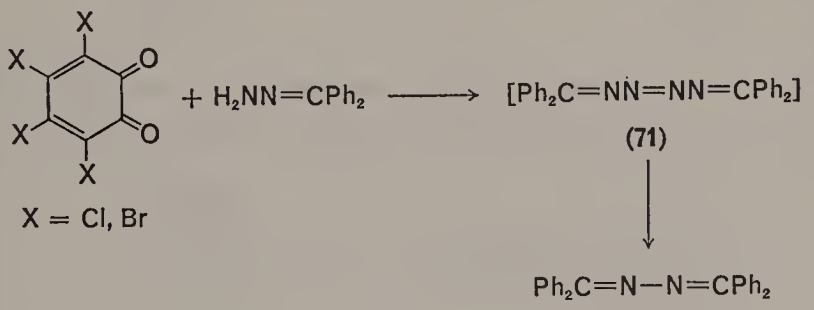
The rate of oxime formation has been studied in some detail with respect to both steric and electronic effects[253]. The steric influence of the rest of the quinone molecule has been used as a diagnostic tool in structure determination (see section V.A.1). A more recent study has involved the calculation of Hückel molecular orbital parameters for various substituted quinone monooximes and a discussion of the rates of dioxime formation by these compounds[254].

The reactions of 1,2-quinones with polyaryl hydrazones and diazo compounds (equation 201) have been studied quite extensively[255, 256].



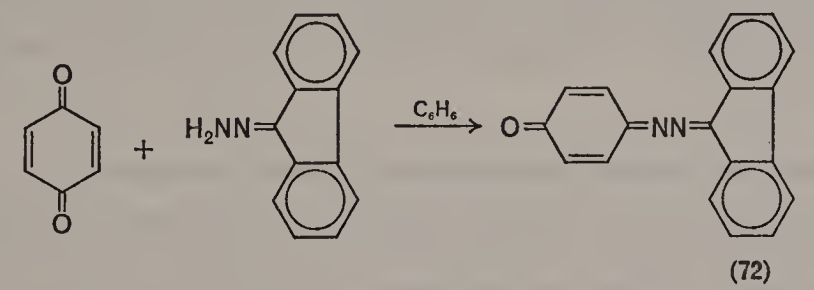
(201)

The corresponding hydroquinone is also a product of the reaction when a hydrazone starting material is used. This fact, along with other evidence, suggests that the diazo compound is an intermediate, if it is not a reactant[257]. Early experiments with tetrahalo-1,2-benzoquinones and benzophenone hydrazone produced benzophenone azine and the corresponding hydroquinone (equation 202); the intermediate **71** was suggested[258]. Similar



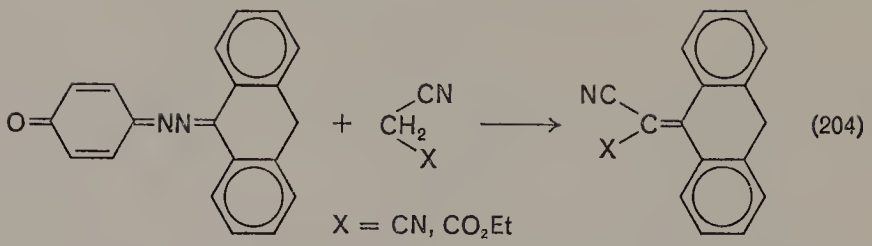
(202)

chemistry was observed between 1,4-benzoquinone and fluorenone hydrazone in ethanol; however, in benzene the quinone imine **72** is formed (equation 203)[258]. A reactant ratio of 1 : 2 produces the quinone bisimine



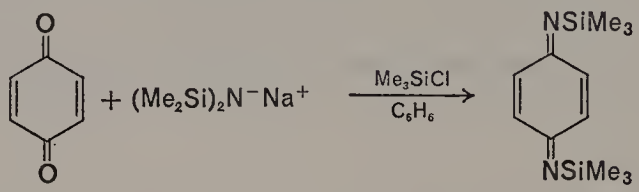
(203)

and other hydrazones (e.g. xanthone and benzophenone) show somewhat similar, but not identical, chemistry. The monoimine has been shown to be an intermediate of some promise in the synthesis of certain alkenes (equation 204)[259]. Finally, using ether as the solvent, the original reaction (equation 201) has been extended to a series of substituted benzophenones[260] and other modifications explored[261–264].



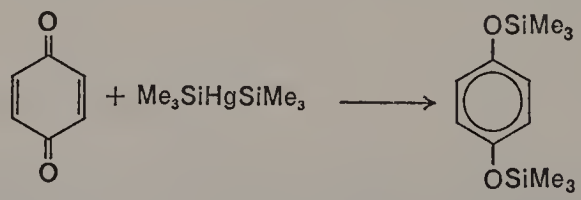
(204)

An interesting silicone-containing compound has been prepared (equation 205)[265]. The product is very reactive (light, air and moisture), but can be purified by sublimation.



(205)

Two groups announced almost simultaneously the reductive silylation of quinones with bis(trimethylsilyl) mercury (equation 206)[266, 267]. The

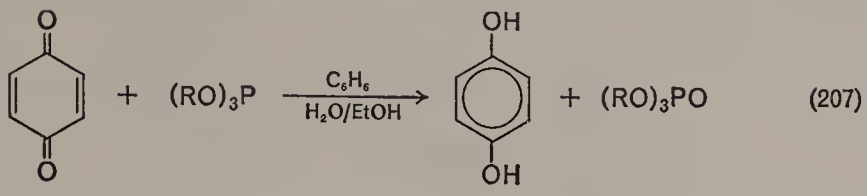


(206)

reaction takes place with 1,2- and 1,4-naphthoquinone as well as simple ketones such as acetone and cyclohexanone. The yields for the quinones are quite satisfactory. Some evidence is presented for a radical intermediate, but the possibility of a molecular reaction leading directly to product is also presented[267].

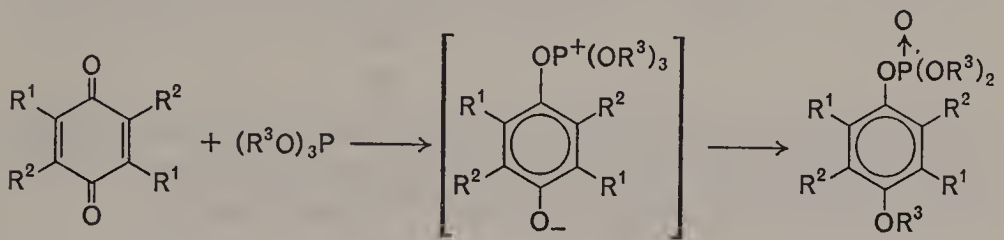
B. *Addition of Tertiary Phosphines and Related Compounds*

A very active area of quinone carbonyl chemistry has involved their interaction with tertiary phosphines. In the first paper of an extensive and detailed study Ramirez and Dershowitz[211] reviewed and criticized the earlier work in the field. Much of the chemistry studied deals with redox questions and will not be treated in this chapter, but both carbonyl and nuclear addition and substitution reactions of interest also emerged (see section II.E.5). For example, it was shown that, in the presence of water, the trialkyl phosphites can serve as efficient reducing agents for quinones (equation 207)[268]. However, when the reaction is carried out in anhydrous



(207)

benzene, the proposed intermediate **73** can undergo the rearrangement reaction shown in equation (208). The product, **74**, can be hydrolysed to the hydroquinone mono-ether. Dialkyl phosphites undergo very similar reactions with chloranil, which are accelerated by light (360–370 nm)[269].

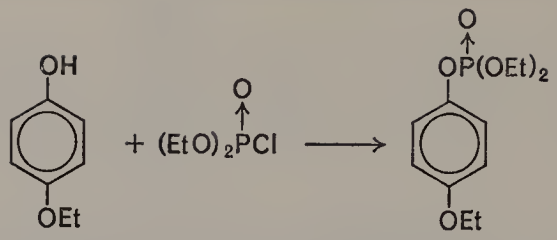


(208)

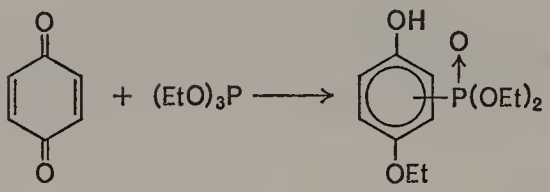
A more detailed report of this useful *O*-alkylation procedure revealed evidence of a stepwise intermolecular mechanism and the intermediate **73**[270]. This intermediate is analogous to that strongly suggested by the evidence from experiments in the triphenylphosphine case (see section II.E.5). It also allows a sensible explanation of the reduction cited above and the formation of very small amounts of diether.

The reactions of trialkyl phosphites with 1,4-benzoquinones bearing few substituents also lead to the hydroquinone mono-ethers under anhydrous conditions[271]. In the presence of water reduction again takes place. Duroquinone, the least potent oxidizing agent of the quinones examined, is not reduced.

These studies of the structure of adducts formed by quinones and trialkyl phosphites have been questioned and a somewhat deeper understanding of the reaction obtained[272]. The product obtained by Kukhtin and colleagues from the reaction of triethylphosphite and 1,4-benzoquinone did not have the same properties as that reported by Ramirez and Dershowitz. The product was also different from that obtained in an independent synthesis (equation 209). On the basis of this evidence, the structure **75** was proposed for the reaction product (equation 210). Identical products are obtained when the crude product is washed with base before vacuum distillation. Some additional interesting facts came out of this study: (i) the product obtained in the absence of base is a



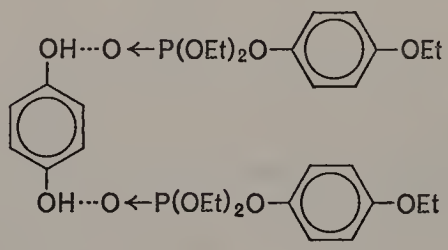
(209)



(210)

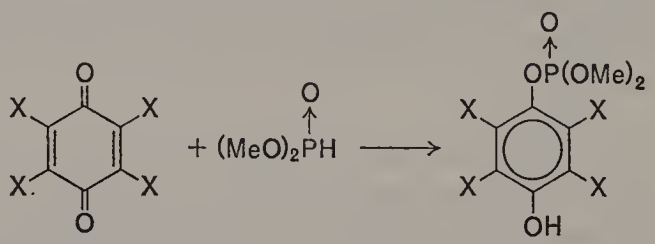
(75)

complex (**76**) that distils without decomposition over a one degree range, (ii) a similar reaction takes place with 1,4-naphthoquinones, and (iii) only the reaction with chloranil gave e.s.r. evidence of radicals.



(76)

Nishizawa has studied the related reaction of *O,O*-dimethyl phosphonate with 1,4-benzoquinone and chloranil (equation 211)[273]. With chloranil,

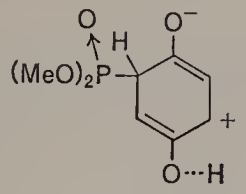


X = H, Cl

(211)

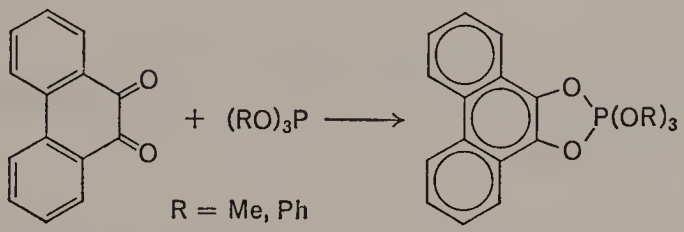
his product is identical to that obtained by Ramirez and Dershowitz[270]; however, he prefers a ring substituted intermediate (**77**) that rearranges rather than tautomerizes.

In a related area Ramirez and his students have studied the reactions of trialkyl and triaryl phosphites with α-diketones including 1,2-quinones[274]. Crystalline 1:1 adducts were obtained with 9,10-phenanthrenequinone (equation 212) and biacetyl. The assignment of the



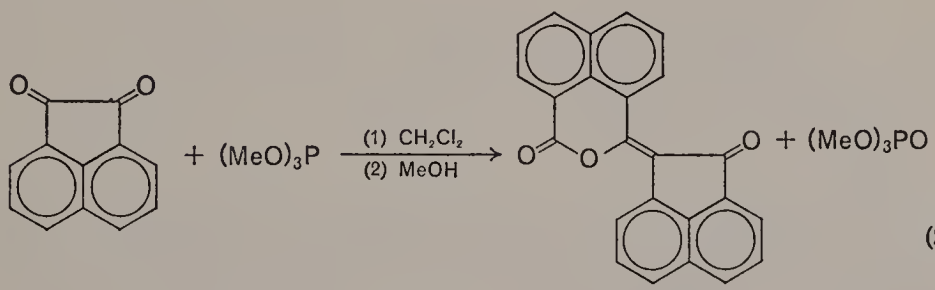
(77)

unusual structure containing a pentacovalent phosphorus was made on the basis of spectral and dipole moment studies. The structures of these and related compounds have been discussed in detail and supported in a later publication[275] and by other authors[276].



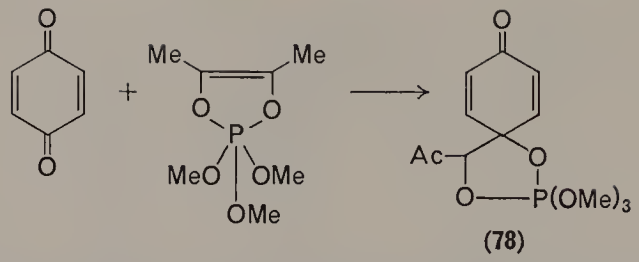
R = Me, Ph (212)

The chemistry of these adducts, especially their reactions with other quinones, is interesting. When two moles of acenaphthenequinone react with trimethyl phosphite a 2:1 adduct is formed. The adduct is cleaved in hot methanol to give the enol lactone shown in equation (213)[277]. Similar reactions occur with biacetyl and a combination of these two α-dicarbonyl compounds[278].



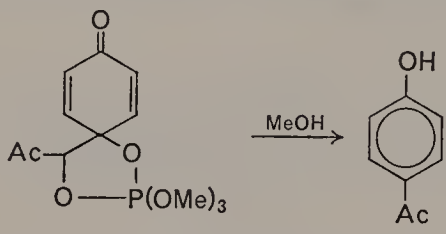
(213)

The reversible addition of simple inorganic ions to quinone carbonyl groups has played a significant role in our understanding of certain quinone reaction mechanisms (see section VIII.D). Recently the irreversible nucleophilic addition of carbon to a quinone carbonyl group has been reported[279]. The addition takes place between 1,4-benzoquinone and a pentaoxyphosphorane of the type we have been discussing (equation 214). The product **78**, like most of the pentacovalent phosphorous compounds, is sensitive to water, but can be recrystallized and undergoes an



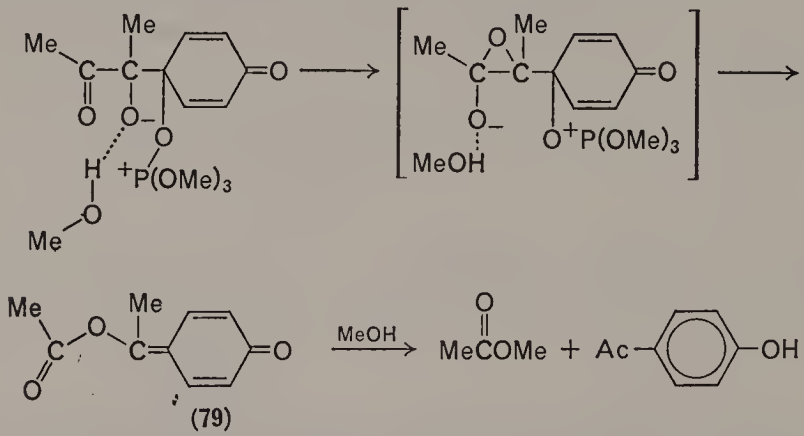
(78) (214)

interesting decomposition (equation 215). These studies have been expanded since the preliminary communication and the mechanism of the



$+ MeCO_2Me + (MeO)_3PO$ (215)

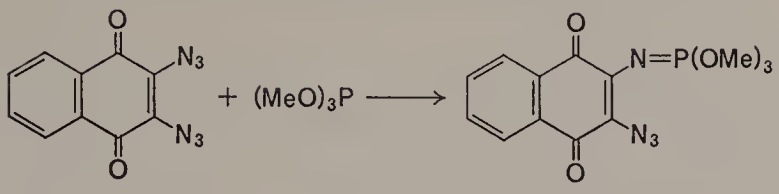
rearrangement explored[280]. Based on the facts obtained from the methanolysis of intermediate **78**, an enol-acetate intermediate (**79**) is proposed (equation 216). Hydrogen bonding by the methanol is clearly indicated because the reaction is much slower in ethanol and does not take



(79) (216)

place in *t*-butyl alcohol. The loss of the stable trimethyl phosphate provides an efficient driving force for the reaction. This reaction also was observed with 1,4-naphthoquinone.

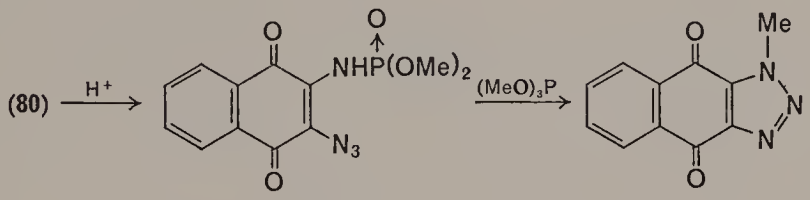
When phosphites are given a choice between carbonyl and azido groups as reactive sites in 2,3-diazido-1,4-naphthoquinone the latter is favoured[281]. In only one instance was a useful product obtained; the usual result being a very low yield and intractable oil mixtures (equation 217).



(217)

(80)

Compound **80** can be hydrolysed with acid to give **81** which also reacted with trimethyl phosphate to give a fair yield of a known heterocycle (**82** in equation 218). This reaction, and a similar one involving triphenylphosphine, is curious because it appears to involve the loss of a single nitrogen atom from an azide group.

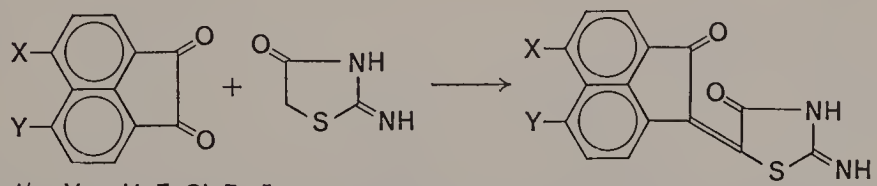


(218)

(81) (82)

C. *Brief Notes*

(1) In hot acetic acid pseudothiohydantoin will condense with acenaphthenequinone and various halogen derivatives in excellent yield (equation 219)[282]. As was pointed out above, acenaphthenequinone is in fact an α-diketone.



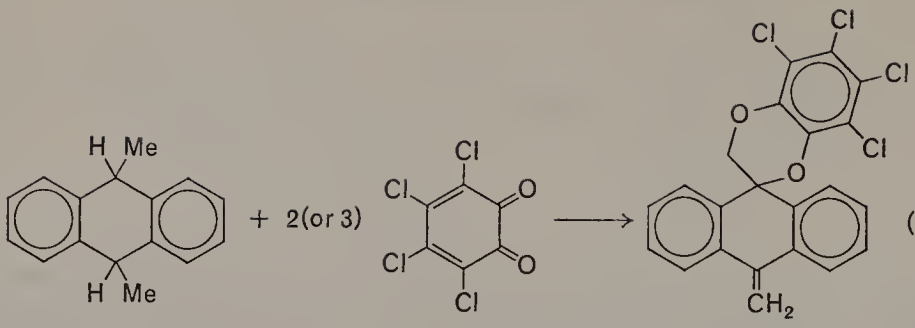
(219)

X and/or Y = H, F, Cl, Br, I

(2) A good deal of interest exists concerning the quinodimethanes or *p*-xylylenes. One recent method that combines their synthesis and evidence for their existence involves the use of high-potential quinones (equation 220)[283]. The spectra, elemental analysis and ozonolysis products all confirm the product structure, **83**.

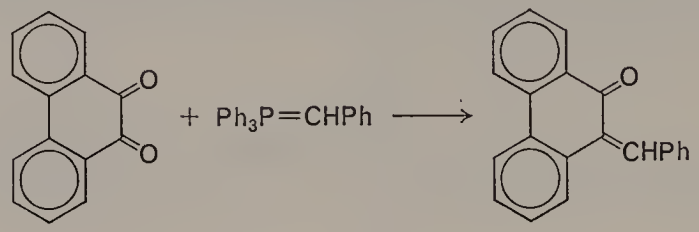
(3) The Wittig reaction of ylides has been applied to quinones (equation 221)[284,285].

Under slightly different conditions the product undergoes what appears to be a subsequent Michael addition with a second mole of ylide followed by cyclization (equation 222).



(220)

(83)



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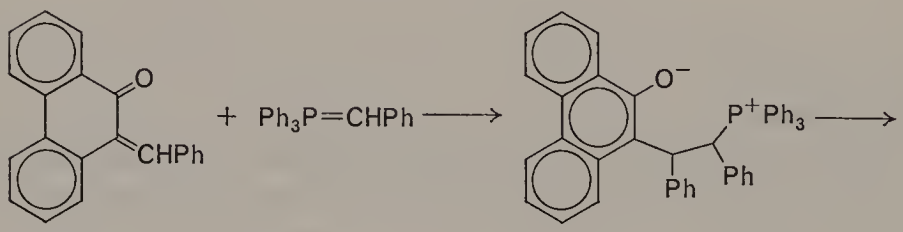
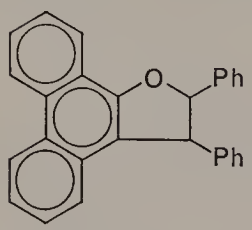
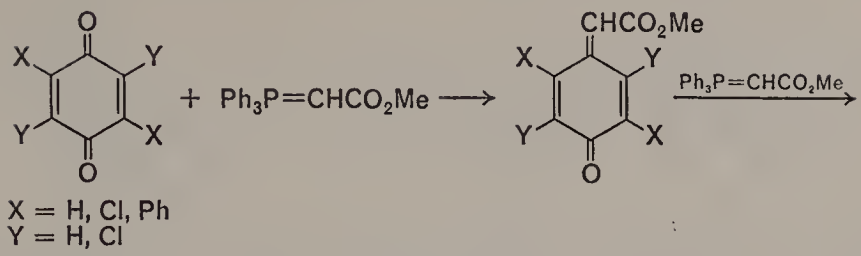
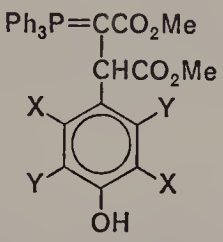




(222)

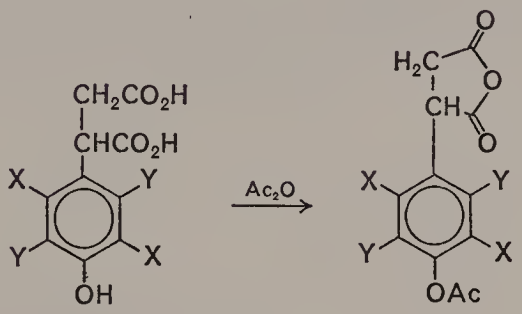
The application of the Wittig reaction to quinones has been expanded considerably by Bestmann and Lang who studied the addition of a methyl acetate residue to 1,4-benzoquinone[286]. As indicated in equation (223), quite similar chemistry was found in the initial phases of the reaction sequence. Further treatment of **84** produced *p*-hydroxyphenyl dicarboxylic acid derivatives (equations 224 and 225). In this same study it was shown that the Wittig reaction of 1,2-benzoquinones can lead to cyclic diethers analogous to those described earlier in this section (equation 226). A final note concerning the Wittig reaction with 1,2-quinones involves an interesting diene ylide and leads directly to cyclized product (equation 227)[287].



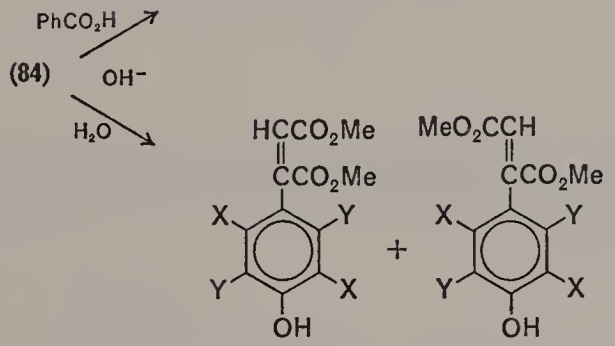


(84)

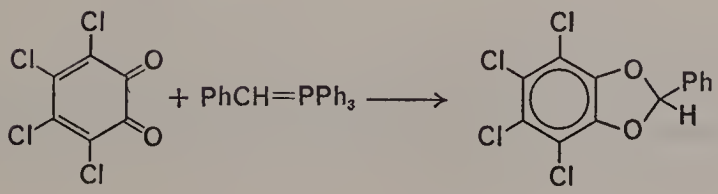
(223)



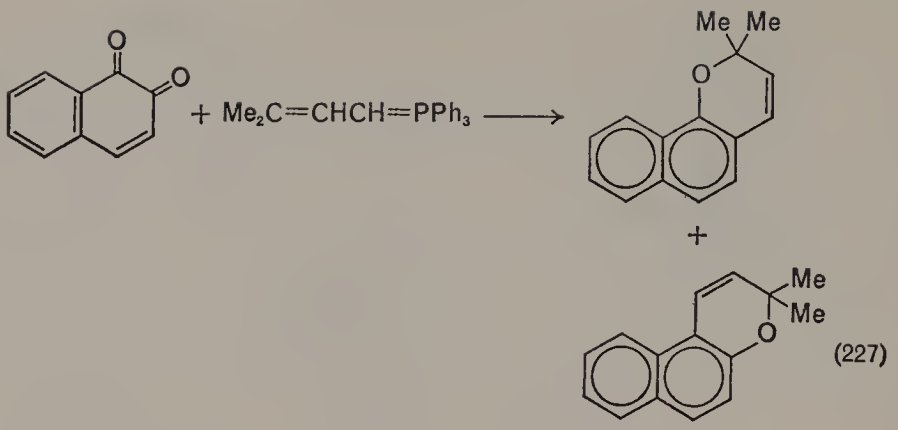
(224)



(225)

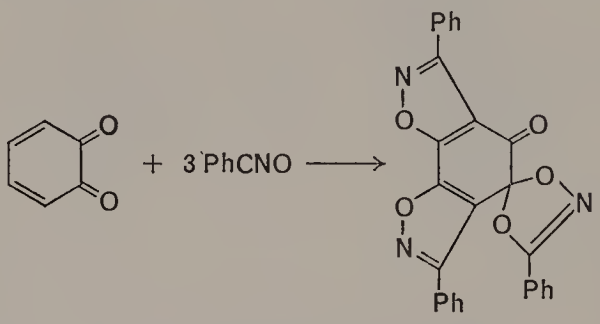


(226)



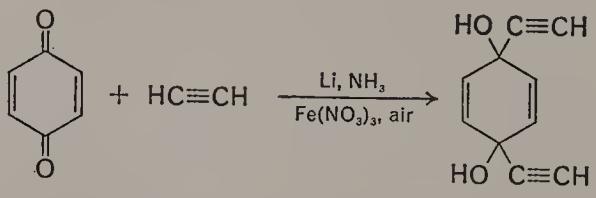
(227)

(4) Benzonitrile oxide will add to 1,2-quinones to produce rather complex heterocycles of the type shown in equation (228)[288]. The product shown is the only one found with 1,2-benzoquinone, but with 1,2-naphtho- and 9,10-phenanthrenequinone it was possible to isolate intermediates in which only the carbonyl groups had been attacked. These results are contrary to an earlier report by Awad and collaborators[289].



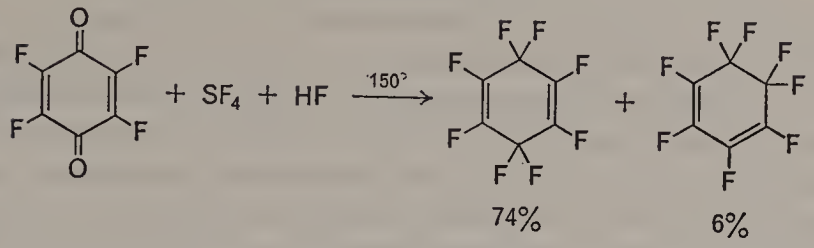
(228)

(5) The yield in the addition of acetylene to the carbonyl groups of 1,4-benzoquinone has been improved (> 70%) through the use of lithium amide (equation 229)[290].



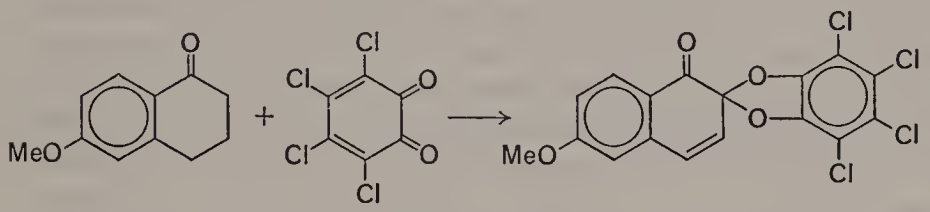
(229)

(6) The synthesis of perfluorocyclohexadienes can be accomplished by the treatment of fluoranil with a mixture of hydrofluoric acid and sulphur tetrafluoride (equation 230)[291].



(230)

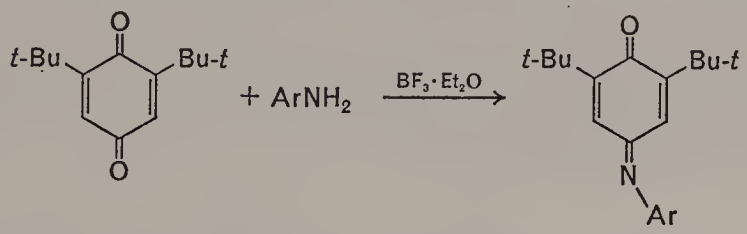
(7) A surprising reaction, formally related to the synthesis of cyclic diethers from diazo compounds, is the reaction of tetrachloro-1,2-benzoquinone with 6-methoxy-1-tetralone (equation 231)[292]. In a later and more



(231)

detailed study it was shown that the reaction is fairly general for tetralones and naphthols and that the most likely reaction pathway involves the dehydrogenation of the tetralone to a naphthol[293].

(8) An interesting exception to the normal mode of aniline addition to quinones (see section II.C) leads to a very useful preparation of highly hindered azomethine dyes (equation 232)[294]. In the case of *p*-phenylene-



(232)

diamine either the mono- or the bis-dye can be prepared. Electron-donating substituents facilitate the reaction and only the highly hindered quinones can be used.

IV. THE ADDITION OF RADICALS TO QUINONES

A. Polymerization Chemistry

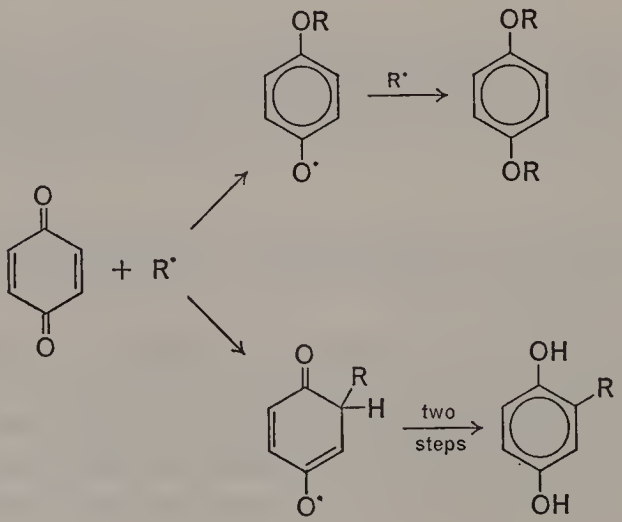
A sizeable literature concerning the chemistry of radicals and quinones has centred on quinones as inhibitors in radical polymerizations. Most of these studies have been concerned with the kinetics and the nature of the polymeric product, but some insight on quinone chemistry has been obtained. With styrene, the fate of the quinone was first thought to

involve either reduction or incorporation in the polystyrene being formed[295]. These ideas were discredited by the yellow colour of the product, the fact that the product(s) are formed at a time when essentially no polymer is formed and finally, its retention in solution at the later polymerization stage. It was then suggested that the quinone must be consumed by reaction with some simple, non-polymeric material[296]. Admittedly, it was not possible to obtain a pure sample of any reaction product.

The relationship between inhibition and copolymerization has been discussed and the suggestion made that slight changes in resonance stabilization of the intermediate radicals control the type of reaction observed[297]. The comparison made was of the difference between maleic anhydride (a superb copolymer participant) and 1,4-benzoquinone (a strong inhibitor) and these observations in spite of the compounds' obvious formal similarity in structure. This line of argument is in accord with radical addition to the quinone as an important step in inhibition.

Somewhat similar conclusions were reached by Price from a study of polystyrene formation in the presence of chloranil[298]. The isolated polymer contained one chloranil residue per polymer molecule and essentially none when the chloranil was added after polymerization, but before isolation. However, in this case there was no evidence of inhibition and it was concluded that chloranil acted as a chain-transfer agent.

On the basis of kinetic data for the inhibition and retardation of the rate of peroxide-initiated polymerization of styrene, Cohen also suggested a combination of carbon and oxygen alkylated products (equations 233 and 234)[299]. The alkylhydroquinone is, of course, free to be re-oxidized and to serve as an inhibitor again.

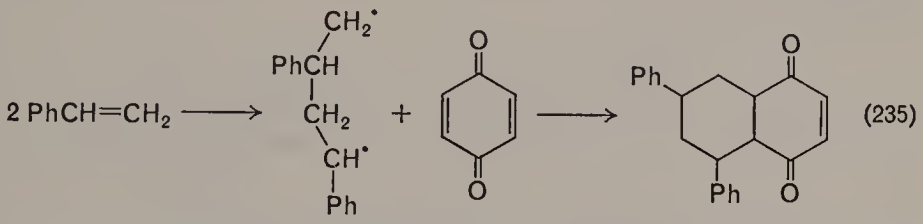


(233)

(234)

In a study designed, in part, to examine the chemical fate of the quinone inhibitor, the monomer allyl acetate was chosen[300]. The short chain length in this polymerization should result in a large number of quinone fragments being attached to the polymer. In a careful examination of the reaction mixture, no quinone could be recovered or found in solution. Cleavage of the polymer with hydriodic acid or cleavage of various polymer fractions gave hydroquinone product. These observations showed that all of the quinone is bound in the polymer. Examination of the u.v. and visible spectra showed that a combination of carbon and oxygen alkylation is most probable.

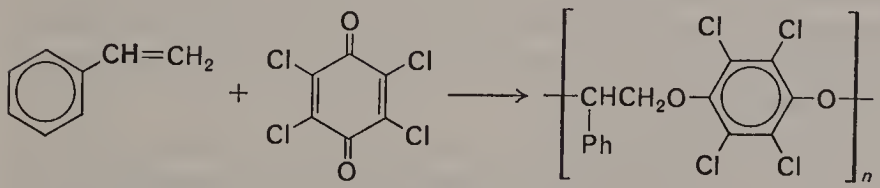
The first report of the isolation of a quinone inhibitor product occurred in the thermal polymerization of styrene[301]. This product corresponded approximately to two molecules of styrene and one of 1,4-benzoquinone. These observations were interpreted in the Diels–Alder fashion shown in equation (235).



(235)

It has been shown that chloranil will copolymerize with styrene in the presence of benzoyl peroxide[302]. The polymeric product contains three moles of styrene to two moles of chloranil. Degradative experiments with hydrobromic acid yielded strong evidence that the quinone is bound to the polymer by hydroquinone ether linkages (equation 236). Thus, at least in this particular case, oxygen attack is observed. Of course, this is not an example of inhibition.

The polymerization of methyl methacrylate can be conveniently initiated with α,α′-azoisobutyronitrile through the thermally generated 2-cyano-2-propyl radicals (equation 237)[303]. The importance of inhibitor–initiator termination and especially of carbon–oxygen bond formation



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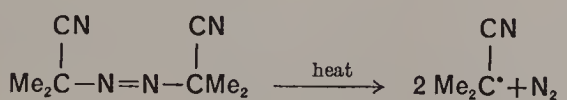
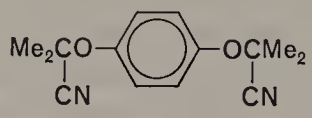


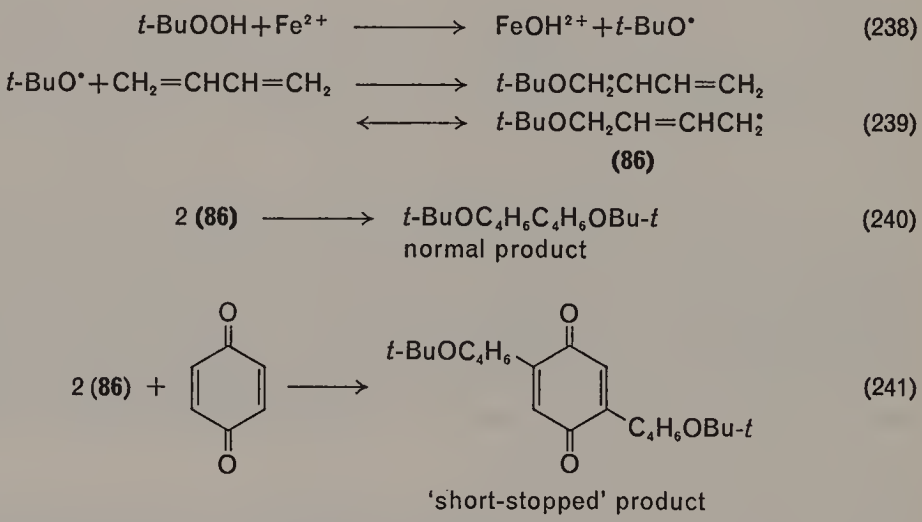
(237)

with quinones was established by the formation of the hydroquinone di(cyanoalkyl)ether (**85**).



(85)

A somewhat different view of the stage at which inhibition takes place is based on evidence supplied by Kharasch and colleagues[304]. When *t*-butyl hydroperoxide and ferrous salts initiate the polymerization of 1,3-butadiene at low temperature, it is possible to inhibit completely the reaction with quinones (equations 238–241). The use of either 1,4-benzoquinone or hydroquinone alone led to a sluggish reaction and the need for large amounts of ferrous ion. Quinhydrone produced a very rapid reaction.



$$t\text{-BuOOH} + Fe^{2+} \longrightarrow FeOH^{2+} + t\text{-BuO}^{\bullet} \quad (238)$$

$$t\text{-BuO}^{\bullet} + CH_2{=}CHCH{=}CH_2 \longrightarrow t\text{-BuOCH}_2^{\bullet}CHCH{=}CH_2 \longleftrightarrow t\text{-BuOCH}_2CH{=}CHCH_2^{\bullet} \quad (239)$$

(86)

$$2\,(\mathbf{86}) \longrightarrow t\text{-BuOC}_4H_6C_4H_6OBu\text{-}t \quad (240)$$

normal product

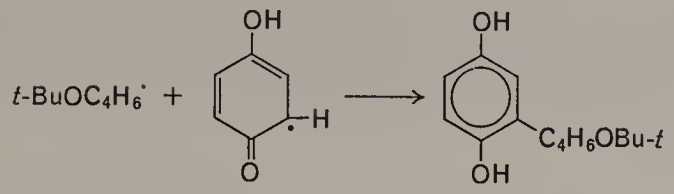
(241)

'short-stopped' product

The following scheme was proposed to account for these observations (equations 242–244).

It was found that 2-methyl-1,4-benzoquinone reacts in a similar fashion, but its semiquinone combines with only one *t*-butoxybutylene radical. Finally, chloranil was shown to terminate through reaction of the oxygen of the semiquinone (equation 245).

These results are consistent with the earlier work of Breitenbach and Renner[302] showing the formation of a copolymer of styrene and chloranil. More recently Kice has arrived at the same conclusion in the polymerization of methyl methacrylate[305]. He found evidence for very little copolymerization when 1,4-benzoquinone is the inhibitor.



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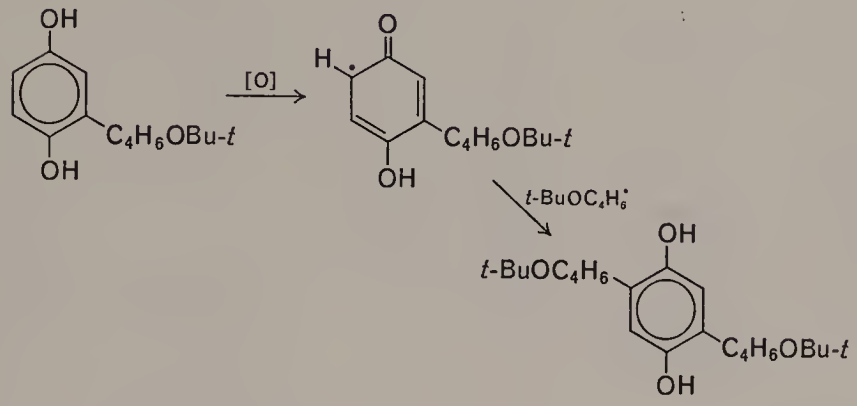

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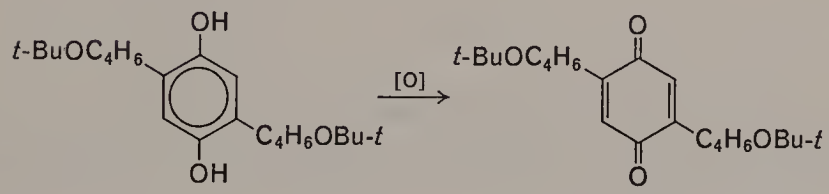

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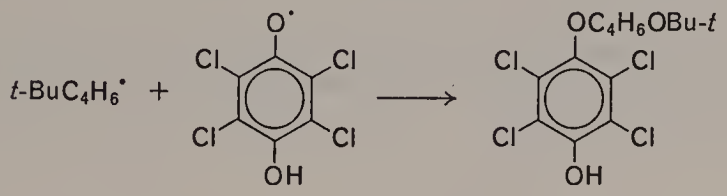


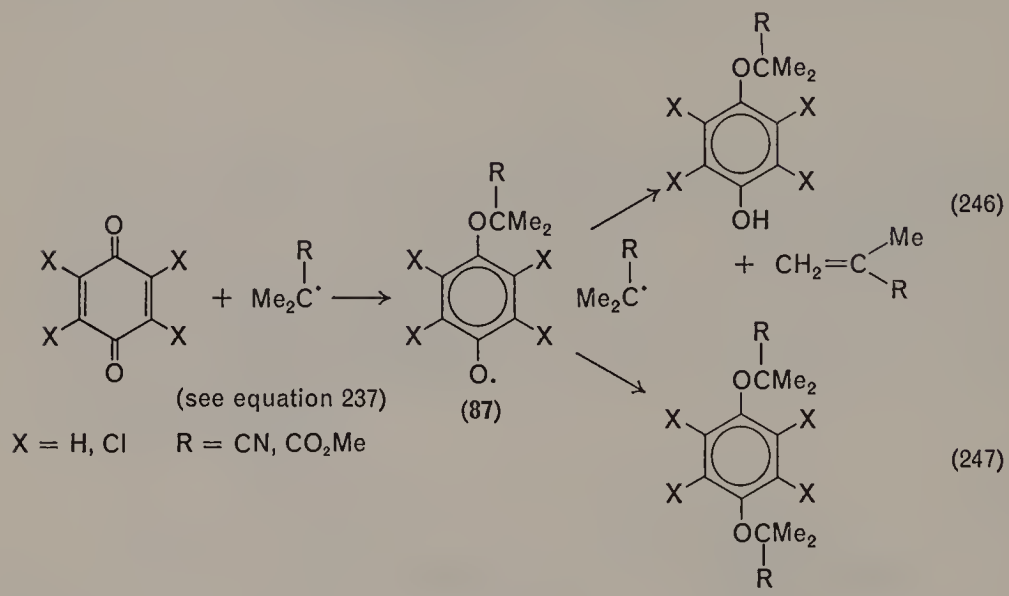
(245)

The studies cited thus far appear to be correct, but give a misleading impression of the fate of 1,4-benzoquinone in polymerization reactions. The polymerization kinetics for both styrene and methyl acrylate appear to be best understood in terms of 1,4-benzoquinone, as well as chloranil, being incorporated in the small amount of polymer formed during the induction period or inhibition phase[306,307]. The evidence once again points to reaction at oxygen.

B. Mechanism of Reaction with Simple Radicals

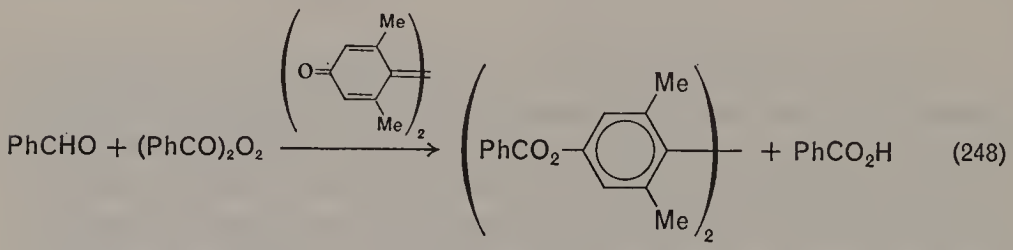
Interest in the effect of quinones on polymerization has stimulated study of the reactions of smaller, less complicated radicals. The widely used initiator α,α'-azoisobutyronitrile and its carbomethoxy analogue

have been generated in the presence of several quinones (equations 246 and 247)[308]. The aliphatic disproportionation products (methyl methylacrylate or methylacrylonitrile) were not isolated, but can be accounted



for by the high molecular weight material formed. The yields of the hydroquinone ethers were satisfactory considering the complexity of the system. Under similar conditions 2-methyl-1,4-naphthoquinone does not react.

A product isolated from the benzoyl peroxide oxidation of benzaldehyde, with a quinonoid retarder, is also consistent with the oxygen attack hypothesis (equation 248)[309].



The study of quinones and 2-cyano-2-propyl radicals has been extended to a series of substituted quinones[310]. The data in Table 8 are given in crude yields because of difficulties in separation and purification. There is some correlation between the redox potential of the quinone and the extent of its reaction with the radical. Steric effects obviously play a role in some cases (e.g. 2,5-di-*t*-butyl-1,4-benzoquinone). The unreliability of the yield data reduces the strength of the argument, but there does seem

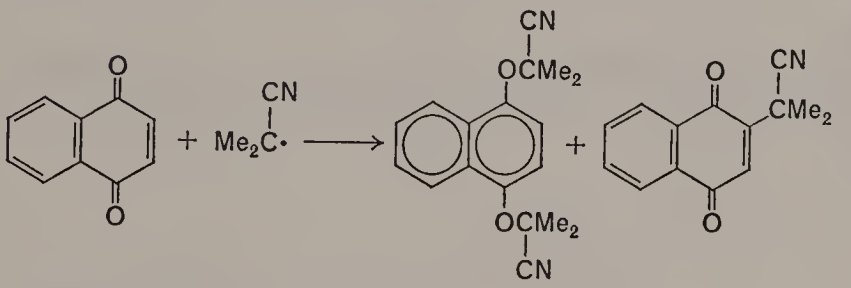
TABLE 8. Product yield and redox potentials for the reaction of 2-cyano-2-propyl radicals and 1,4-benzquinones[310]

Quinone substituent(s)	Yield (%)			Quinone redox	Phenol[b] critical oxidation
	Monoether	Diether	Dimer[a]	Potential (V)	Potential (V)
Cl_4	17	67	44·1	0·703	—
2,5-$(AcO)_2$	23	32	18·0	—	—
None	56	10	25·7	0·711	1·089
2-Me	31	46	26·0	0·653	1·037
2,6-Me_2	8·6	41	37·6	0·600	0·985
2,5-Me_2	5·9	35	47·5	0·597	0·985
2-Me-5-*i*-Pr	1·0	32	49·2	0·589	—
2,5-$(EtO)_2$	2·3	26	57·8	0·480	0·619
2,5-*t*-Bu_2	0	0	—	0·554	—
Me_4	0	0	67·0	0·466	—

[a] Tetramethylsuccinonitrile.

[b] Of the corresponding monohydric phenol; e.g. 1,4-benzoquinone–phenol.

to be a correlation between ratio of mono : di ethers and the critical oxidation potential of the corresponding monohydric phenol. This potential can be supposed to be a measure of the stability of the aryloxy radical, **87**. The polycyclic quinones react only slightly, if at all, as would be expected from their redox potentials. A small amount of ring addition is found with 1,4-naphthoquinone and 2,5-dimethyl-1,4-benzoquinone as well as ether formation (equation 249).

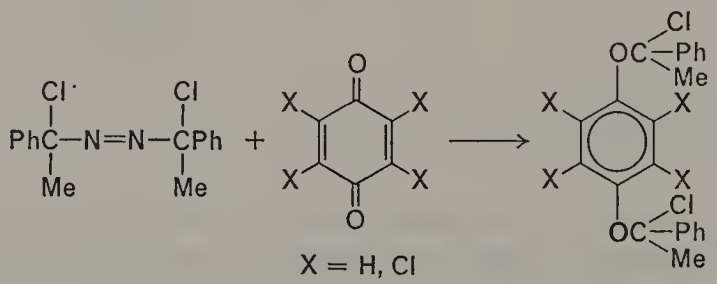


(249)

The conflicting evidence regarding product structure in quinone termination of polymerization reactions (i.e. carbon–carbon versus carbon–oxygen bond formation) has been explained as the result of our using incomparable studies of very reactive radicals (Me$^{\bullet}$ and Ph$^{\bullet}$) and much less reactive radicals (growing polymer chains). A detailed study of the methyl affinities of quinones adds strength to this argument[311,312].

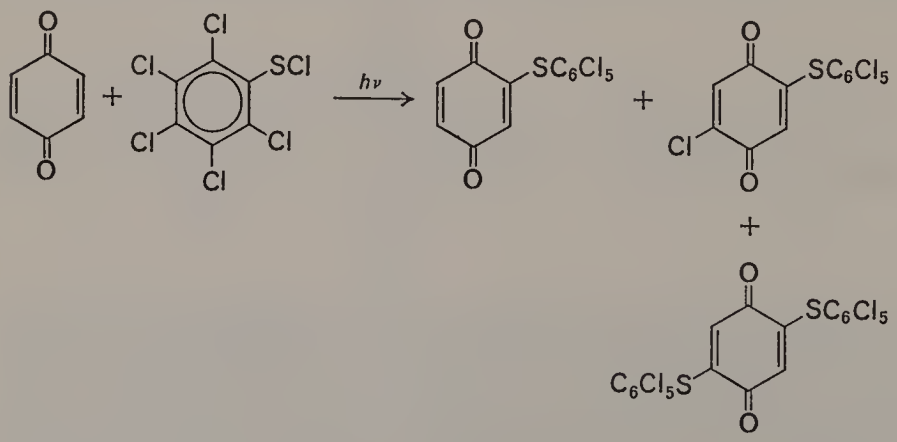
Szwarc and collaborators suggest that the isolation of products may not give unambiguous answers concerning the initial point of radical attack. They prefer to apply a kinetic argument based on the rate of reaction of methyl radicals with various substituted quinones. It was found that predictions based on both electronic and steric effects are consistent only with the observed rates for carbon–carbon bond formation; i.e. ring addition. It was also determined that styryl radicals are less than half as reactive as methyl radicals under the conditions employed.

A few reports of the reactions of various radicals with quinones have appeared, but none of these could be considered detailed studies. For example, the thermal decomposition of bisazo compounds to form radicals has been expanded slightly (equation 250)[313]. The ether products hydrolysed readily in aqueous ethanol to give the appropriate hydroquinone and acetophenone.



(250)

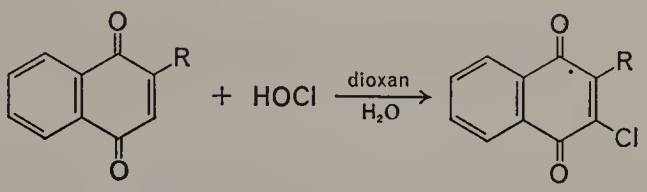
Earlier the possibility of radical addition of thiols was mentioned as a possible alternative to nucleophilic addition (see section II.B.2). While such a mechanism has been invoked, the only promising work is that of Kharasch and Ariyan with sulphenyl chlorides (equation 251)[314]. The



(251)

reaction does not take place in the dark, but no e.s.r. signal was found. The structure of the disubstituted quinones was assumed to be 2,5.

Aqueous hypochlorous acid has been reported to cause the epoxidation of quinones, but a careful examination of such reaction mixtures revealed that no reaction takes place[315]. When solution is obtained with added dioxan, the quinone is converted to the chloro derivative in good yield (equation 252). With peroxide-free solvents very low yields were obtained.



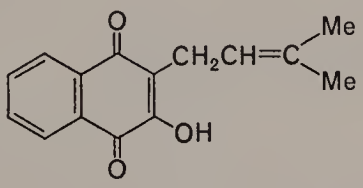
R = H, Me (252)

The *in situ* generation of hypochlorous acid converted 1,4-naphthoquinone to an approximately equimolar mixture of 2-chloro- and 2,3-dichloro-1,4-naphthoquinone.

C. Alkylation

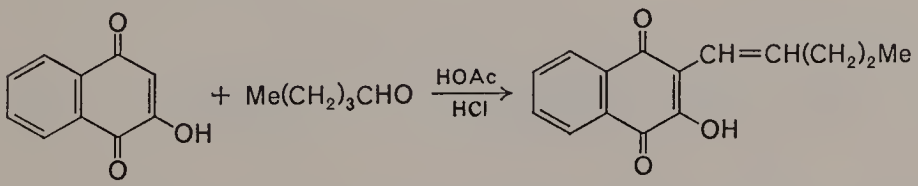
1. Historical introduction

The naturally occurring quinonoid compound lapachol **88** has held a great deal of interest for synthetic organic chemists over a very long



(88)

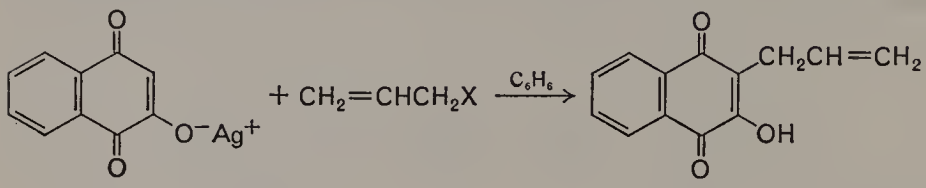
period of time[2,316]. Some of the earliest work was concerned with the structure of the alkyl side-chain and introduced the useful aldehyde alkenylation reaction (equation 253)[317].



(253)

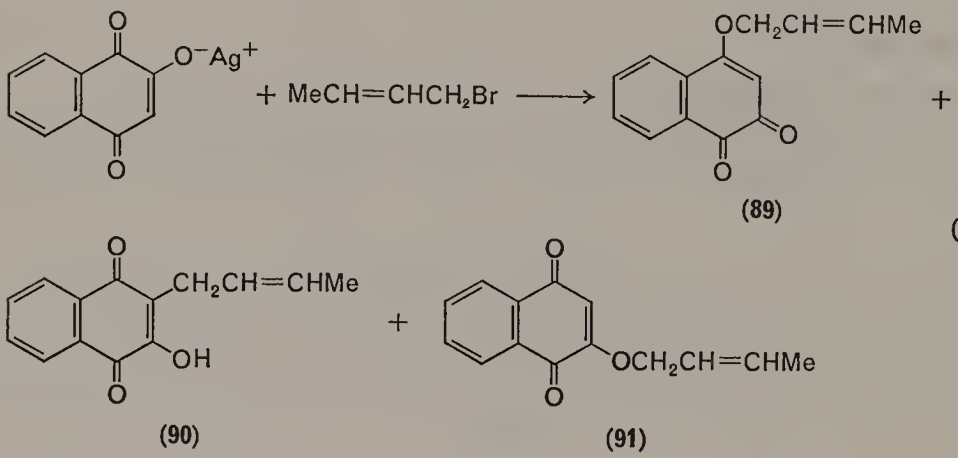
In his studies of the tautomeric equilibrium of *ortho*- and *para*-quinones, Fieser found that very reactive unsaturated and benzylic alkyl halides react with the silver salt of 2-hydroxy-1,4-naphthoquinone to produce 2-alkyl-3-hydroxy derivatives (equation 254)[318]. The reaction was regarded

as 1,2-addition followed by the elimination of silver halide. Alkylation on oxygen also takes place in most instances. The detailed reasons for the amounts of *O*- and *C*-alkylation are undoubtedly more complex than the reactivity of the halide.



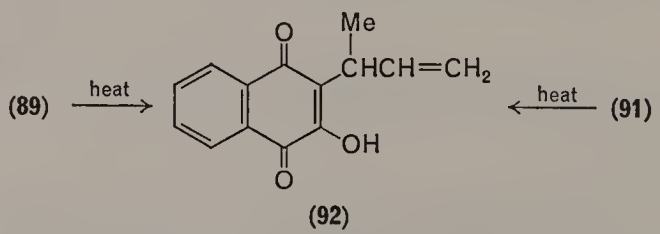
(254)

The alkylation of the silver salt of 2-hydroxy-1,4-naphthoquinone has also been used as a synthesis of lapachol[319]. The question of direct alkylation versus Claisen rearrangement was answered by the synthesis of the two possible *O*-crotyl ethers of 2-hydroxy-1,4-naphthoquinone (equation 255). The Claisen rearrangements of both **89** and **91** produce a



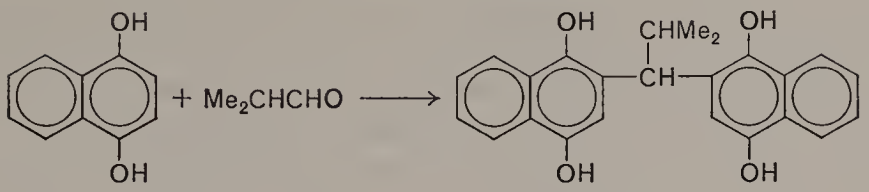
(255)

single compound, **92**, that is isomeric with the direct alkylation product, **90**. The change of structure in the Claisen rearrangement was already known[320] and the facts require a direct alkylation of the quinonoid ring.



(256)

The aldehyde alkenylation reaction (equation 253) is not general; 1,4-naphthoquinone is reduced and then converted to a product containing two hydroquinone residues (**93** in equation 257)[321]. Hooker had



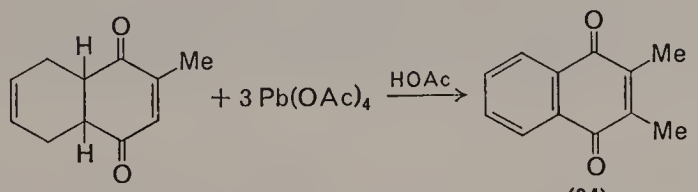
(257)

(93)

already reported that under certain conditions two moles of quinone can condense with aldehydes. In view of the rather extensive subsequent literature concerning these compounds, including their synthesis by independent routes, there seems to be little question of the correctness of the structures. It is probably significant that Fieser fails to mention Raudnitz and Puluj in the eleven posthumous Hooker papers he completed, wrote or edited[322].

2. Acyl peroxide alkylation

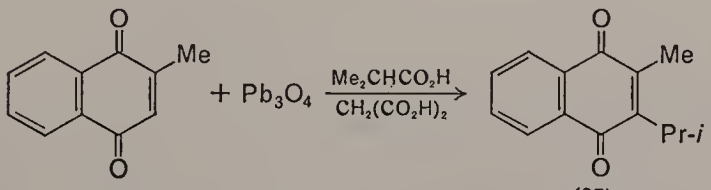
Fieser and his students have made extensive contributions to the techniques available for the alkylation of quinones. One of the earliest, perhaps one of the most important, is the remarkable methylation with lead tetraacetate (equation 258)[323]. The structure of product **94** was definitely



(258)

(94)

established and the generality of the reaction explored. The addition of an active-hydrogen compound permits smooth alkylation of 1,4-naphthoquinone under mild conditions and in quite reasonable yields. It is also possible to employ higher homologues of the lead salt and thus to introduce longer alkyl chains. These lead salts can be generated *in situ* (equation 259).

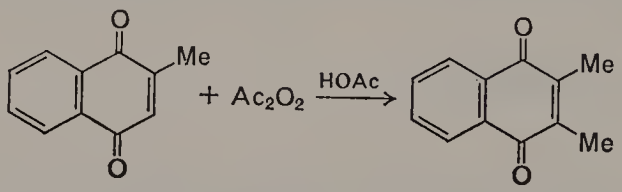


(259)

(95)

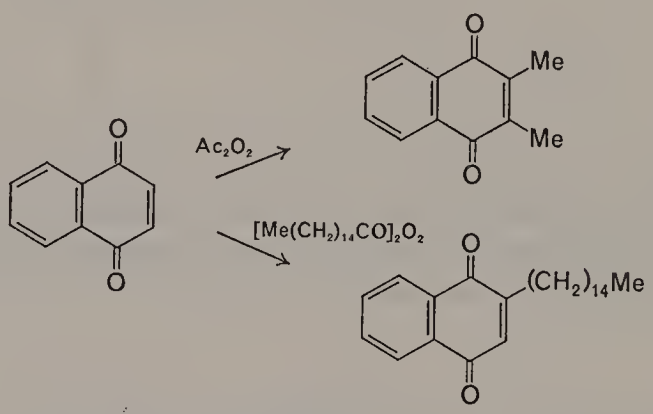
Treatment of 2-isopropyl-1,4-naphthoquinone with lead tetraacetate also produces **95**. It is interesting to note that the introduction of a methyl group adjacent to a larger alkyl group is subject to much more steric retardation than the reverse process (e.g. equation 259).

A later study of this methylation by lead tetraacetate, and alkylation with higher homologues, produced some interesting mechanistic evidence[324]. When 2-methyl-1,4-naphthoquinone is heated at 90–100°C in acetic acid with excess lead tetraacetate, no reaction occurs. Upon addition of a wide variety of materials gas is evolved, usually vigorously, and 2,3-dimethyl-1,4-naphthoquinone is formed. Included in the list of promoters are water, alcohols and hydrocarbons (e.g. benzene and cyclohexane). All of these, except *t*-butyl alcohol, promote the decomposition of lead tetraacetate to carbon dioxide and a neutral, flammable gas, thought to be ethane. Several of the observations concerning the reaction suggest that it might be related to the Kolbe reaction and led Fieser and Oxford to study alkylations with diacyl peroxides (equation 260). It was



(260)

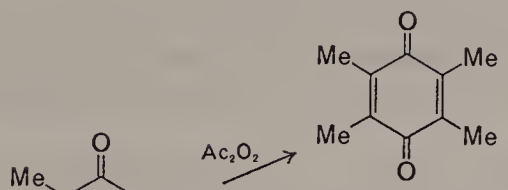
found that the method could be applied for the introduction of a wide variety of alkyl groups including some alkenyl or cycloalkenyl groups. The reaction is subject to a steric effect that makes it somewhat more selective with the higher acid peroxides (equations 261 and 262).



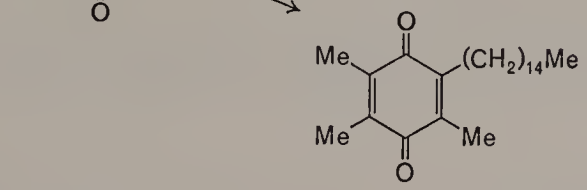
(261)

(262)

Alkylation can also be accomplished in the 1,4-benzoquinone series (equations 263 and 264). Methoxy groups appear greatly to reduce the reactivity of the quinone while hydroxy and bromo groups (on the basis of limited study) seem to enhance reactivity. The bromine atom may serve a very useful synthetic role as a blocking group (equation 265). The results obtained with dibenzoyl and dicinnamoyl peroxides were not promising, but might be improved by changing the experimental conditions.



(263)



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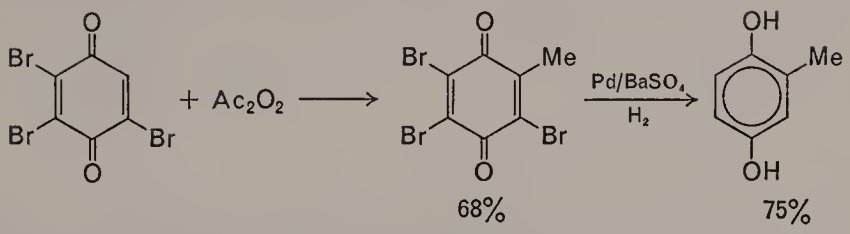
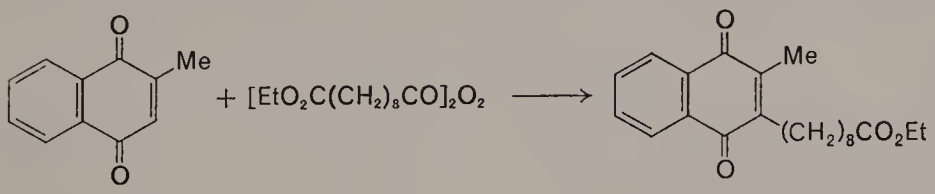


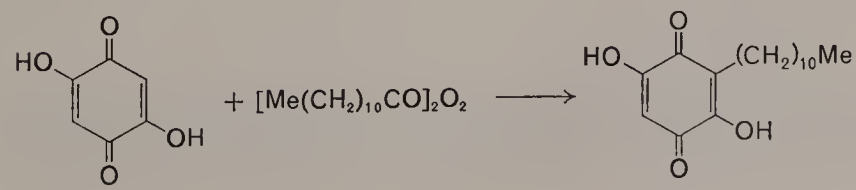
(265)

Finally, it is not necessary to purify the peroxides to achieve quite acceptable product yields. In general, the reagent was prepared by the reaction of the appropriate acid chloride with excess sodium peroxide in ligroine.

A large number of applications of the peroxide alkylation method, some with important extensions, have been made by Fieser and collaborators. For example, the introduction of alkyl groups ending in other functional groups has been accomplished (e.g. equation 266)[325]. The synthetic aspects of structure determination for some interesting natural products have been achieved (e.g. equation 267)[326]. It may be



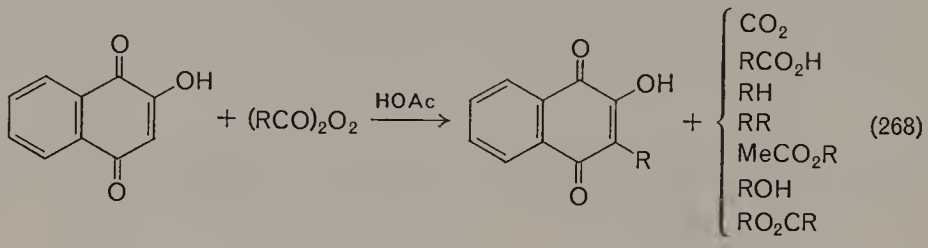
(266)



(267)

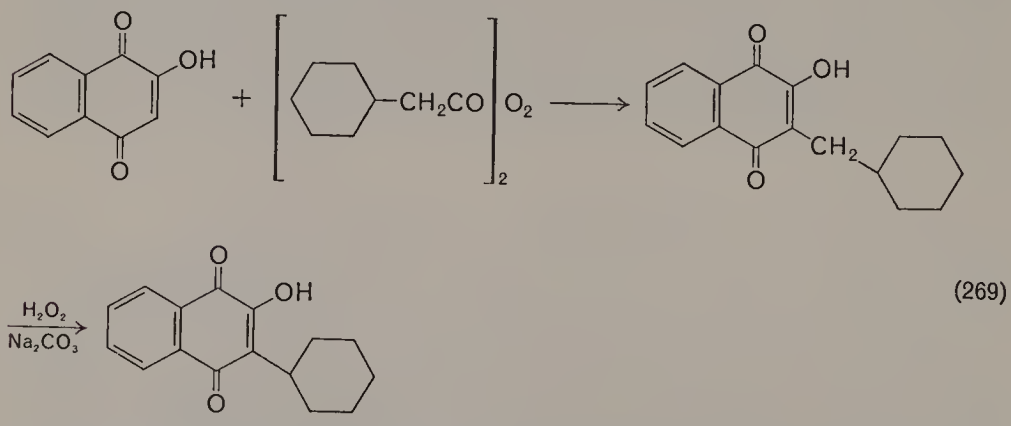
noted that there are limitations of unknown extent in this alkylation procedure; Fieser and Chamberlin reported low yields and difficulty in obtaining crystalline product, especially in cases involving long, unsaturated hydrocarbon chains.

The magnificent effort made to find naphthoquinones with anti-malarial activity was, to a very large extent, centred on the alkylation reactions with acyl peroxides[327]. While the main purpose of this work was the synthesis, characterization and testing of potential drugs, the observations made are useful in understanding the alkylation reaction. Some of the by-products have been identified (equation 268) and clearly



(268)

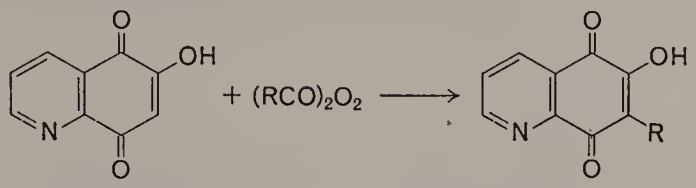
conform with the expected radical process. Four major structural limitations were found: peroxides of α-carbon branched chain, cycloalkane, aromatic and benzylic carboxylic acids all gave very low yields, if they reacted at all. A wide variety of substituents and functional groups may be included in the rings and chains without interfering with the peroxide alkylation. The compounds cited above as being difficult to prepare directly were usually obtained in quite reasonable yield by the synthesis of the next higher homologue and the application of the Hooker oxidation (equation 269)[322, 328].



(269)

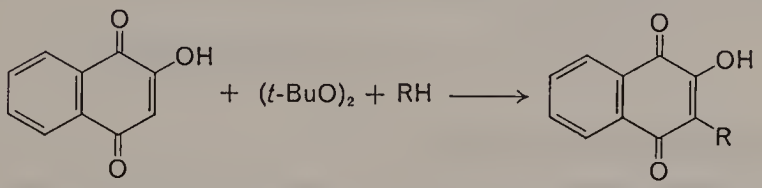
The heterocyclic quinones 6(or 7)-chloro- and 6-hydroxy-5,8-quinoline-quinone have been alkylated using the diacyl peroxide method (equation

270)[329–332]. A very wide range of R groups has been employed and the yields have been fair to good in most cases. The 7-hydroxy isomer has also been used in one instance.



(270)

A very interesting recent kinetic study has led to the synthetic complement of Fieser's alkylation reaction[333]. The decomposition of *t*-butyl peroxide in the presence of a hydrocarbon and 2-hydroxy-1,4-naphthoquinone leads to the 3-alkyl-2-hydroxy-1,4-naphthoquinone (equation 271). The chief synthetic limitation of this reaction lies in the fact that



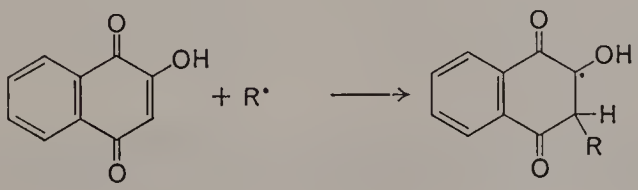
(271)

several products will be formed if hydrogen abstraction from the hydrocarbon leads to more than one radical. For simplicity in the kinetic study, cyclohexane and potential benzylic radicals were chosen and they gave excellent yields of product. The 3-alkyl products obtained in these model cases are just those most difficult to prepare by the earlier route.

The proposed mechanism involves the radical-chain process shown in equations (272) to (276) (plus the usual termination reactions). The rate of decomposition of *t*-butyl peroxide was studied both with an excess and with less than a stoicheiometric amount of 2-hydroxy-1,4-naphthoquinone. In the former case the observed rate was very much faster than that of the peroxide alone. With a limited amount of quinone, two rates were found: a fast initial rate when the quinone was present and a second

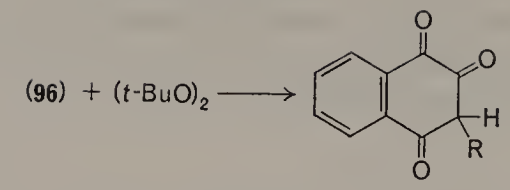
$$(t\text{-BuO})_2 \longrightarrow 2\,t\text{-BuO}^{\bullet} \qquad (272)$$

$$t\text{-BuO}^{\bullet} + \text{RH} \longrightarrow \text{R}^{\bullet} + t\text{-BuOH} \qquad (273)$$



(274)

(96)



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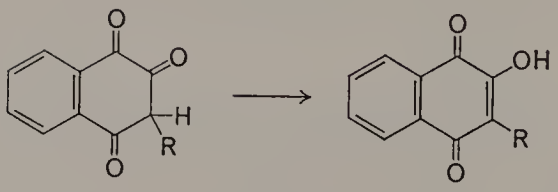


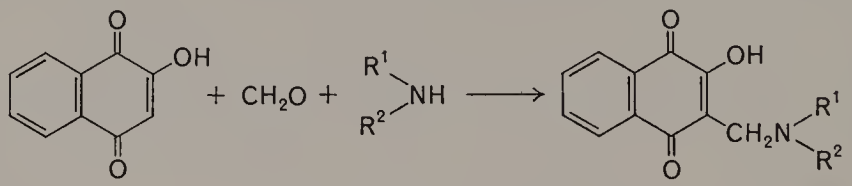
(276)

slower rate close to that of the peroxide alone. These observations are consistent with the proposed mechanism which requires the following rate expression for peroxide loss (equation 277):

$$-\frac{d\,[\text{peroxide}]}{dt} = k[\text{peroxide}] + k[\mathbf{96}]\,[\text{peroxide}] \qquad (277)$$

3. Related alkylation reactions

As yet another aspect of their antimalarial search, the Harvard–Abbott team investigated the application of the Mannich reaction (equation 278)[334]. Amines that gave the most satisfactory results were primary,

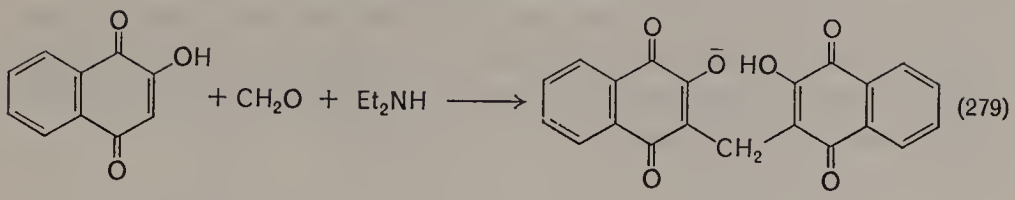


(278)

R^1, R^2 = H, alkyl, heterocyclic ring

secondary and alicyclic. Most of the products were stable enough to be recrystallized in the usual manner, but in some cases, e.g. when R^1 and R^2 make up a morpholine ring, the purification was effected by solution in dilute hydrochloric acid and precipitation with cold sodium acetate solution. Some very strange observations were made in this study; for example, dimethylamine and piperidine gave excellent yields of product while diethylamine gave only the salt of 3,3′-methylene-bis-2-hydroxy-1,4-naphthoquinone (**97** in equation 279). Both mono- and diammonium salts appear to be formed.

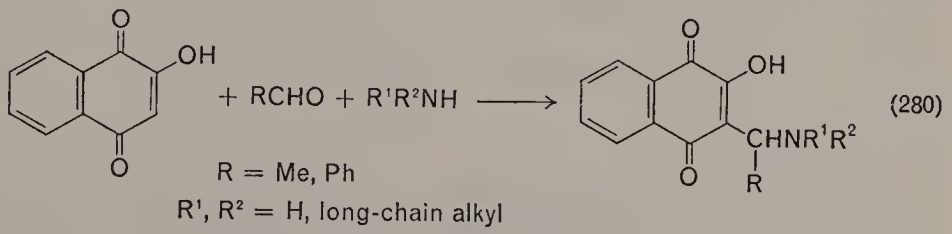
A later study was directed at placing bulkier groups on the nitrogen in order to improve the antimalarial activity[335]. Under milder conditions than reported earlier excellent yields of products were obtained with



(279)

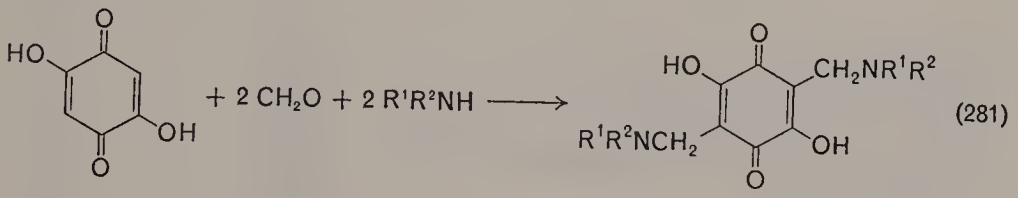
(97)

C_8–C_{18} *n*-alkyl primary amines. The products yielded crystalline hydrochlorides that were recrystallized from ethanol. The higher secondary amines gave only analogues of **97** and anilines gave insoluble products that were not characterized. It was found that acetaldehyde and benzaldehyde can be used in place of formaldehyde, while propionaldehyde and crotonaldehyde cannot (equation 280). The reaction took place very



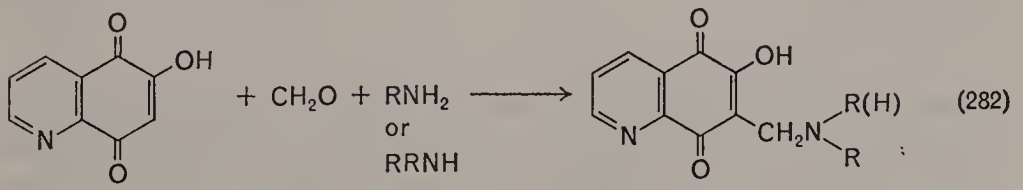
(280)

readily with 2,5-dihydroxy-1,4-benzoquinone and gave the 3,6-bis product (equation 281).



(281)

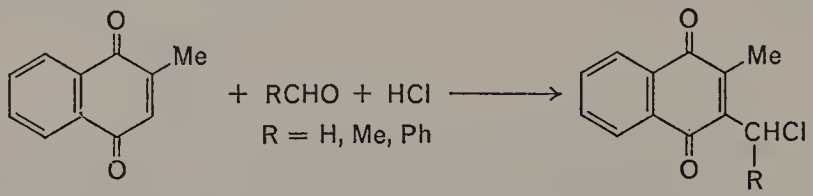
The Mannich reaction of primary and secondary amines has been applied to 6-hydroxy-5,8-quinolinequinone with reasonable success (equation 282)[329]. Once again diethylamine showed abnormal behaviour and failed to produce the expected product.



(282)

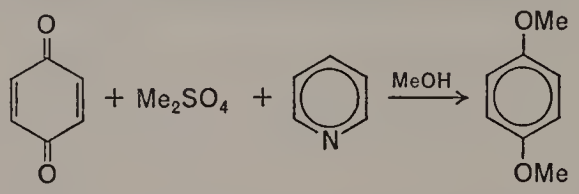
A somewhat similar reaction has been used to prepare chloromethyl derivatives of 1,4-naphthoquinones (equation 283)[336]. The scope of the reaction is severely limited because 1,4-benzoquinones prefer to add HCl

rather than chloroalkylate and very few aldehydes are useful. In fact, only certain combinations of quinone and aldehyde appear to react cleanly. The 2,3-bis-chloromethyl product is obtained from 1,4-naphthoquinone and formaldehyde.



(283)

An example of reductive *O*-methylation of quinones has been reported[337]. The reaction (equation 284) is not general and roughly the yield is a function of the redox potential of the quinone as indicated in Table 9.

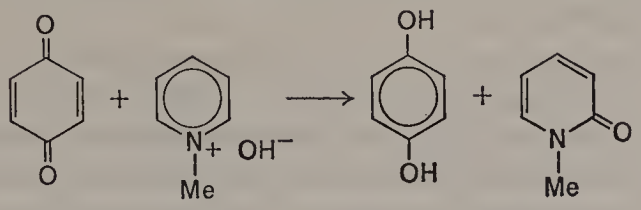


(284)

TABLE 9. Reductive methylation of quinones[337]

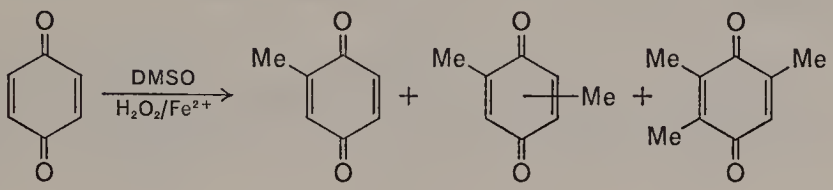
Quinone	Redox potential (V)	Yield (%)
1,4-Benzoquinone	0·711	74
2,5-Diphenyl-1,4-benzoquinone	0·673	79
2-Methyl-1,4-benzoquinone	0·657	60
2-Methyl-5-isopropyl-1,4-benzoquinone	0·589	30
1,2-Naphthoquinone	0·576	10
1,4-Naphthoquinone	0·483	14
2,3,5,6-Tetramethyl-1,4-benzoquinone	0·480	0
2,5-Dimethoxy-1,4-benzoquinone	0·470	0
2,5-Dihydroxy-1,4-benzoquinone	0·434	0
Retenequinone	0·410	0
Anthraquinone	0·155	0

It was shown that no reduction occurs in the absence of dimethyl sulphate and that no reaction takes place without pyridine. The known Decker reaction suggests that *N*-methylpyridinium hydroxide is the reducing agent[338]. When 1,4-benzoquinone was treated with this reagent alone it was reduced to hydroquinone and *N*-methyl-2-pyridone was isolated (equation 285).



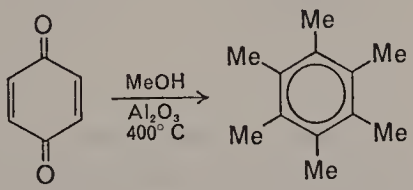
(285)

When 1,4-benzoquinone in dimethylsulphoxide solution is treated with an equimolar amount of hydrogen peroxide in the presence of ferrous ion, a mixture of various methyl-1,4-benzoquinones is produced in low yield (equation 286)[339]. This interesting reaction requires extensive modification if it is to have any synthetic utility.



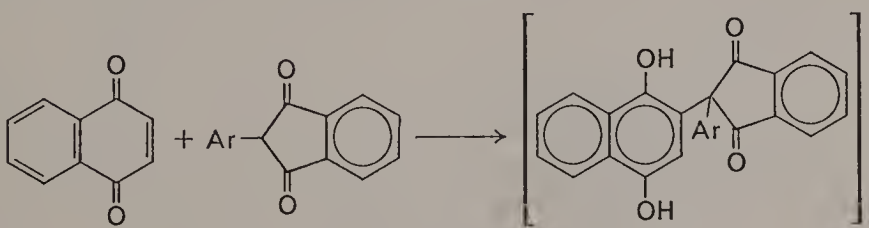
(286)

In an effort to find a simple preparation of pentamethylbenzene, 1,4-benzoquinone in methanol was treated with alumina at high temperature (equation 287)[340]. The only product characterized was hexamethylbenzene. Once again, this reaction could be of great importance if greater control of it could be established.



(287)

Finally, an exotic alkylation reaction has been reported recently (equation 288)[341]. The naphthohydroquinones formed initially are rather unstable and were not isolated, but could either be oxidized or acetylated to stable products.

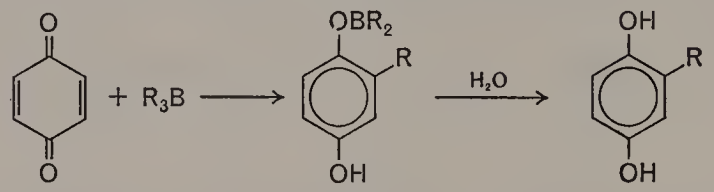


(288)

Ar = Ph, 4-MeC_6H_4, 4-$NO_2C_6H_4$, 4-ClC_6H_4

4. Hydroboration

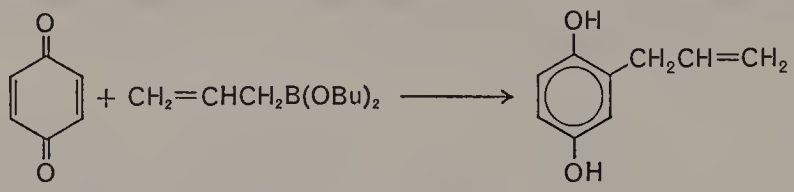
In view of the extensive use of alkylboranes in organic synthesis, it is not surprising that they have been applied to the alkylation of quinones[342, 343]. The reaction at first appeared to be restricted to 1,4-benzoquinones. Actually, only 1,4-benzoquinone itself was investigated carefully. There is every reason to believe that a wide variety of functional groups might be introduced and that conditions might be found under which more highly substituted quinones will react satisfactorily. The isolation of the monodialkylborinic acid ester of the alkylhydroquinone (**98**) offers some mechanistic information (equation 289). The quinol ester, probably formed initially, may rearrange under the influence of a second mole of trialkylborane acting as a Lewis acid.



(289)

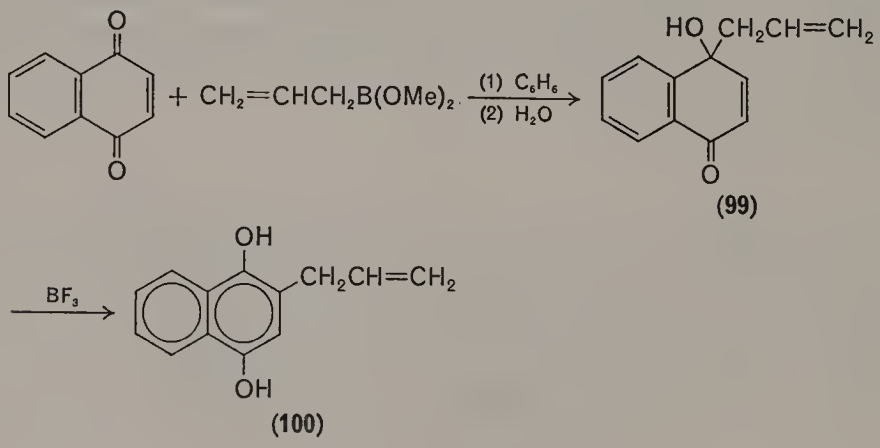
(98)

A study of the reaction of boric acid esters has added to the synthetic range of quinone hydroboration (equation 290)[344]. The reaction takes



(290)

place smoothly and the yield is quite good. A similar reaction with 1,4-naphthoquinone, under milder conditions, allows the isolation of an intermediate, **99**, of mechanistic significance (equation 291). The structure



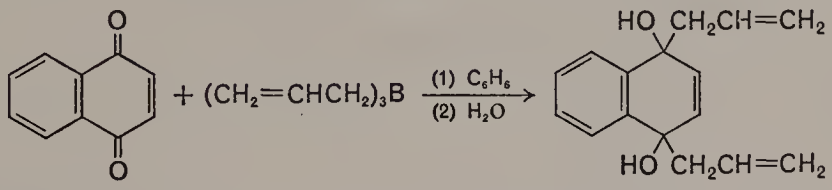
(291)

(99)

(100)

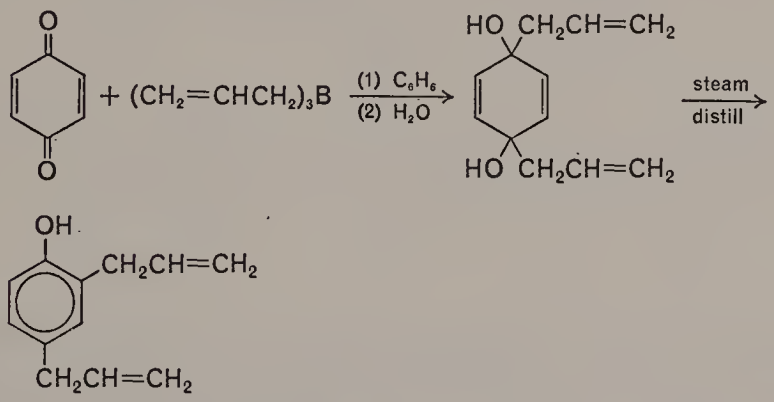
of **99** was determined from its i.r. spectrum. In refluxing benzene the final product, **100**, is obtained directly. Apparently the boric ester acts as the Lewis acid.

The reactivity of triallylborane towards quinones is somewhat greater than the trialkylboranes and both 1,4-benzoquinone and 1,4-naphthoquinone give a good yield of the di-1,2-carbonyl addition product (equation 292). When the analogous 1,4-diallyl-1,4-dihydroxy-2,5-cyclohexadiene



(292)

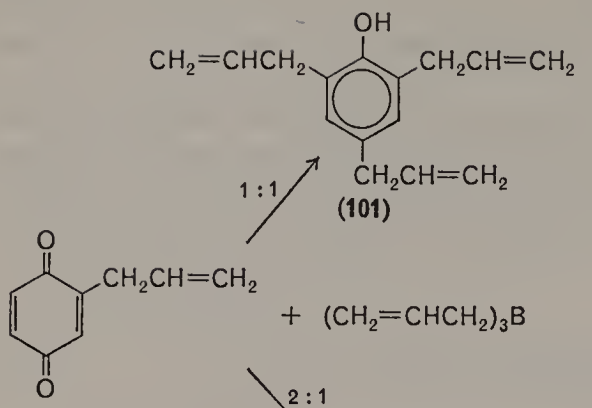
(actually either of the two separated geometric isomers *cis*-major, *trans*-minor) is steam distilled, the known compound 2,4-diallylphenol is formed (equation 293).



(293)

Questions related to hydroboration of substituted 1,4-benzoquinones have been studied in a few cases (i.e. *n*-butyl and 2-allyl-1,4-benzoquinone with triallylborane)[344,345]. The nature of the reaction appears to depend strongly on the ratio of reactants (equations 294 and 295). The overall yield (75% and 67% respectively), while not quantitative, are high enough for the product distribution to be a reasonably accurate estimate of the reaction outcome. The butyl group led only to 4,6-diallyl product (equation 296)[345]. Reaction with 1,2-naphthoquinone gave the bis-carbonyl addition product analogous to equation (292).

Until recently the hydroboration of 1,4-naphthoquinone had not been studied as extensively as 1,4-benzoquinone[346]. It was found that, in addition to alkylation, a significant amount of reduction (15–20%) takes place and complicates the separation and purification of product.



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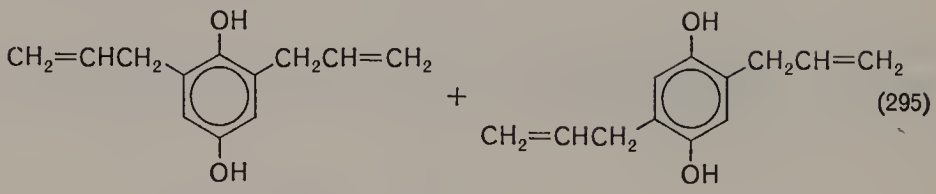

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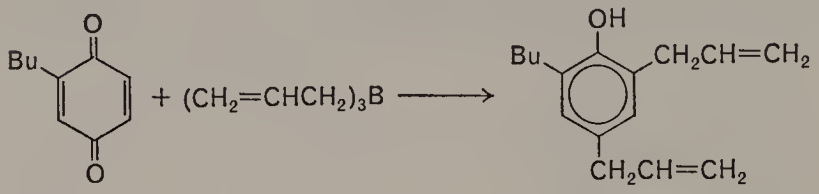
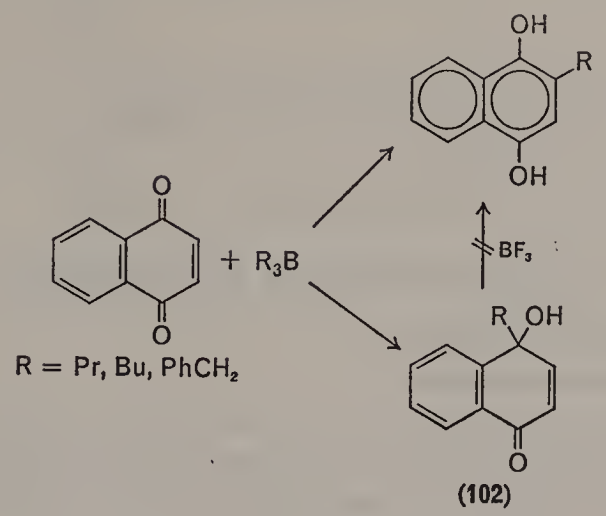


(296)

This problem can be overcome most easily by simply oxidizing the products at once and isolating the desired quinone. The 1,4-naphthoquinones appear to react by a 1,4-addition mechanism because the product of 1,2-addition to the carbonyl group (**102**) is not converted to the 2-alkyl-1,4-naphthalenediol by boron trifluoride. This difference from earlier work with allylboranes suggests two different reaction paths (equations 297 and 298). The reactions of 1,4-benzoquinone and 1,4-naphthoquinone with dibenzylborinic anhydride were studied (equation 299). The yields were only fair and 1,4-naphthoquinone gave a little **102** as well as 2-benzyl-1,4-naphthalenediol.

A recent study sheds additional light on the mechanism of alkylation with trialkylboranes[347]. Kabalka offers evidence that the alkylation is a radical process by showing that iodine, and to a smaller extent galvinoxyl, inhibits the addition of triethylborane to 1,4-benzoquinone. He pictures the mechanism as a radical addition to the carbon–carbon double bond (equations 300–302). A consequence of this hypothesis is that the so-called



(297)

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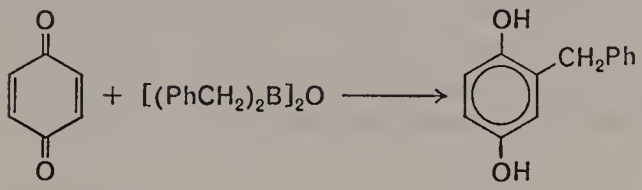

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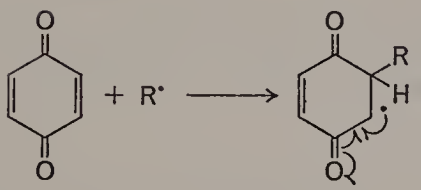

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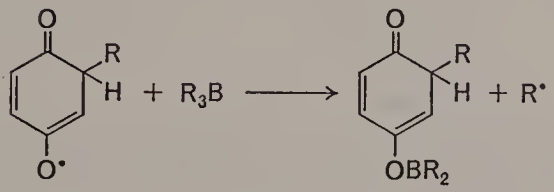

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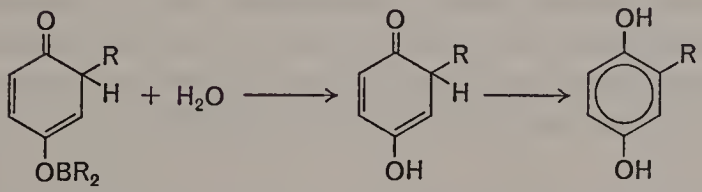
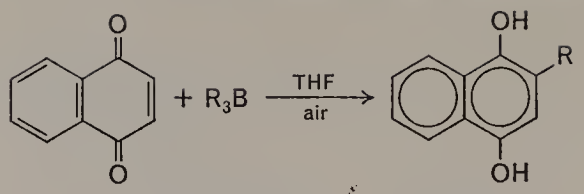


(302)

unreactive quinones (see, however, references 344–346) simply suffer from short chain lengths and require more efficient initiation. This point was demonstrated by the excellent yields of 2-alkyl-1,4-naphthalenediols obtained when air was passed through the reaction mixture (equation 303).



(303)

R = Et, Bu, C_6H_{11} 85–95%

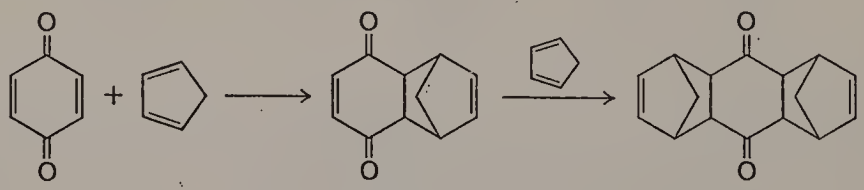
V. CYCLOADDITION TO QUINONES

A. The Diels–Alder Reaction

1. Historical introduction

A wide variety of quinones have been used in the diene synthesis developed by Diels and Alder. The synthetic facts in the earlier literature have been systematically reviewed and will not be treated here[348]. Our main concern is with quinonoid dienophiles which have provided understanding of the mechanistic details of this important synthetic tool. Current synthetic efforts have been included where they are somewhat different from the earlier reports. An important current review will appear shortly[348a].

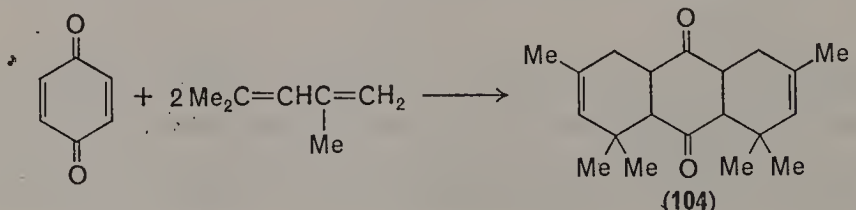
A quinone Diels–Alder reaction of particular interest had actually been carried out more than twenty years before Diel's and Alder's papers began to appear[349], but was not correctly understood until their re-investigation (equation 304)[350,351].



(304)

(103)

I have found only one early example of a quinone Diels–Alder reaction not mentioned by Butz and Rytina. The rate of oxime formation was used as evidence for the structure of a Diels–Alder adduct (equation 305)[253]. It was found that the product obtained formed a monooxime in two hours and a dioxime very slowly. On this basis the structure **104** was chosen because one carbonyl group is much more hindered than the other.

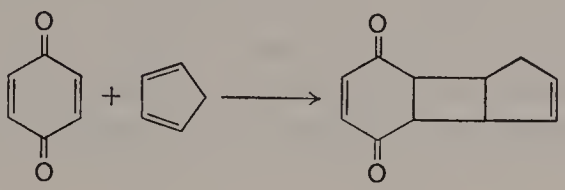


(305)

(104)

2. Mechanistic studies

Some of the earliest serious mechanistic studies of the Diels–Alder reaction involved the kinetics of addition of 1,4-benzoquinone to cyclopentadiene (equation 304)[352]. Both of the reaction steps are second-order and the rate of the first is about 100 times that of the second in benzene at 25°C. In a later and more detailed study of these reactions Wassermann examined the thermochemistry as well as the kinetics[353]. The question of a reasonable explanation of the observed 1,4-, rather than 1,2-addition, was approached first from a thermochemical point of view. The calculated and observed heats of formation were in excellent (perhaps fortuitous) agreement, assuming only about 10 kcal of ring strain in the product (**103**). From these data it was possible to calculate the gas-phase heats of reaction for both the observed 1,4-addition (first half of equation 304) and the hypothetical 1,2-addition (equation 306). Both of these reactions



(306)

proved to be exothermic (24 kcal and 19 kcal respectively). While the absolute values of the heats of reaction are approximate, there is no thermodynamic reason to prefer one path over the other.

An additional examination of the earlier kinetic study was also carried out. The various probable competing reactions were considered and conditions selected where they were unlikely to interfere and where the yield of expected product (**103**) was essentially quantitative. A wide variety of catalysts and inhibitors were examined along with light and magentic fields; no change in rate was observed. Wassermann concluded that a radical chain reaction was very improbable. The temperature dependence of rate in both benzene and ethanol followed the Arrhenius equation and gave activation energies of 14·2 kcal (benzene) and 12·7 kcal (ethanol).

The kinetic results require that the 1,4-addition and/or the 1,2-addition be described by only the Z and E constants of the Arrhenius equation. This requirement allowed Wassermann to consider the various steric situations that would be best suited for 1,4- as contrasted with 1,2-addition. From these models and calculations, it was shown that the Z values for the two modes of reaction could not be very different and therefore those constants cannot be used to explain the predominance of 1,4-addition.

A final effort to explain the observed reaction product on the basis of the activation energy(E) required a consideration of the induced dipole in cyclopentadiene as a result of the quinone carbonyl groups. The resulting values showed clearly that orientation for 1,4-addition produces larger induction energies than those for 1,2-addition. Wassermann reasoned that the repulsive forces for the two modes of addition should not be very different and thus the activation energy for 1,2- should be greater than for 1,4-addition. Calculated rate constant ratios for the two reactions appeared to be sufficient to explain the observed exclusive formation of **103**.

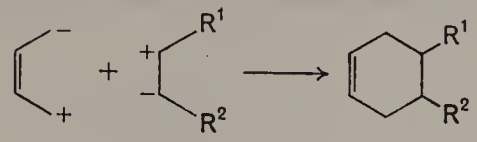
The Diels–Alder reaction possesses kinetic characteristics that make it suitable for a comparison study of gas- and solution-phase mechanisms. Wassermann has compared his studies of quinone–cyclopentadiene additions in solution to several analogous gas-phase studies[354]. The observed kinetics produce temperature-independent Arrhenius A values* of the order of 10^6 l/moles. Because these values are several orders of magnitude lower than either the gas- or solution-phase bimolecular collision frequencies (ca. 10^{11} l/moles), it follows that only a small fraction of the collisions of molecules with sufficient energy result in reaction. The so-called 'normal' and 'slow' bimolecular reactions[355] were discussed and evidence offered that the collision frequencies in the gas- and solution-phases can be of the same order of magnitude for both reaction types. The most significant conclusion relative to the Diels–Alder reaction is that the reason for the large difference between the Arrhenius A and the collision frequency is the complicated structure of the reactants rather than restricted electronic transitions. This study offered rather strong additional support for the importance of transition-state geometry which became significant at a much later date in the development of physical organic chemistry.

The Diels–Alder reaction is known to be reversible and Wassermann has studied the resulting equilibria in several systems involving quinone dienophiles[356]. His results show once again that both the heat of reaction and the statistical probability of reaction are very similar in the gas-phase and hydrocarbon solution.

The question of the exact electronic distribution in the Diels–Alder reaction has been a source of study and debate for a long time and quinones have played a modest role in that story. Two early formulations suggested that (i) two ionic resonance contributors were involved (equation 307)[357], or (ii) the diene served as an electron donor at both ends and the dienophile

* In Wassermann's earlier papers the symbol Z was used in place of A.

accepted electrons at both carbon atoms (equation 308)[358]. The scheme shown in equation (308) cannot be applied when the dienophile is



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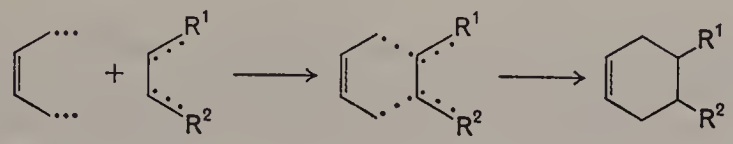


(308)

substituted unsymmetrically. The authors of the ionic proposal studied a series of dienophiles in which the electronegativity of the substituents R^1 and R^2, as well as their location, was varied[359]. The diene employed, bicyclohexenyl, was also used as the solvent (5-fold excess). This latter experimental detail proved to be very wise, especially with the quinones where the excess not only drives the equilibrium toward product, but reduces subsequent dehydrogenation. The results shown in Table 10

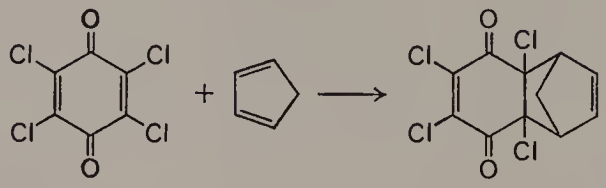
TABLE 10. Adducts of bicyclohexenyl with various dienophiles[359]

Dienophile	Temperature (°C)	Yield (%)
Maleic anhydride	80	95
1,4-Benzoquinone	80	85
1,4-Naphthoquinone	100	99
Fumaric acid	200	80
Benzalacetone	180	76
Dibenzalacetone	180	95
Cinnamic acid	180	75
β-Nitrostyrene	80	95

clearly indicate that neither the yield nor the reaction temperature can be correlated with symmetrical and unsymmetrical dienophiles. This observation was taken as support for the ionic mechanism as presented in equation (307). There appears to be no evidence for a change in reactivity over the series of quite different electronic situations.

As the amount of mechanistic detail concerning the Diels–Alder reaction has grown, it has become increasingly apparent that not only the electronic, but also the geometric situation in the transition state is

very important. An interesting kinetic approach to this aspect of the reaction has been provided in the addition of cyclopentadiene to selected quinones[360]. The addition of cyclopentadiene to chloranil (equation 309)



(309)

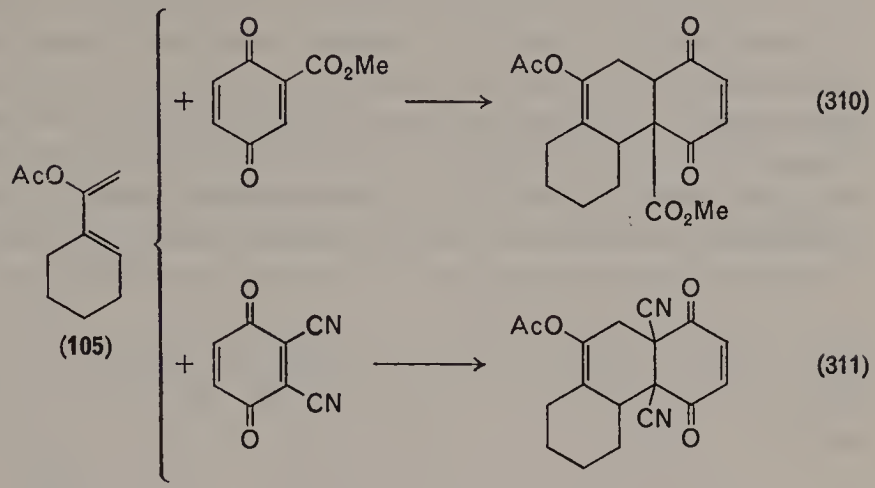
may be compared with equation (304). The greater bulk of the chlorine atoms relative to hydrogen should cause variation in the Arrhenius equation constants A and E unless the transition state is non-planar. The data in Table 11 show essentially no variation in A and only a slight range of E

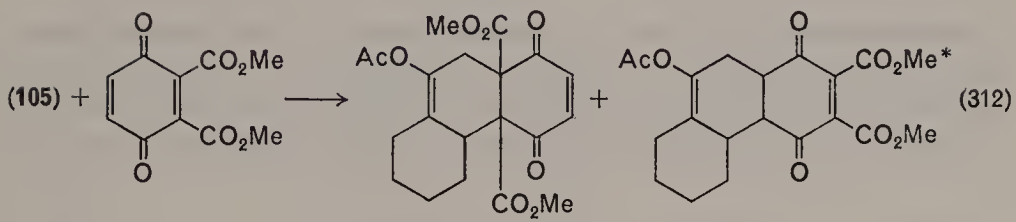
TABLE 11. Arrhenius parameters for the reaction of cyclopentadiene with various dienophiles[360]

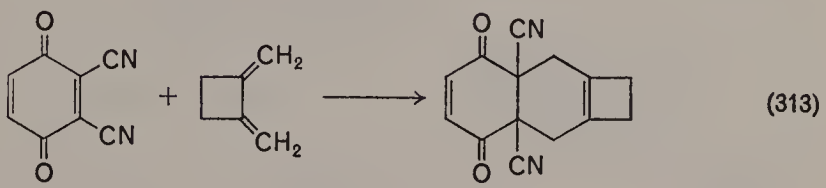
Dienophile	log A (A in 1/mole s)	E (kcal)
Chloranil	6·2 ± 0·5	14·5 ± 0·5
1,4-Benzoquinone	6·5 ± 0·4	11·6 ± 0·6
1,4-Naphthoquinone	4·8 ± 0·9	10·0 ± 1·0
Cyclopentadiene-benzoquinone (**103**)	5·5 ± 0·9	13·2 ± 1·0
Acraldehyde	6·1 ± 0·3	13·7 ± 0·5
Cyclopentadiene	6·1 ± 0·4	16·4 ± 0·6

values. The latter variation is far too small to argue convincingly for a planar transition state.

Any proposed mechanism for the Diels–Alder reaction must account for the rather specific nature of orientation observed when unsymmetrically substituted dienophiles are employed. An explanation has been advanced that takes both steric and electronic effects into account, but it is somewhat limited[361]. This limitation was not serious until the reactions of 1,1′-acetoxy-vinylcyclohexene (**105**) with quinones bearing electron-withdrawing substituents were reported (equations 310 and 311)[362]. These examples show clearly that, with sufficient electronic activation, a large amount of steric interaction can be overcome. There are, however, limits and two carbomethoxy groups produced the mixture of isomers shown in equation (312). The extraordinary reactivity of 2,3-dicyano-1,4-benzoquinone was also illustrated by its rapid reaction with 1,2-dimethylenecyclobutane (equation 313)[363].



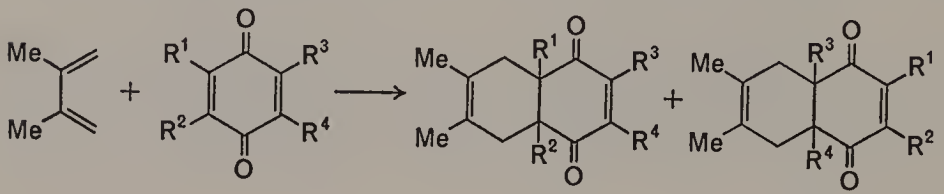




At about the same time a spectrophotometric study of the reactions of 1,4-benzoquinone and 1,4-naphthoquinone with cyclopentadiene, isoprene and piperylene produced some very significant information about the mechanism[364]. It was possible to follow the formation of the expected adducts in all cases, including both the mono- and diadducts of 1,4-benzoquinone. However, with 1,4-benzoquinone, absorption was found in the 290 nm region preceding the formation of each adduct and decreasing as the adduct formed. Because known molecular compounds between quinones and aromatics absorb in this region, it was felt that evidence of significant intermediates had been obtained. These absorptions were not observed with 1,4-naphthoquinone: perhaps this is the result of a more rapid rate of conversion of the intermediate to the adduct.

* Isolated as the hydroquinone.

The reactions of **105** with a variety of unsymmetrically substituted 1,4-benzoquinones have been observed and the product structures determined[365–367]. From these studies has come a somewhat better picture of the electronic and steric requirements of the reaction. In their general discussion of the Diels–Alder reaction of 1,4-benzoquinones, Ansell and colleagues report the reactions of simpler dienes, such as 2,3-dimethylbutadiene, with mono-, di-, tri- and tetrasubstituted 1,4-benzoquinones[368]. The general situation (equation 314) is that a symmetrical diene and an



(106) (107) (314)

unsymmetrically substituted 1,4-benzoquinone can form isomeric monoadducts (**106** and **107**). The results of a representative sample of the large number of examples studied are shown in Table 12. The additions to the tetrasubstituted 1,4-benzoquinones are especially interesting in that they

TABLE 12. Adducts of 2,3-dimethylbutadiene and various substituted 1,4-benzoquinones[368]

1,4-Benzoquinone substituent(s)	Angular groups	Yield (%)
Me	H, H	61
MeO	H, H	30
Cl	H, H	42
CO_2Me	H, CO_2Me	95
CN	H, CN	85
COMe	H, COMe	86
2,3-$(CN)_2$	CN, CN	96
2,3-$(CO_2Me)_2$	H, H/CO_2Me, CO_2Me	25, 25
2-Me, 3-NO_2	H, H	35
2-OAc, 5-Me	OAc, H	36
5-Cl, 2,3-$(CN)_2$	CN, CN	88
5-Me, 2,3-$(CO_2Me)_2$	CO_2Me, CO_2Me	76
2-CO_2Me, 3,5-Me_2	Me, H	23
5-MeO, 2,3-Me_2	Me, Me/MeO, H	20, 13
2-CO_2Me, 3,5-$(Me)_2$	Me, CO_2Me	81
2,6-$(CO_2Me)_2$, 3,5-Me_2	Me, CO_2Me	90
Me_4	Me, Me	87
$(MeO)_4$	MeO, MeO	95

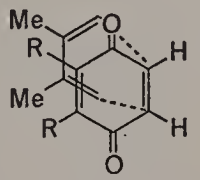
show that even the unreactive tetramethoxy-1,4-benzoquinone can be made to form an adduct in excellent yield if the product has the required thermal stability.

The general agreement of these data with the earlier ideas expressed by Ansell is clear. An electron-withdrawing group attached to the carbon–carbon double bond of a quinone does activate the dienophile. The balance between steric and electronic effects is apparent, especially in the relationships between cyano and carbomethoxy groups. An order of activating effect was proposed: $CN > COMe > CO_2Me > CF_3 > H > F > Cl > Me > OAc > NMePh > OMe > SMe$. The study also included some examples of 1,3-butadiene addition and in these data (Table 13) a third

TABLE 13. Comparison of Diels–Alder products from 1,3-butadiene and 2,3-dimethylbutadiene and various 1,4-benzoquinones[368]

1,4-Benzoquinone substituent(s)	1,3-Butadiene		2,3-Dimethylbutadiene	
	Angular groups	Yield (%)	Angular groups	Yield (%)
CO_2Me	H, H	6	H, CO_2Me	95
CO_2Me	H, CO_2Me	65	—	—
2,3-$(CN)_2$	H, H	16	CN, CN	96
2,3-$(CN)_2$	CN, CN	62	—	—
2,3-$(CO_2Me)_2$	H, H	70	H, H	25
2,3-$(CO_2Me)_2$	—	—	CO_2Me, CO_2Me	25

influence on product structure was observed. If an *endo*-transition state is assumed, it is reasonable to expect the arrangement shown in structure **108** to be less probable than the transition state leading to product with angular R substituents. In a similar manner, transition states with 1,3-butadiene and a 2,3-disubstituted quinone should be more probable than **108**. Thus, a second steric effect must be considered in predicting the

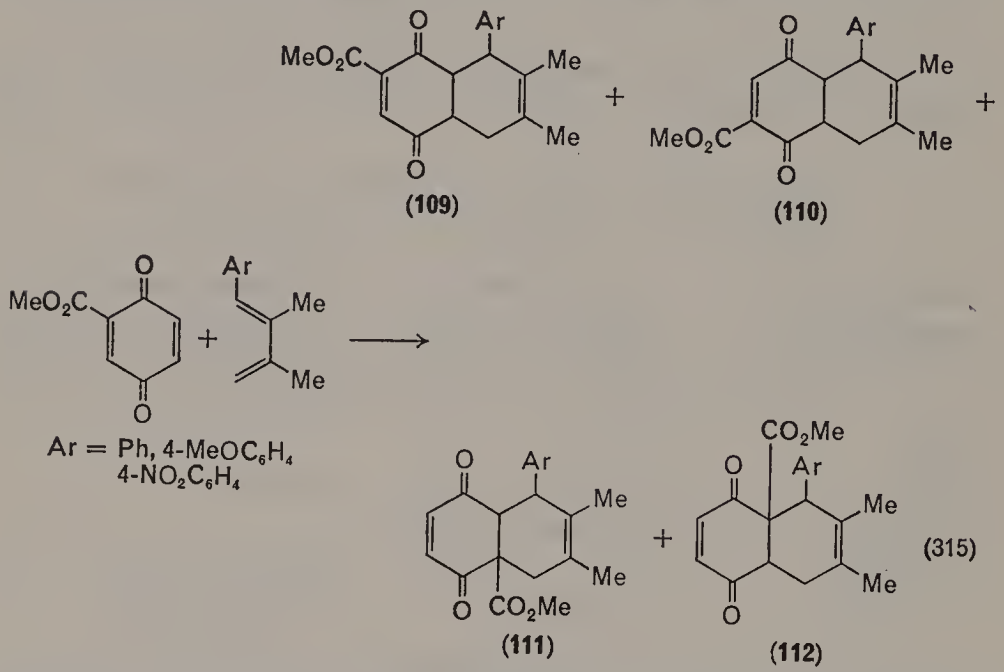


(108)

major product of the Diels–Alder reaction of an unsymmetrical benzoquinone. In the limited number of examples that have been studied, the observed facts are in accord with the predictions of this effect; e.g. 2,3-dicarbomethoxy-1,4-benzoquinone gives mixtures of products with

isoprene, 1-vinylcyclohexene and 1,1′-acetoxyvinylcyclohexene, as well as 2,3-dimethylbutadiene.

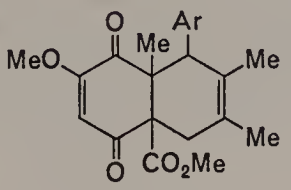
Finally, Ansell and Clements have examined the other aspect of these orientation questions; i.e. the relative orientation of substituents[369]. When an unsymmetrical 1,4-benzoquinone and an unsymmetrical diene undergo a Diels–Alder reaction, there are four possible isomeric products that can result (equation 315). The factors that determine the 'side of



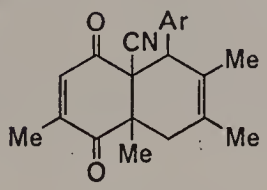
addition' (i.e. **109–110** versus **111–112**) have just been discussed; now we are interested in a choice between the individual members of the pairs of structures. The diene chosen allows variation in the electronic situation while holding the steric factor quite constant. The 2,3-dimethyl groups in the diene are useful for the interpretation of the n.m.r. spectra of the products. The specific quinone shown in equation (315) (2-carbomethoxy-1,4-benzoquinone) was found to give a single product in high yield with each of the three dienes. As would be expected, neither **109** nor **110** was obtained in any case. The n.m.r. spectra of the adducts clearly indicated structure **112**, where Ar = 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$ and Ph.

A series of di- and trisubstituted 1,4-benzoquinones were studied to examine electronic and steric effects in the dienophile on the product orientation. It was found that the electronic natures of the diene and the dienophile have no effect on the orientation of product involving a single angular group. In each case (angular group = Me or CO_2Me) the arrangement of angular and aryl groups is *ortho* relative to the newly formed ring.

The trisubstituted quinones gave products **113** and **114**. All of these data are consistent with a transition state in which both bonds are partially



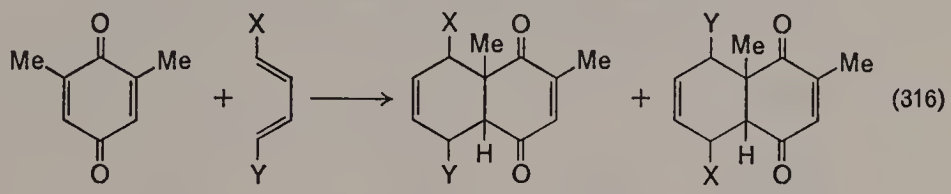
(113)



(114)

and unevenly formed, thus possessing some diradical character. The structure of product **113** requires that a radical centre be more stabilized by hyperconjugation with a methyl group than by delocalization to a carbonyl. This situation is explained on the basis of steric inhibition of resonance. This explanation is made more convincing by the lowered i.r. frequency of the carbonyl group. With the related cyano example **114** no such problem exists because of the group's linear structure.

Recently, an effort has been made to obtain more detail concerning the Diels–Alder transition state through a study of product orientation when unsymmetrical 1,4-disubstituted 1,3-butadienes react with 2,6-dimethyl-1,4-benzoquinone (equation 316)[370]. Two cases were studied: 1-acetoxy-1,3-pentadiene (X = AcO, Y = Me) and methyl sorbate (X = CO_2Me, Y = Me). Schmidt suggests that these reactants allow the comparison of



(316)

(115) **(116)**

methyl with an electron-donating group (acetoxy) and an electron-withdrawing group (carbomethoxy) while keeping the steric situation approximately the same.

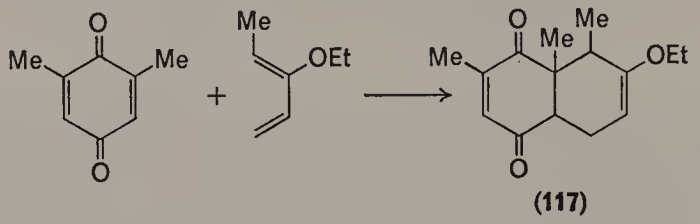
The results, with satisfactory total product yield, showed:

X = AcO **115** : **116** 4 : 1

X = CO_2Me only **115** could be found

Thus, while the carbomethoxy group has a more powerful directive effect than the acetoxy group, both electron-donation and electron-withdrawal influence the geometry of the transition state in the same direction. These results further suggest that the polarities of reactants are not the most significant considerations in predicting the nature of a Diels–Alder transition state.

This work has been expanded to include the methoxy group: an even stronger electron-donating substituent than acetoxy (equation 316; X = MeO, Y = Me)[371]. The only product found was **115**. Finally, 3-ethoxy-1,3-pentadiene and 2,6-dimethyl-1,4-benzoquinone produced only **117**, showing the lack of influence of a non-terminal group when a terminal group other than hydrogen is present (equation 317). This last



(317)

(117)

experiment also shows the importance of methyl versus hydrogen as a directing influence in the Diels–Alder reaction and leads to the following scale of directive importance:

$$MeO = MeO_2C > AcO > Me > H$$

The kinetics of the two earlier reactions (equation 316: X = AcO and MeO_2C, Y = Me) have also been reported[372]. Selected rate data and thermodynamic parameters are given in Tables 14 and 15. The three

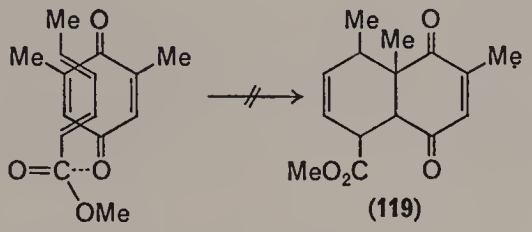
Table 14. Rates of addition of substituted 1,3-pentadienes to 2,6-dimethyl-1,4-benzoquinone (equation 316)[372]

Product	X	T (°C)	k, 1/mole s ($\times 10^5$)
(115)	AcO	140·4	1·17
(116)	AcO	140·4	1·34
(115)	CO_2Me	140·0	0·955
(115)	AcO	159·2	3·32
(116)	AcO	159·2	3·38
(115)	CO_2Me	159·0	2·80
(115)	AcO	176·0	8·44
(116)	AcO	176·0	6·92
(115)	CO_2Me	178·0	7·40

adducts are formed at very similar rates and the fourth possibility (**116**: X = CO_2Me or **117**) is not found even in trace amounts. The large negative entropy values require the highly oriented transition state that would result from an arrangement such as **118** if any of the missing product **119** were found (equation 318).

TABLE 15. Thermodynamic parameters for the addition of substituted 1,3-pentadienes to 2,6-dimethyl-1,4-benzoquinone (equation 316)[372]

Product	X	Activation energy (kcal/mole)	Entropy of activation (e.u.)
(115)	AcO	21·75 ± 0·82	−29·36 ± 1·92
(116)	AcO	18·33 ± 0·63	−37·32 ± 0·48
(115)	CO_2Me	21·91 ± 1·01	−29·44 ± 2·33



(118) (119) (318)

Liu and Schmidt suggest, on a preliminary basis, an unsymmetrical transition state in which the less hindered carbon atom of the dienophile takes the lead in σ bond formation. The bond formation is preferably initiated by that carbon atom of the diene possessing the higher electron density. The distribution of isomers in the case of 1-acetoxy-1,3-pentadiene (equation 316: X = AcO) is explained on the basis of the rigid structure of the transition state as indicated by the large negative entropy of activation.

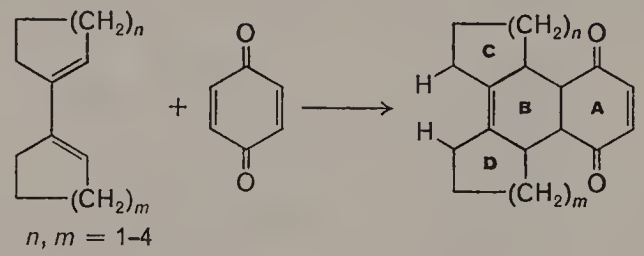
Three recent studies of more limited scope bear on the details of Diels–Alder chemistry involving quinones.

(1) The *para*-localization energy technique of Hückel molecular orbital calculations has been applied to both 1,2- and 1,4-benzoquinones[373]. This approach allowed the explanation of the dienophilic character of the carbon–carbon double bonds of these types of molecules.

(2) A detailed thermostudy of the Diels–Alder reaction of 1,4-benzoquinone with 2,3-dimethyl-1,3-butadiene and isoprene has been reported[374]. Two distinct steps can be observed and it can be shown that they correspond to the formation of the mono- and di-adduct. When the reaction is carried out at higher temperature, the *cis–cis* to *trans–trans* isomerism can be observed. Finally, when the reactants are present in equimolar amounts, a second exothermic effect corresponding to the isomerization of ketone to hydroquinone is found.

(3) A recent series of papers has dealt with retro-Diels–Alder reactions that occur under electron bombardment in the mass spectrometer[375–377].

From the organic chemist's point of view the most important finding is related to the conformation of the newly formed ring. The types of Diels–Alder adducts studied are shown in equation (319) (the syntheses of such adducts have been reported)[378]. With small **C** and **D** rings (m, n = 1 or 2), a special type of retro-Diels–Alder reaction took place involving the two allylic hydrogens shown. The most abundant ions were those of the retro-Diels–Alder bicyclodiene and hydroquinone. With larger **C** and **D**

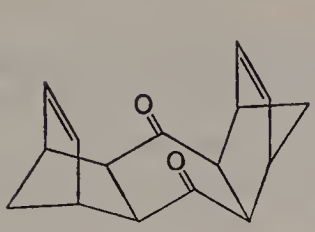


(319)

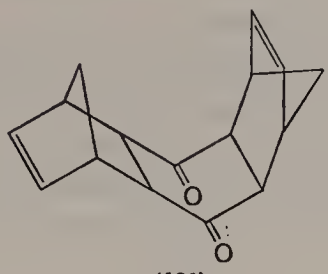
rings (n, m = 3 or 4), the adduct was very much more stable and the molecular ion became the most abundant. These observations are explained on the basis of changes in the conformation of the **B** ring brought about by different size **C** and **D** rings. The conformational changes brought about by smaller **C** and **D** rings bring the allylic hydrogens into a more favourable position relative to the quinone carbonyl groups. When the remaining quinone carbon–carbon double bond is reduced, only a normal retro-Diels–Alder reaction is observed. If the quinone double bond is part of an aromatic ring (i.e. 1,4-naphthoquinone was the original dienophile), both paths are observed. Thus, it appears that each of these structural features plays a significant role in the retro-Diels–Alder reaction in the mass spectrometer.

The stereochemistry of the Diels–Alder reaction has been of concern to chemists since the reaction first began to find very wide application. Of special interest at this point is the stereochemistry of the adduct formed when two moles of cyclopentadiene add to 1,4-benzoquinone. This adduct was assumed to possess the *endo–cis–endo*-configuration (**120**) for a very long time[379]. Both Winstein and Cookson and their colleagues have published convincing evidence that the *endo–trans–endo*-configuration (**121**) is correct[380,381].

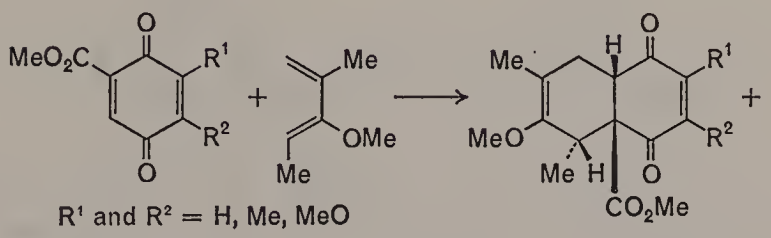
Several Diels–Alder adducts of substituted 1,4-benzoquinones were prepared in an attempt to determine their stereochemistry using n.m.r. spectroscopy (equation 320)[382]. The gross structural features were assigned in all but one case; however, it was not possible to determine the complete stereochemistry.



(120)

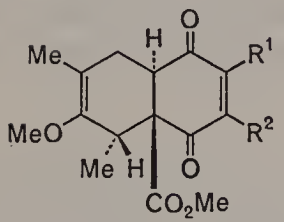


(121)

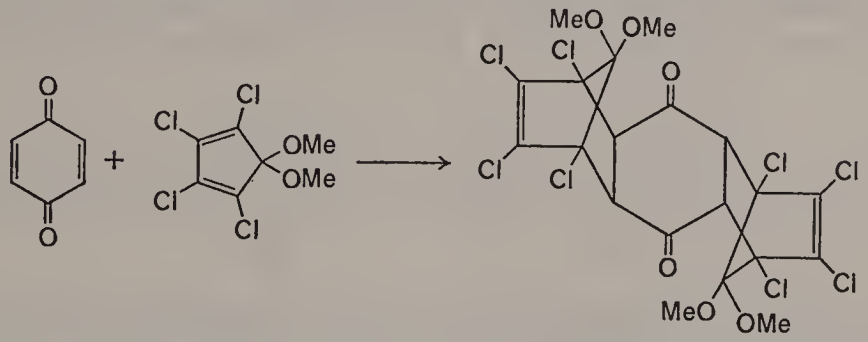


R^1 and R^2 = H, Me, MeO

(320)



The stereochemistry of the Diels–Alder adduct of 1,4-benzoquinone with two moles of 1,2,3,4-tetrachloro-5,5-dimethoxycyclopentadiene has been investigated, using variable-temperature n.m.r. spectroscopy (equation 321)[383]. The results strongly suggest the planar cyclohexadione ring shown, but do not rule out two boat conformations, if they are still in rapid equilibrium at −100°C.

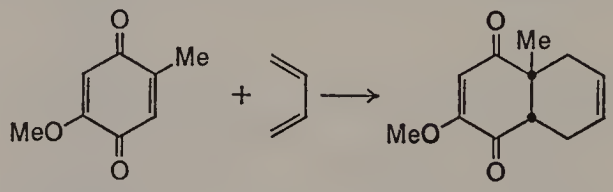


(321)

In view of the very large amount of study devoted to the mechanism of Diels–Alder reactions involving quinones, it is rather surprising that no Woodward–Hoffman treatment has appeared. The importance of this fresh approach to the interpretation of cycloaddition reactions requires its application here.

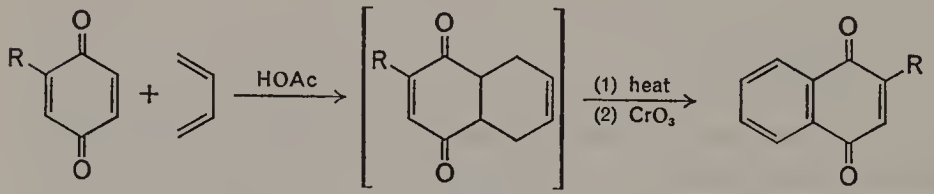
3. Synthetic survey

Since the earlier review[348], a dramatic example of the significance of quinone Diels–Alder reactions in recent synthetic organic chemistry is given by Woodward. He and his collaborators launched the first successful total synthesis of a non-aromatic, naturally occurring steroid (*dl*-$\Delta^{9(11),16}$-bisdehydro-20-norpogesterone), with such a reaction (equation 322)[384].



(322)

The work of Fieser and collaborators in the synthesis of potential antimalarial drugs has provided many useful synthetic techniques; among them a significantly improved diene synthesis of naphthoquinones (equation 323)[137]. Acetic acid is a very desirable solvent in that it avoids

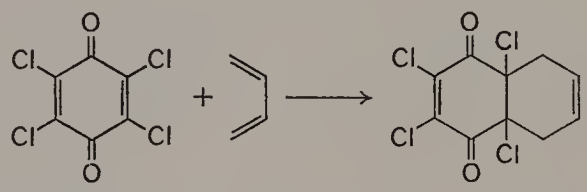


(323)

(122)

the use of pressure equipment and the need to work up the intermediate **122**. This procedure has been refined by later studies[385].

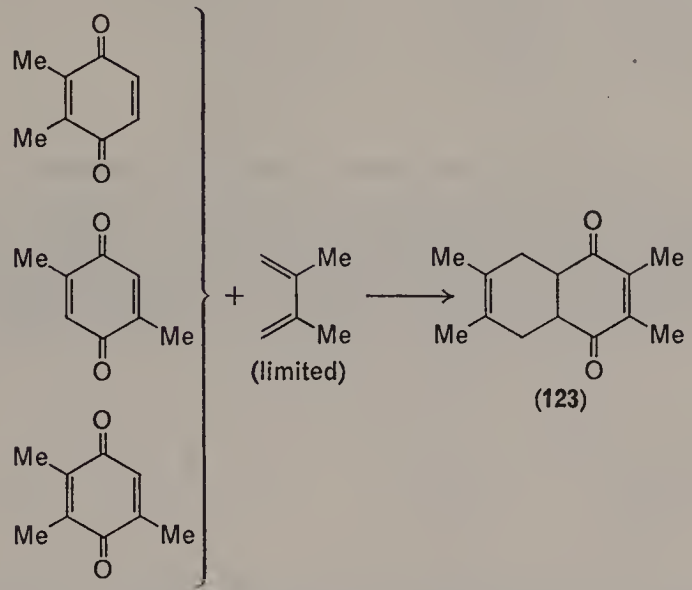
The addition of simple dienes to chlorinated 1,4-benzoquinones has been reported (equation 324)[386]. A number of slightly more complicated



(324)

dienes were used successfully (e.g. isoprene, 2,3-dimethylbutadiene and 1-acetoxy-1,3-butadiene); a number of chlorinated dienes, 2-lauroxybutadiene, 1,4-diphenylbutadiene, etc. did not add to chloranil. It was found that 2,5-dichloro-1,4-benzoquinone can also act as a dienophile although the isolated adducts were quite unstable to light. In benzene solution they could be converted to 2-chloro-1,4-naphthoquinones.

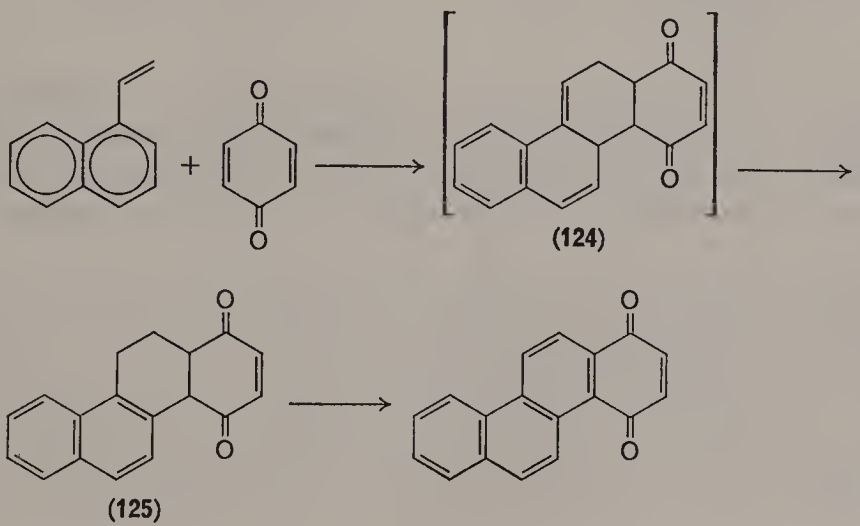
As a part of the separation and characterization of the components of the antibiotic gonyleptidine, Fieser and Ardao employed the difference in reactivity of various methylated 1,4-benzoquinones (equation 325)[38].



(325)

The product **123** is not affected by the hydrosulphite reduction of the other two quinones which can then be removed by basic extraction.

The general interest in polycyclic aromatic compounds has prompted the study of Diels–Alder reactions of 1- and 2-vinylnaphthalene with quinones (equations 326 and 327)[387,388]. The initial adduct **124** can be isolated or oxidized *in situ* depending upon the experimental conditions employed[388]. An analogous hydrogenated intermediate could not be isolated in the case of 5,6-benzophenanthrene-1,4-quinone (**126**). The



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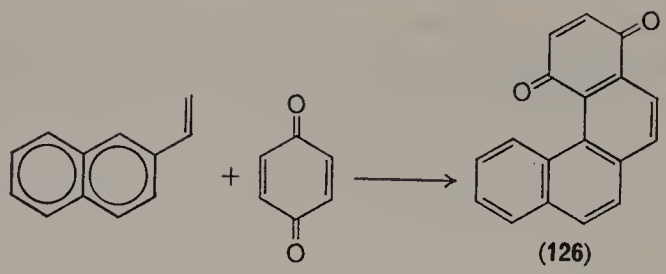
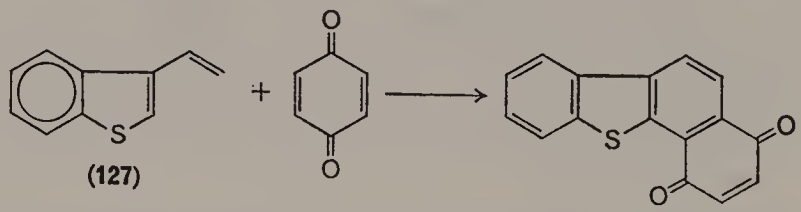


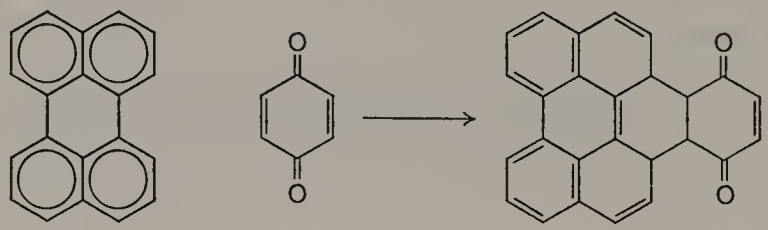
(126) (327)

reaction of 1-vinylnaphthalene with 1,4-naphthoquinone took place satisfactorily, but 2-vinylnaphthalene failed to produce the expected adduct. Styrene, 1-propenylnaphthalene and other similar compounds failed to react. In an analogous reaction, 3-vinylthionaphthene (**127**) reacts with 1,4-benzoquinone in excellent yield (equation 328)[389].



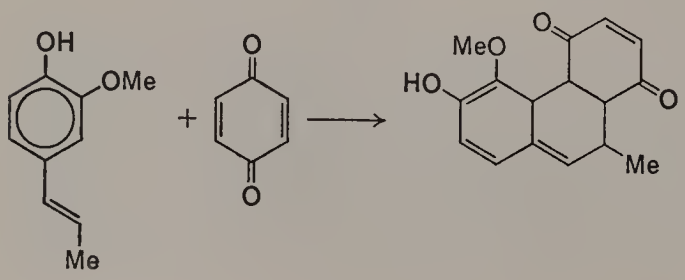
(127) (328)

The interest in polycyclic aromatic systems and their synthesis via Diels–Alder reactions of quinones continues (equation 329)[390]. The bis-adduct can also be isolated and an analogous reaction with 1,4-naphthoquinone takes place.



(329)

Vinyl aromatic systems are more generally useful as dienes with substituted 1,4-benzoquinones and the introduction of a methoxy group can activate the diene so that reaction with 1,4-benzoquinone itself is possible (for example, equations 330 and 331)[391]. The present application



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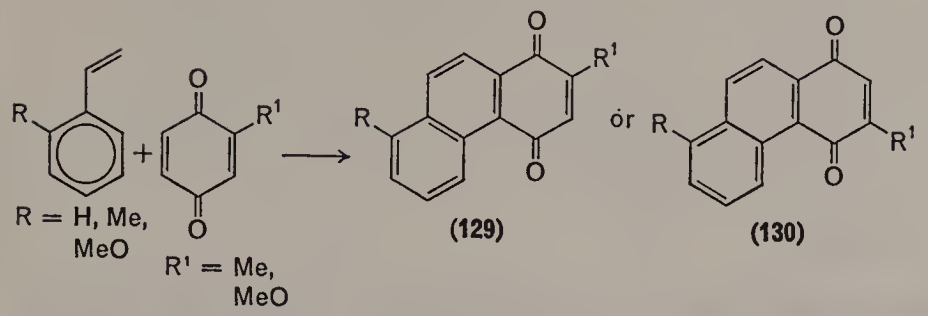
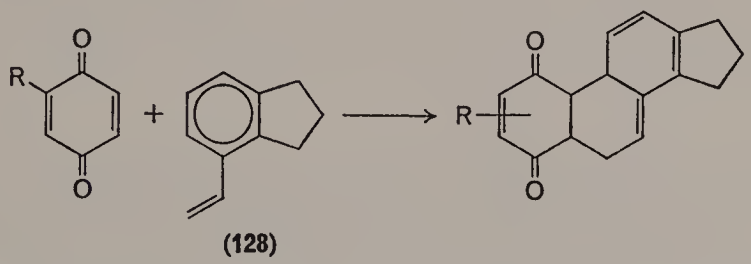


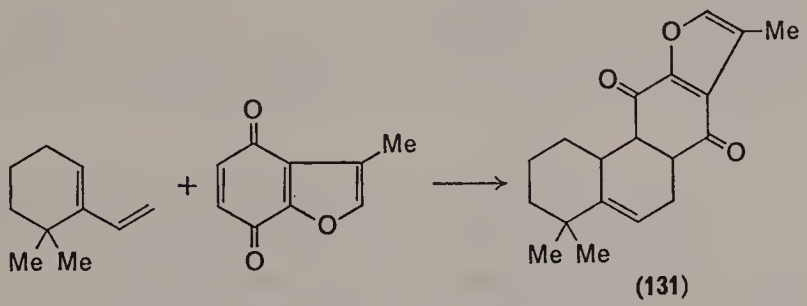
(331)

of this information is in the synthesis of compounds related to the steroids by reaction with 4-vinylindane (**128** in equation 332). In this particular instance, 1,4-benzoquinone does react, but an attempt to introduce an angular methyl group using 2-methyl-5-methoxy-1,4-benzoquinone produced only starting material after heating for eight days.



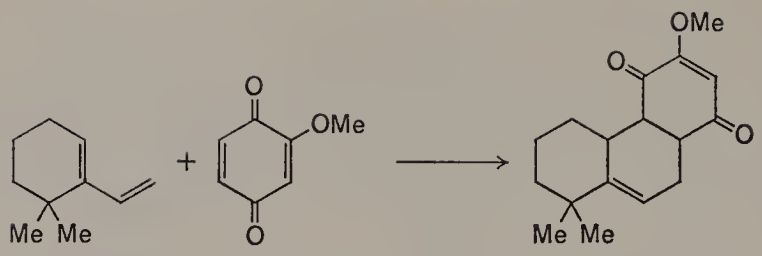
(332)

A somewhat similar reaction was used as the starting point for the synthesis of an important series of natural compounds (equation 333)[392].



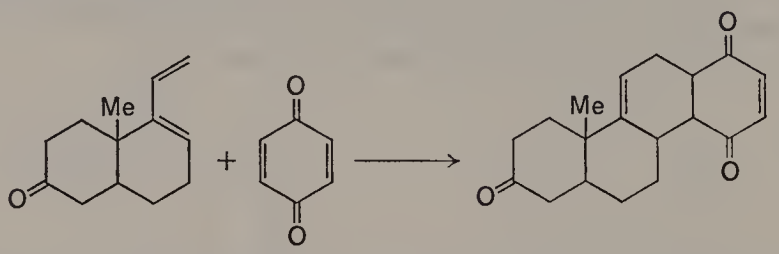
(333)

The fact that only a single product (**131**) was obtained and that it was the structure shown, called into question Lora-Tamayo's earlier structural assignments; e.g. product **129** was claimed in equation (331) when R = H or Me and R^1 = MeO. The result obtained with 2-methoxy-1,4-benzoquinone added strength to the argument (equation 334). A careful re-examination of the earlier work showed that in both cases (i.e. R = H or Me and R^1 = MeO) the product actually obtained has structure **130**[393].



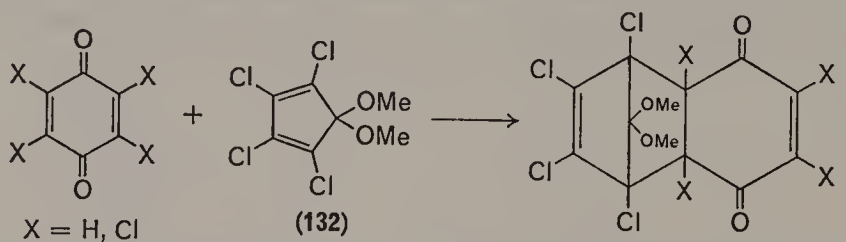
(334)

Another steroid synthesis involves the **D**-ring and allows the introduction of angular groups (equation 335)[394]. Related reactions, and much subsequent chemistry, provide entries to a variety of 'natural' and 'inverted' *cis–cis* steroids.



(335)

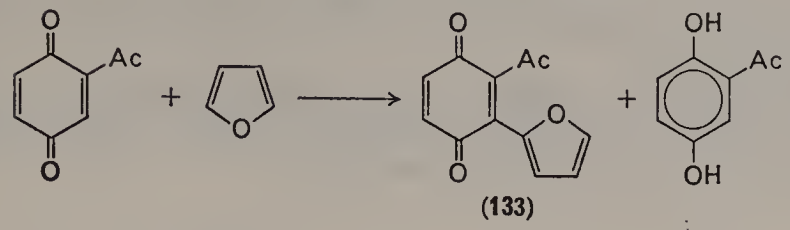
An effort has been made to prepare some interesting chlorinated 1,4-naphthoquinones by the Diels–Alder reaction of **132** with various 1,4-benzoquinones[395]. The project failed at a later point, but yielded some interesting new compounds in the cyclization step (equation 336). The



(336)

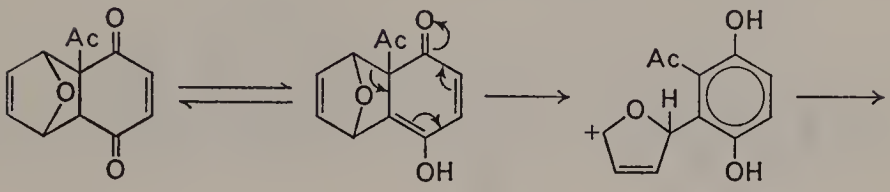
failure of the reaction with 2,5-dichloro-1,4-benzoquinone and chloranil is consistent with an earlier report[395a]. Additional verification of that study and some new adducts were obtained with cyclopentadiene.

In contrast to the chemistry of the cyclopentadienes, furan was found to add to 2-acetyl-1,4-benzoquinones in an abnormal fashion (equation 337)[396]. It was suggested that the 2-acetyl-3-(2-furyl)-1,4-benzoquinone (**133**) might be formed by a dienone-phenol rearrangement of the normal adduct in its enol form (equation 338). The substituted hydroquinone **134** could react with the starting quinone to produce the observed products. The actual quinone product **133** undergoes a normal Diels–Alder reaction with 1,3-butadiene (equation 339)[397].

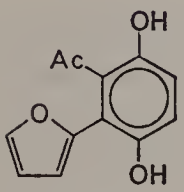


(337)

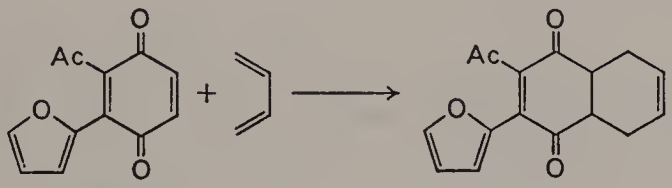
(133)



(338)



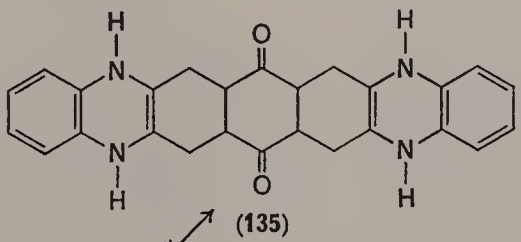
(134)



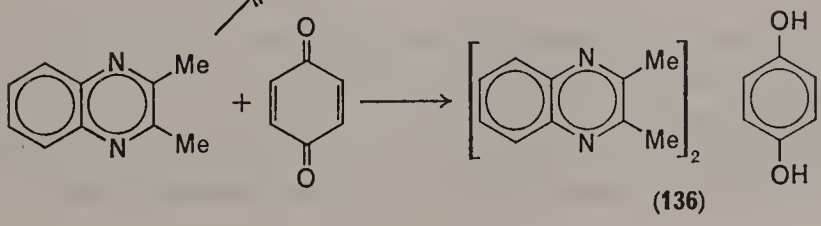
(339)

(133)

An interesting and prevalent error in Diels–Alder chemistry of quinones is the alleged adduct (**135**) of 2,3-dimethylquinoxaline and 1,4-benzoquinone[398]. Two groups recognize the formation of a complex, **136**, at nearly the same time (equation 340)[399, 400]. The source of the hydroquinone was



(135)

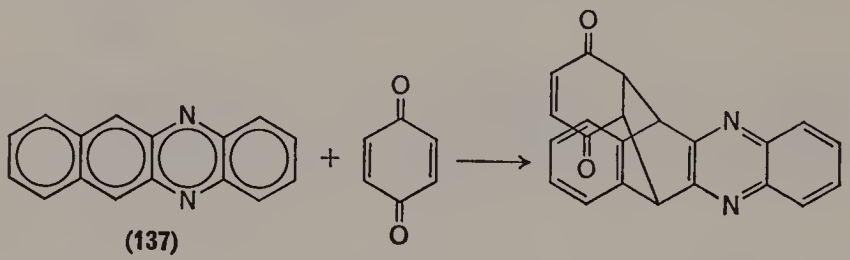


(340)

(136)

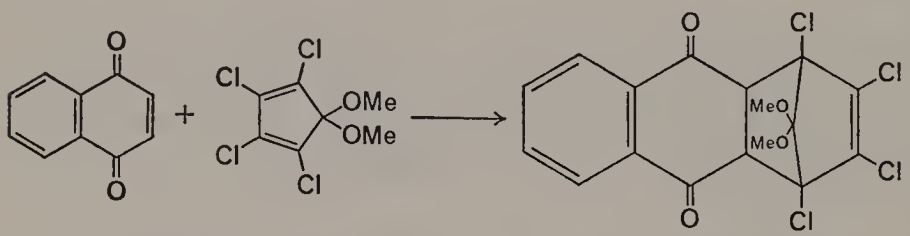
not determined, but the polymeric by-product suggests hydrogen abstraction from the quinoxaline.

A heterocyclic system vaguely related to that just discussed is benzo[b]-phenazine (**137**); this compound has been shown to react with the dienophile 1,4-benzoquinone (equation 341)[401].



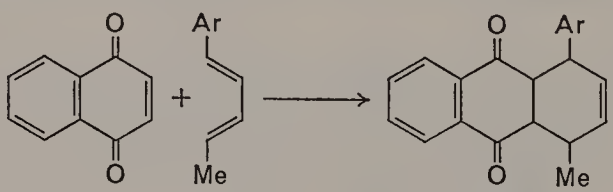
(137) (341)

It has been possible to prepare certain substituted anthraquinones by the Diels–Alder reaction of 1,4-naphthoquinone with 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene (equation 342)[402]. The removal of the bridgehead carbon atom could be carried out in several different ways to lead to a number of products.



(342)

In recent years a method for the preparation of 1-aryl-1,3-pentadienes has been developed and used to prepare the little studied 1-methyl-4-arylanthraquinones (equation 343)[403]. The initial product **138** can be



(343)

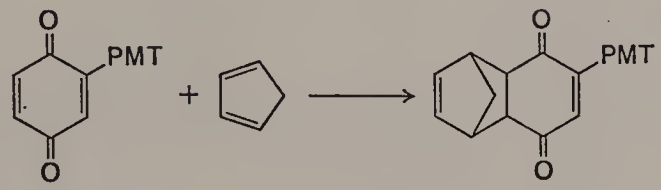
(138)

Ar=Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$, 2- or 4-$O_2NC_6H_4$, 4-Me-3-$O_2NC_6H_3$

oxidized *in situ* to the substituted anthraquinone. Conditions have been found for analogous preparations of 2-methyl- and 2,3-dimethyl-1-arylanthraquinones[404].

In their study of the addition of 1-phenyl-5-mercaptotetrazole (HPMT) to various 1,4-benzoquinones, Gates and collaborators carried out some

interesting new Diels–Alder reactions[4]. The three dienes used (2,3-dimethylbutadiene, 1,3-cyclohexadiene and cyclopentadiene) added smoothly and in good yield to 2-(1′-phenyl-5′-tetrazoylthio)-1,4-benzoquinone (e.g. equation 344). Similarly, the quinones prepared from the Diels–Alder adducts without a thio substituent add HPMT (equation 345). The



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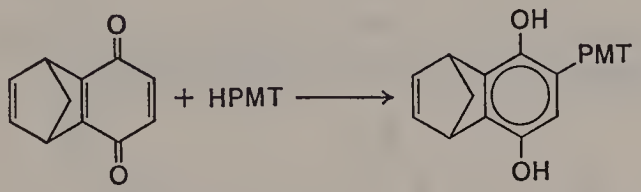
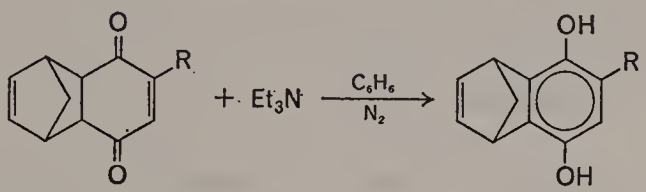


(345)

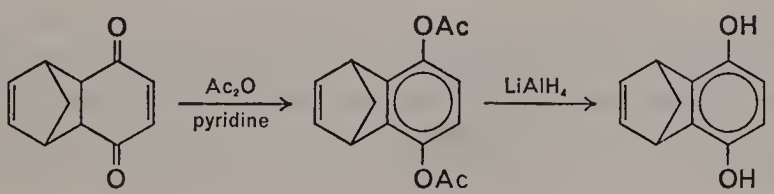
preparation of this last quinone reactant represents the most significant contribution of this study to Diels–Alder chemistry. The adducts of cyclopentadiene, unlike those of the other two dienes, do not undergo acid-catalysed aromatization to the corresponding hydroquinone, which can be oxidized by the usual reagents. It was found that the cyclopentadiene adducts are converted to their hydroquinones by treatment with triethylamine in benzene, preferably under anaerobic conditions (equation 346). The yields, with the exception of the 1,4-benzoquinone adduct, are



(346)

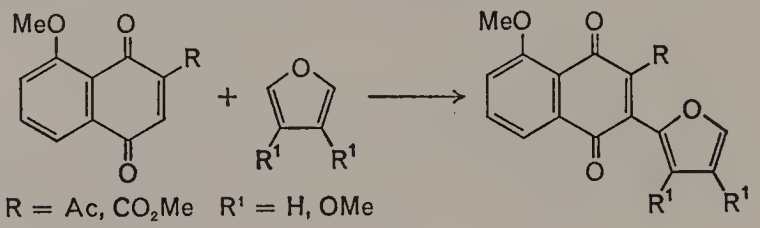
R = H, Me, Ph, PMT

quite satisfactory. The parent compound can be prepared in high yield by reductive acetylation and lithium aluminium hydride cleavage of the initial adduct (equation 347)[405].



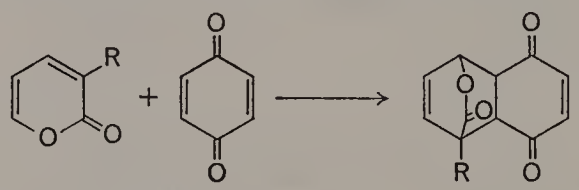
(347)

In a continuation of the study of the 'abnormal' addition of furans to quinones with electron-withdrawing groups, 2-carbomethoxy- and 2-acetyl-8-methoxy-1,4-naphthoquinone were prepared[406]. Both of these quinones failed to undergo the usual Diels–Alder reaction with either furan or 3,4-dimethoxyfuran (equation 348). A potentially useful synthesis of



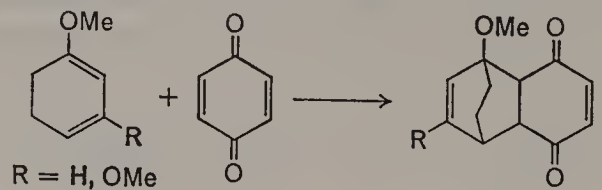
R = Ac, CO_2Me R^1 = H, OMe (348)

1,4-naphthoquinones involves the addition of α-pyrones to 1,4-benzoquinones followed by decarboxylation (equation 349).



R = H, OMe (349)

The availability of a reasonable synthetic route to 1-methoxycyclohexa-1,3-dienes has made possible the study of their Diels–Alder reactions with quinones (equation 350)[407]. The initial adduct **139** can undergo a variety

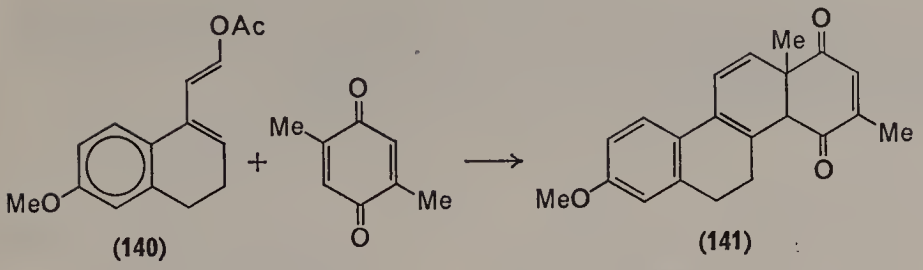


R = H, OMe (350)

(139)

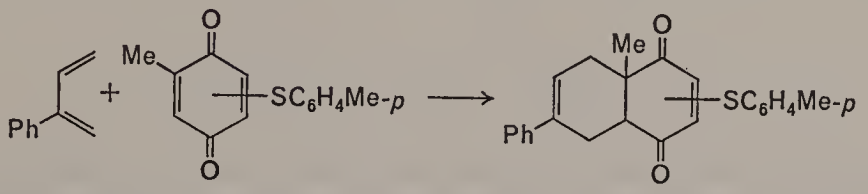
of interesting reactions, including photochemical formation of cage compounds, acid-catalysed loss of the bridge and the formation of derivatives of dibenzofuran. Substituted 1,4-benzoquinones have also been successful dienophiles. Procedures have been worked out for converting a number of mono- and di-adducts related to **139** to polycyclic aromatic quinones[408].

The ability to introduce an angular methyl group in the 16-position in certain steroids is very desirable and one possible route to such materials is shown in equation (351)[409]. The elimination of acetic acid to give the observed product **141** is consistent with other observations of the 1-acetoxy-diene, **140**.



(140) (141) (351)

Still another route to the introduction of an angular methyl group involved the addition of *p*-toluenethiol to 2-methyl-1,4-benzoquinone (see section II.B.3) and its subsequent removal (equation 352)[39]. The

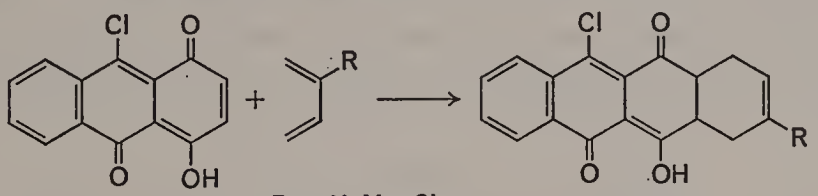


(352)

presence of an angular methyl group, rather than the angular thio group, was demonstrated by comparison of the u.v. spectra of the adduct with appropriate model compounds[41].

A brief survey of the possible routes to the synthesis of halogenated anthraquinones, along with their merits and drawbacks, has been presented[410]. The general conclusion, that using halogenated cyclopentadienone acetal is the preferred route[402], has been emphasized with additional synthetic work[411].

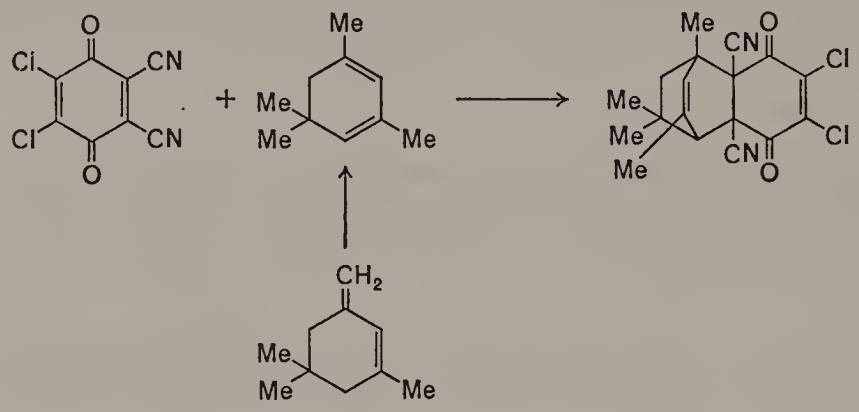
The Diels–Alder reaction of 1,3-dienes with certain chlorohydroxyanthraquinones provides an approach to compounds related to the tetracyclines (equation 353)[412]. The halogenated cyclopentadienone acetals have also been used in this approach. The various initial adducts (e.g. **142**) can be dehydrogenated to hydroxynaphthacenequinones.



R = H, Me, Cl (142) (353)

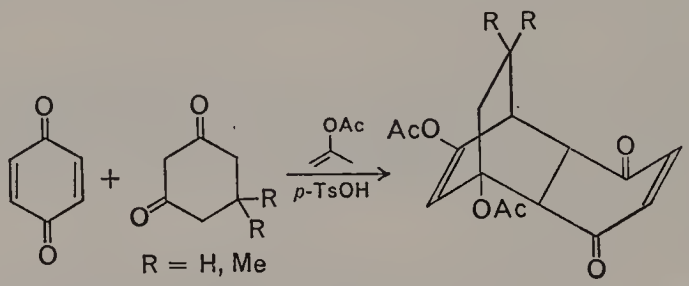
The tetrasubstituted quinone 2,3-dichloro-5,6-dicyano-1,4-benzoquinone has been used extensively as a dehydrogenating agent, but not in the diene synthesis. Recently the detailed structure of its Diels–Alder adduct with 1,5,5-trimethyl-3-methylenecyclohexene has been reported[413].

Under the reaction conditions the diene isomerized to 1,1,3,5-tetramethylcyclohexa-2,4-diene and the latter forms the adduct (equation 354). The structure was established by X-ray structure analysis.



(354)

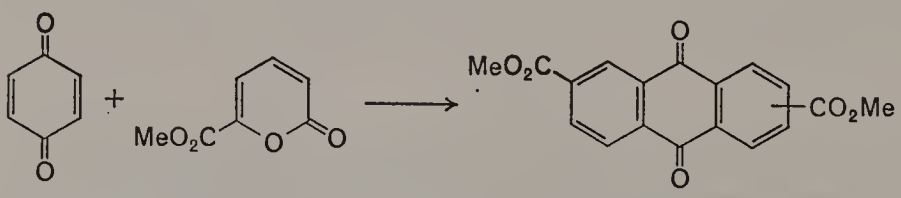
It has been shown that cyclic bis enol acetates can be generated *in situ* and that, in the presence of 1,4-benzoquinone, Diels–Alder adducts are formed (equation 355)[414]. Isophorone reacts to give an approximately



(355)

equimolar mixture of the two expected products. Other α,β-unsaturated carbonyl compounds (e.g. crotonaldehyde) gave only tars. The structure and chemistry of the adducts are described in some detail.

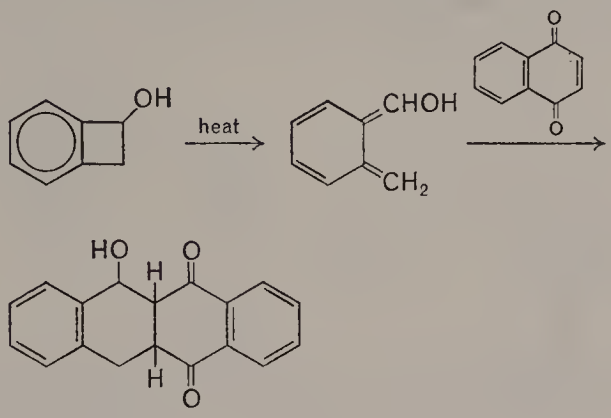
A recent extension of the Diels–Alder reaction between 1,4-benzoquinone and pyrones involves the use of the 5-carboxylic esters (equation 356)[415]. The product obtained was homogeneous, but the specific structure



(356)

of the product (2,6- or 2,7-dicarbomethoxy) was not determined. The presumed intermediates before decarboxylation were not isolated.

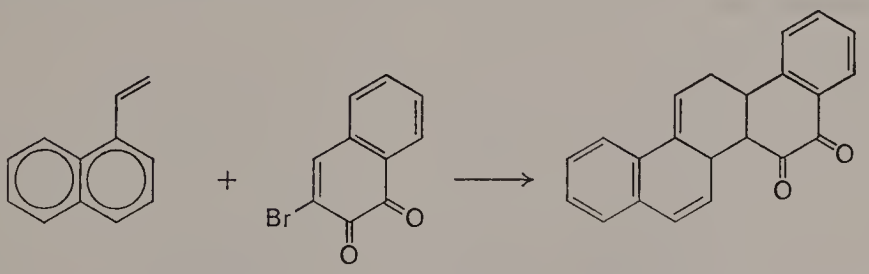
The thermolysis of benzocyclobutenol generates an interesting hydroxy-1,2-quinone dimethide that will react with 1,4-naphthoquinone (equation 357)[416]. The yield in this reaction was very good while the comparable photochemical reaction gave a complex mixture.



(357)

4. Diels–Alder reactions of 1,2-quinones

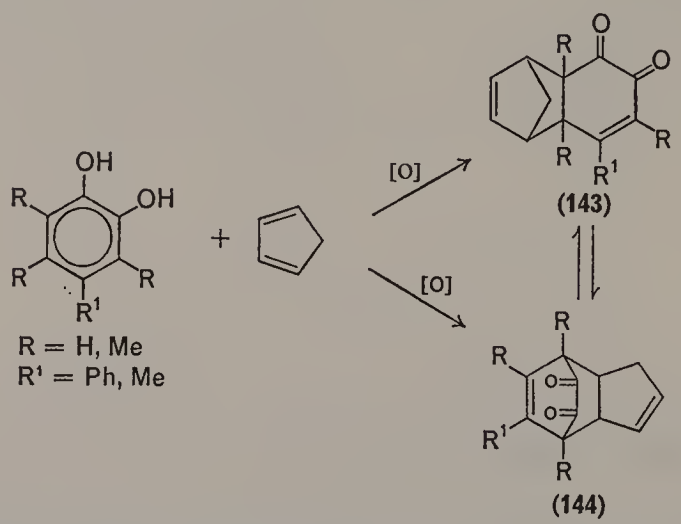
Compared to the enormous literature of the Diels–Alder chemistry of 1,4-quinones, relatively few 1,2-quinones have been studied until recently. The problems are, to some extent, illustrated by the study of the structure of picenequinone[417]. One suggestion for the structure of picenequinone is that expected from the Diels–Alder reaction between 1-vinylnaphthalene and 1,2-naphthoquinone after dehydrogenation (equation 358). Using 1,2-naphthoquinone only tar was obtained, but with 3-bromo-1,2-naphthoquinone dehydrobromination and dehydrogenation could be accomplished *in situ* and a reasonable yield of material corresponding to picenequinone was obtained.



(358)

In the past few years the interest in cycloaddition reactions of 1,2-quinones has grown very rapidly. Two English groups have played a major role in these studies: Ansell (Queen Mary College, London) and Horspool (Dundee) and their collaborators have published extensively and the latter has written a general review of the field[418].

Much of the Diels–Alder chemistry of the 1,2-benzoquinones is concerned with cyclopentadiene adducts. A recent study of these reactions by Ansell begins with a detailed review of the field[419]. The chief problem was the structure of the adduct; i.e. whether the quinone acts as a diene[420, 421] or a dienophile[422, 423] (equations 359 and 360). The correct explanation of

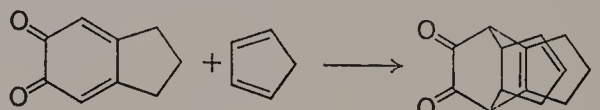


(359)

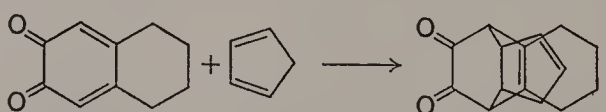
(360)

these differing views was suggested by Ansell and Gosden[424]. As shown above, the two adducts (**143** and **144**) can be interconverted thermally via a Cope rearrangement. This mechanistic picture has been supported by a number of subsequent studies[419]. It seems clear that many 1,2-benzoquinones act as dienophiles and give the kinetically controlled product. The chief exceptions are those quinones with substantial steric demands (e.g. tetramethyl- and 3,6-dimethyl-1,2-benzoquinone). In many of the cases studied an interesting interplay of steric and electronic effects could be seen.

A still more recent study involved some bicyclo 1,2-quinones and shows that substitution in the 4,5-positions of the quinone also results in diene behaviour (equations 361–363)[425].



(361)



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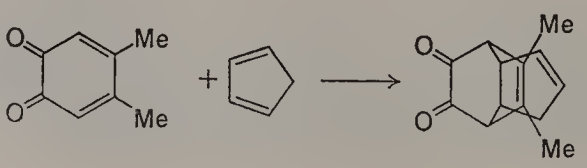
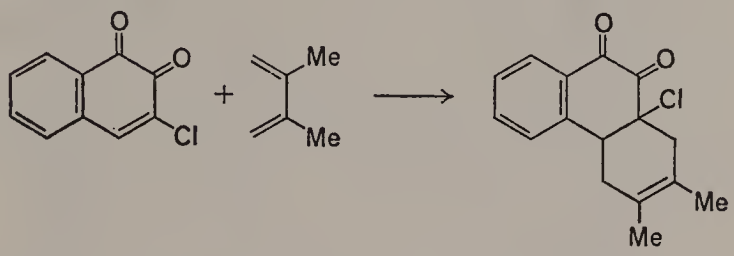


(363)

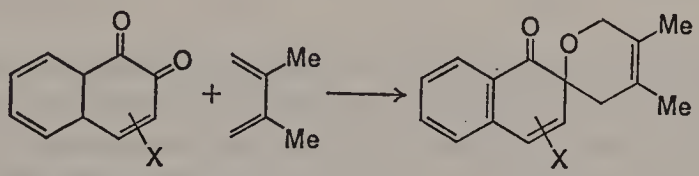
The study of Diels–Alder chemistry of 1,2-quinones has continued at a brisk pace as the following brief notes indicate.

(1) The reaction of 3-chloro-1,2-naphthoquinone with 2,3-dimethylbutadiene has been reinvestigated[426,427]. The structure originally reported for the 1:1 adduct was confirmed and is the usual Diels–Alder product (equation 364). Various other 3- and 4-substituents on the quinone ring



(364)

were re-investigated[428,429] or examined for the first time[430]. With halogen located in the 4-position, a carbonyl addition product was obtained (equation 365). The 3-methoxy derivative gave the normal Diels–Alder



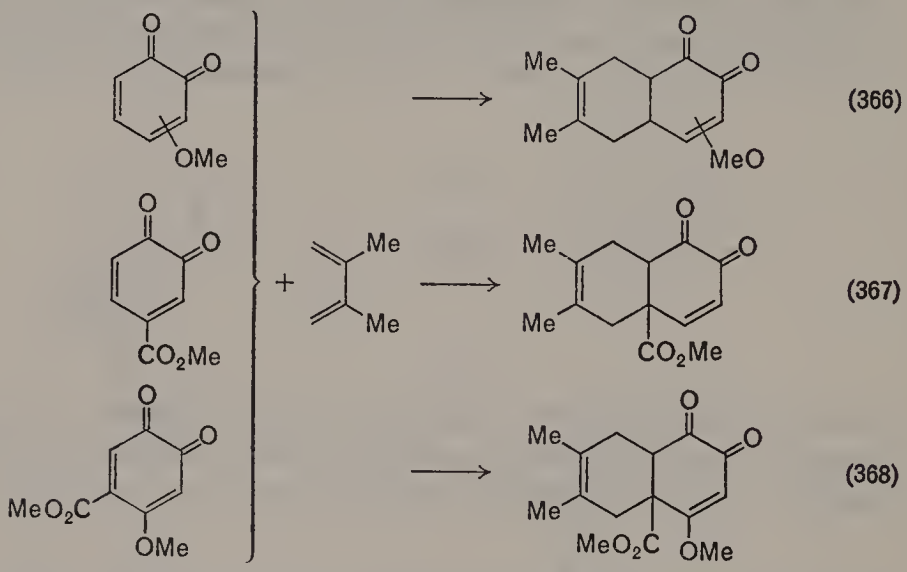
(365)

X = 4-Cl, 4-Br, 3-MeO, 3, 4-Cl_2 (145)

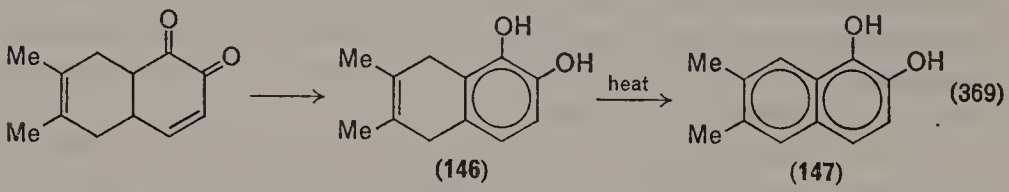
adduct and the spirodihydropyran (**145**) in the ratio of 3 : 1. Strong electron-withdrawing groups (4-cyano, 3-carbomethoxy and 3-nitro) all undergo the normal Diels–Alder reaction. The example of 3-nitro-1,2-naphthoquinone is especially interesting in that it is unusual to find a product with an angular nitro substituent. The mechanism and the product structures have been reported in some detail[431].

(2) The 1,2-benzoquinones are even more sensitive than the 1,2-naphthoquinones and very few successful Diels–Alder reactions have been reported until recently; exceptions are cyclopentadiene[419] and dimerization. Using a large excess of diene (10–25 molar), it has been shown that a large number of such quinones will react with simple acyclic dienes[432]. The yields vary, but are often quite good. Two of the quinones, 4-cyano and 4-carbomethoxy, could not be isolated and were prepared *in situ* by oxidation of the corresponding catechol in the presence of the diene. In the 4-cyano case, only nickel peroxide was effective, while a variety of oxidants were used to generate the 4-carbomethoxy-1,2-benzoquinone (silver oxide was the best).

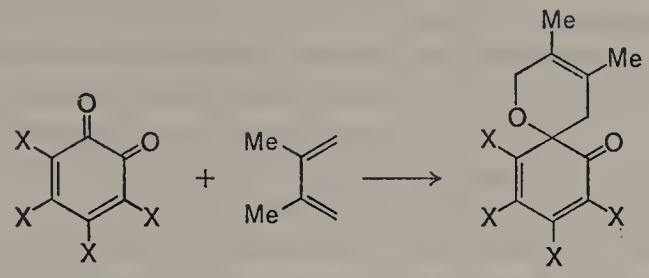
The adducts from unsymmetrical mono- and disubstituted quinones showed dienophilic reactivity of the more electron-deficient carbon–carbon double bond (e.g. equations 366–368). The initial adducts shown were, in



most cases, not the only product isolated. Usually, at least a part of the adduct aromatized and often purification (sublimation) caused dehydrogenation (**146** and **147** in equation 369). Trimethyl- and trichloro-1,2-benzoquinones were also studied and of the four substrates, 3,4,5-trimethyl-1,2-benzoquinone decomposed too rapidly to allow adduct formation. The other three substrates gave adducts of the monosubstituted alkene linkage.



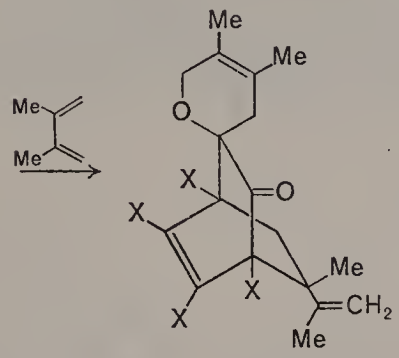
These studies have been expanded to the tetrahalo-1,2-benzoquinones and interesting new chemistry has been reported[433]. An earlier investigation of the reactions of such quinones with 2,3-dimethylbutadiene found a 1:2 adduct, for which an incorrect structure was proposed[434]. Re-investigation showed that with equimolar reactants at 0°C, a 1:1 adduct is formed in high yield. The i.r. spectra of the 1:1 adduct showed a single α,β-unsaturated carbonyl group and by analogy with earlier work[430] a spirodihydropyran structure (**148**) was assigned (equation 370). Such a system retains the 1,2-benzoquinone's diene system and reacts with a



X = Cl, Br

(148)

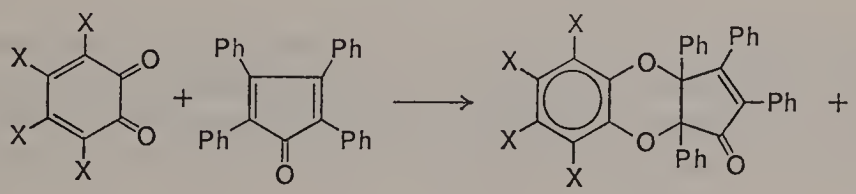
(370)



(149)

second mole of 2,3-dimethylbutadiene to produce the same 1:2 adduct **149** found by Horner and Merz[434] with excess diene. The structure of the product **149** was assigned on the basis of its ability to undergo a Cope rearrangement and the spectra (i.r. and n.m.r.) of the rearranged product.

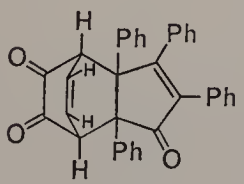
(3) The compound, 2,3,4,5-tetraphenylcyclopenta-2,4-diene-1-one (tetracyclone), is well known as a fine electron-deficient diene in Diels–Alder syntheses, but rarely does it act as a dienophile. Recent examples of such behaviour have been reported with 1,2-benzoquinone and its tetrachloro derivative (equation 371)[435]. Tetrachloro-1,2-benzoquinone gives only a very high yield of the dioxan derivative (**150**; X = Cl).



X = H, Cl

(150)

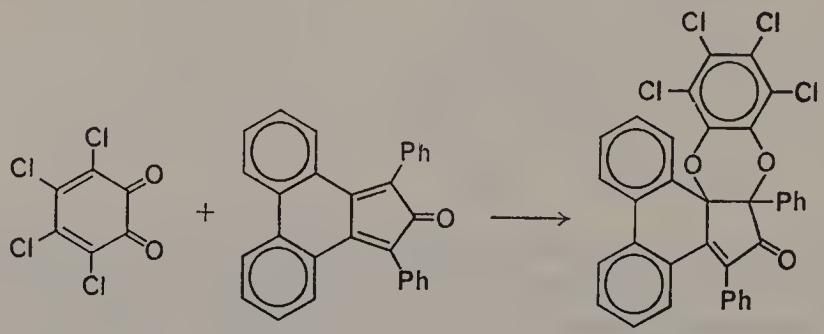
(371)



(151)

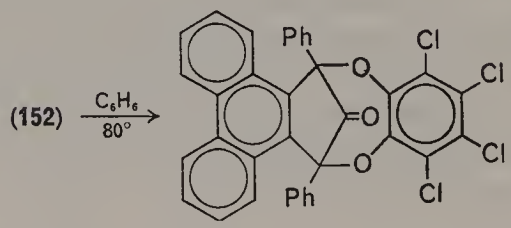
Further examination of the reaction of tetrahalo-1,2-benzoquinones with various cyclopentadienones revealed that dioxan formation is, by far, the most common reaction[436]. A variety of substituent patterns were used and it was concluded that steric effects are of much greater significance than electronic effects. The only instance of the quinone acting as a carbon diene (**151**) is the unsubstituted case reported earlier[435].

Other dioxan-type cycloaddition reactions have been reported between tetrahalo-1,2-benzoquinones and, for example, 2,5-dimethyl-3,4-diphenyl-cyclopentadienone[437]. Of special interest is the example shown in equation (372). The expected initial adduct **152** undergoes a very facile rearrangement to an eight-membered ring containing two oxygen atoms and a carbonyl bridge (equation 373).



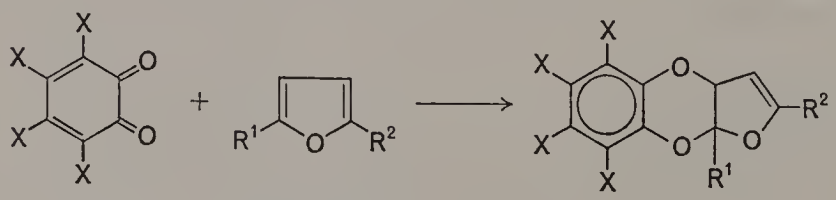
(372)

(152)



(373)

(4) Still another unusual aspect of 1,2-benzoquinone Diels–Alder chemistry is illustrated by reactions with various furans. The ability of furans to act as dienes is well known, but the observed mode of reaction with 1,2-benzoquinones is as a dienophile (equation 374)[438]. An interesting

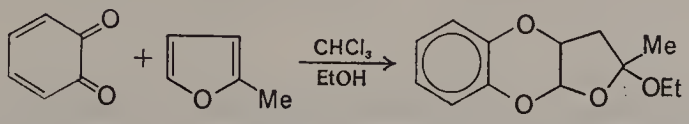


(374)

X = H, Cl

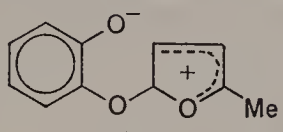
R^1 = H, Me, Ph
R^2 = H, Ph

piece of mechanistic detail was found when the reaction was carried out in chloroform (containing the usual ethanol stabilizer) and ethanol was incorporated in the product (equation 375). This observation, and some



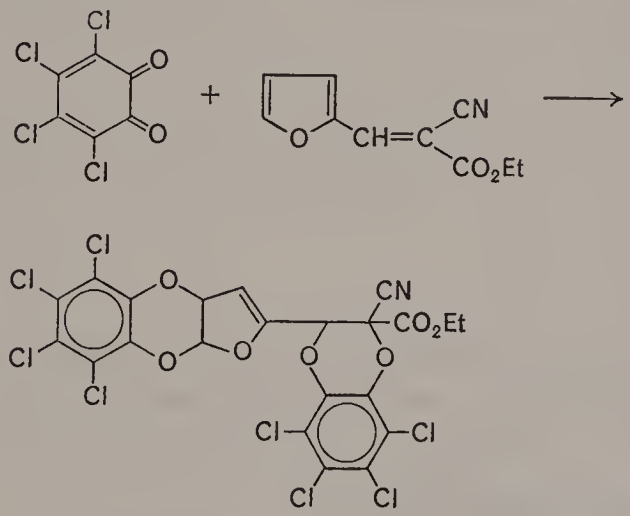
(375)

related experiments, suggest a two-step mechanism rather than a concerted cycloaddition. Electrophilic attack of the quinone on the furan to produce a stabilized carbonium intermediate (**153**) was suggested.



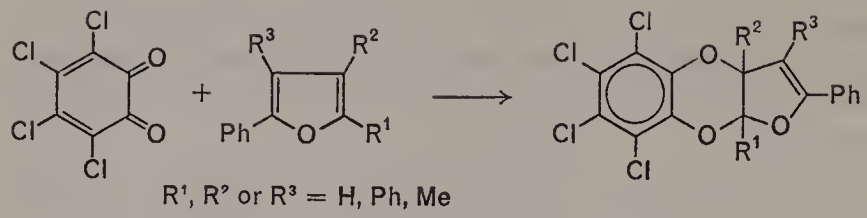
(153)

A series of furans with 2-vinyl side-chains and tetrachloro-1,2-benzoquinone react with interesting results[439]. Even though the vinyl group was substituted with strong electron-withdrawing groups, the addition usually took place on the furan ring (equation 374: X = Cl; R^1 = H; R^2 = —CH=CYZ, with Y = H, CN, CO_2Et and Z = CN, NO_2, CO_2Et, COPh). A single exception was found in which the vinyl side-chain also acted as a dienophile (equation 376).



(376)

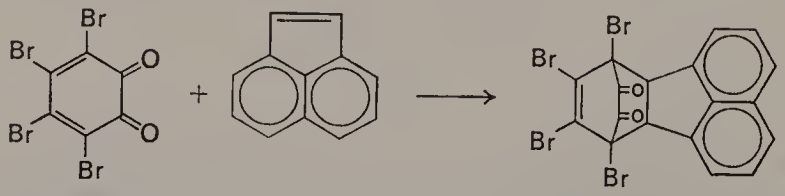
Further study with furans containing various combinations of methyl and phenyl substituents has confirmed the generality of the dioxan-forming reaction (equation 377)[440]. Some additional evidence for the



(377)

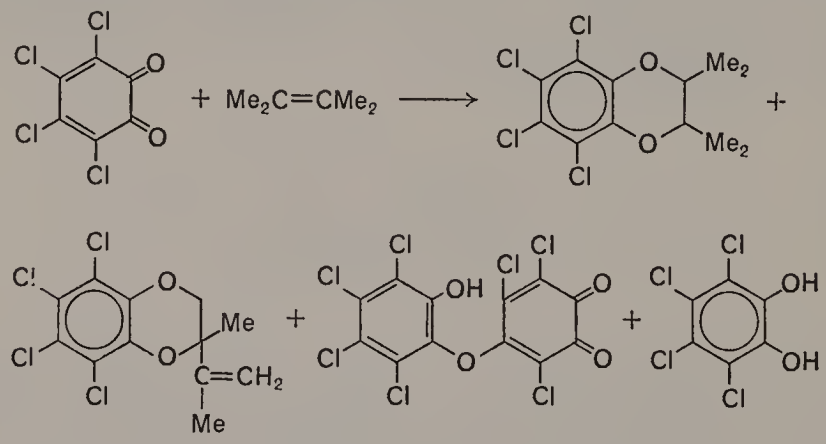
two-step carbonium ion intermediate mechanism is presented and once again steric effects appear to outweigh electronic effects in determining the structure of the product.

(5) Finally, two reports have been made of relatively unactivated double bonds entering into reactions with tetrahalo-1,2-benzoquinones. The first involves acenaphthylene and the quinone as a diene (equation 378)[441].



(378)

The second is the addition of 2,3-dimethyl-2-butene to tetrachloro-1,2-benzoquinone and leads to several products besides the expected dioxan derivative (equation 379)[442]. The preliminary experiments reported suggest



(379)

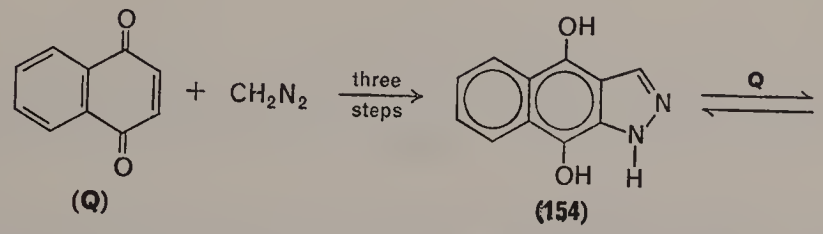
that two competing reaction paths are operating: (i) direct cycloaddition leading to the benzodioxan, and (ii) an allylic radical sequence leading to the other products. Tetrabromo-1,2-benzoquinone gives similar products.

B. Cycloaddition of Diazo Compounds

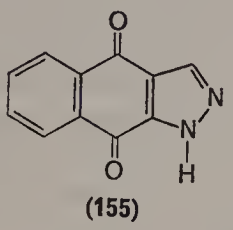
The first observation of the addition of diazomethane to 1,4-benzo- and 1,4-naphthoquinone was made in the last years of the 19th century[443, 444]. It was more than thirty years later, after Diels and Alder had rekindled the

interest in cycloaddition chemistry, that Fieser re-examined and expanded the field[445]. The additional study was motivated both by the feeling that von Pechmann did not understand the structure of the product and the desire to explore the possible synthesis of cyclopropane derivatives of quinones and hydroquinones.

Fieser and Peters found that von Pechmann's elemental analyses were not quite correct and that the addition of diazomethane follows the well-established pathway; i.e. reductive addition, isomerization, enolization and cross-oxidation (equation 380). The intermediate **154** and product

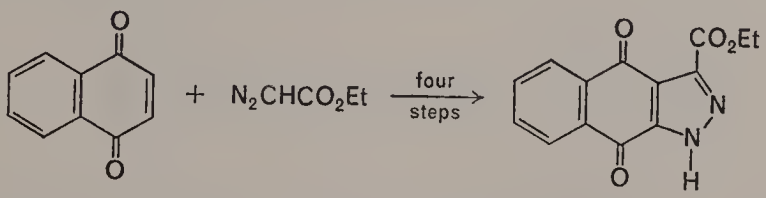


(380)



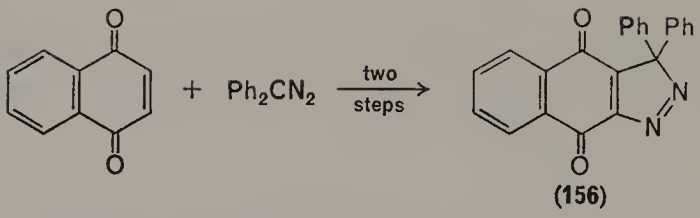
155 are interesting in that the hydroquinone is yellow and the quinone is colourless under most circumstances. The evidence, including electrochemical data, leaves no doubt that the structures are correct.

Ethyl diazoacetate and diphenyldiazomethane also add cleanly to 1,4-naphthoquinone. The former adds slowly allowing ample time for the cross-oxidation reaction to take place (equation 381). Thus, in contrast to



(381)

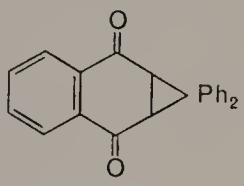
diazomethane, no intermediate is isolated. The addition of diphenyldiazomethane was carried out in an effort to prevent rearrangement to a pyrazole ring. Chemical evidence shows that the product does contain a cyclic azo arrangement (equation 382). The pyrolysis of **156** did lead to some product that was tentatively assigned a fused cyclopropyl structure.



(382)

(156)

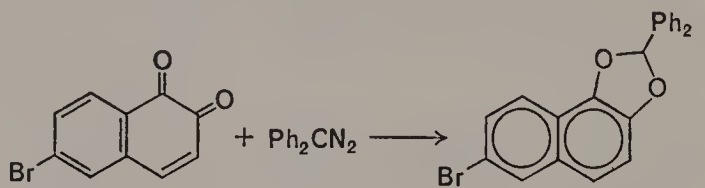
This pyrolysis has been carefully re-examined and the correct structure **156a** and mechanism determined[446, 447].



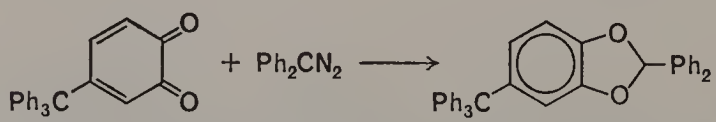
(156a)

The use of dialkylazomethanes produced even less satisfactory results. It was found that 1,4-benzoquinone also adds diphenyldiazomethane, but the chemistry of the product appeared less interesting and was not pursued.

This study of the addition of diazo compounds to quinones has included the 1,2-naphthoquinones[448]. With diazomethane only resinous products were obtained and this was thought to be connected with the relatively low stability of the starting quinone. The use of the more stable 6-bromo-1,2-naphthoquinone failed to produce crystalline product and only starting material could be obtained with the milder reagent ethyl diazoacetate. The conclusion, that the alkene linkages of 1,2-quinones are not reactive toward diazo compounds, is clearly supported by the reactions of diphenyldiazomethane with the heterodiene system (equations 383 and 384).

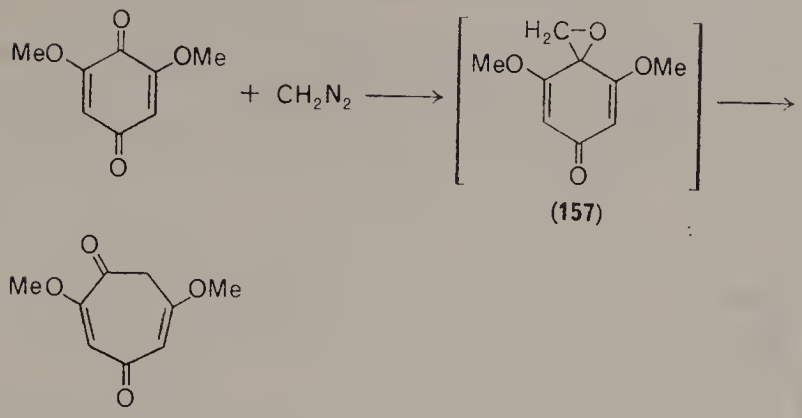


(383)



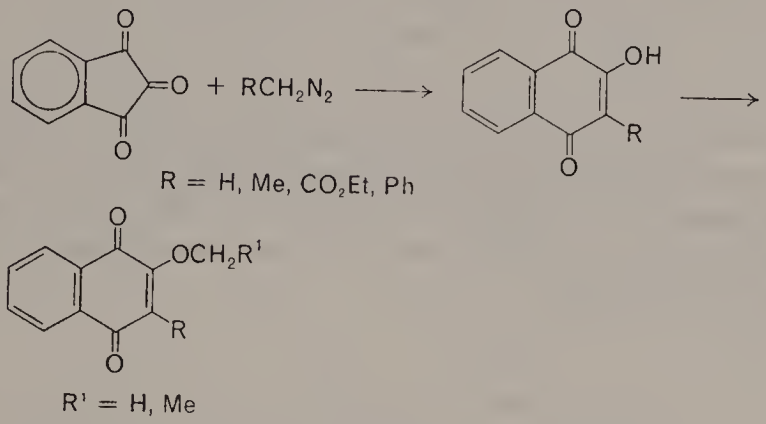
(384)

An interesting ring enlargement reaction of quinone with diazomethane has been reported[449]. It was suggested that the intermediate **157** may be involved (equation 385). A related ring enlargment of trioxoindan has



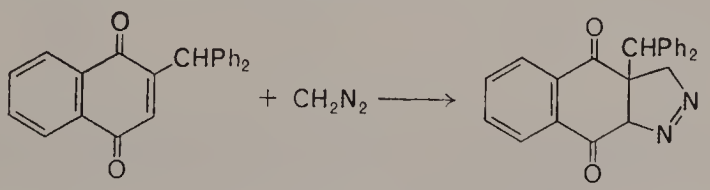
(385)

been shown to produce quite reasonable yields of substituted 2-hydroxy-1,4-naphthoquinones (equation 386)[450]. In certain cases, the actual product isolated was a 2-alkoxy derivative.



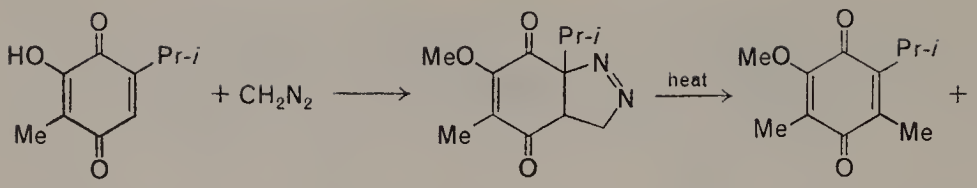
(386)

Fieser and Hartwell succeeded in stopping the reaction sequence at the pyrazoline stage by using the so-called 'blocked' quinone 2-diphenylmethyl-1,4-naphthoquinone (equation 387)[448].

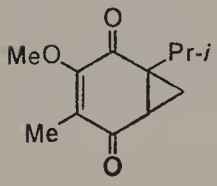


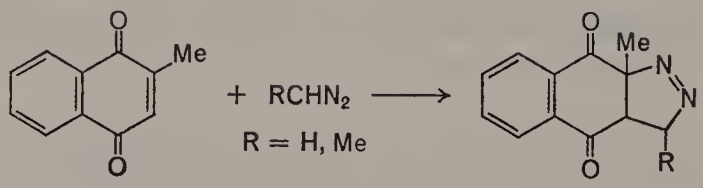
(387)

A continuation of this work with blocked quinones produced a cyclic azo compound that pyrolysed to a fused cyclopropyl derivative (equation 388)[193]. When this work was extended to a re-examination of 2-methyl-1,4-naphthoquinone and diazomethane, several conflicting literature reports were resolved[451]. The addition takes place in the expected manner (equation 389) and the adduct exhibits chemistry analogous to that found



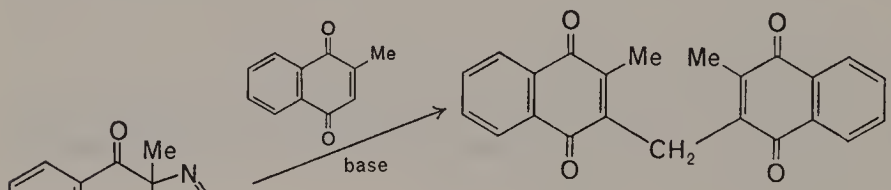
(388)



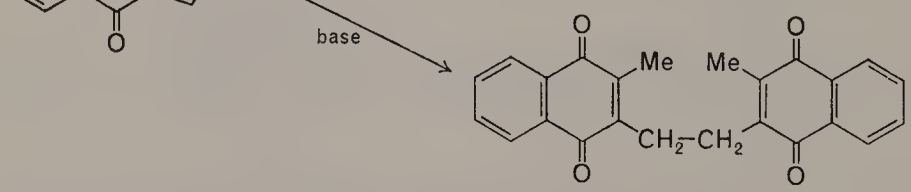


(389)

for 2-hydroxythymoquinone. Diazoethane also added in the expected manner; diphenyldiazomethane did not react under the same conditions. The base-catalysed dimerization of adducts of this general structure provides a convenient route to methylene and dimethylene diquinones (equations 390 and 391)[452].

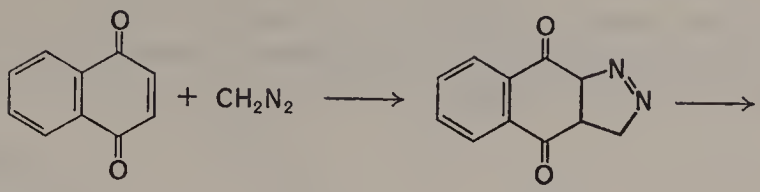


(390)



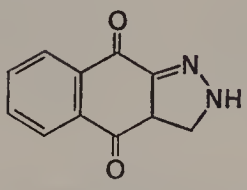
(391)

A recent extension of this quinone addition has resulted in the isolation of the expected initial adduct (**158** in equation 392)[453]. This compound is quite unstable and is easily converted to a yellow isomer that had generally been pictured as a 1,4-naphthalenediol derivative. Evidence is presented for believing that **159** is the correct structure.



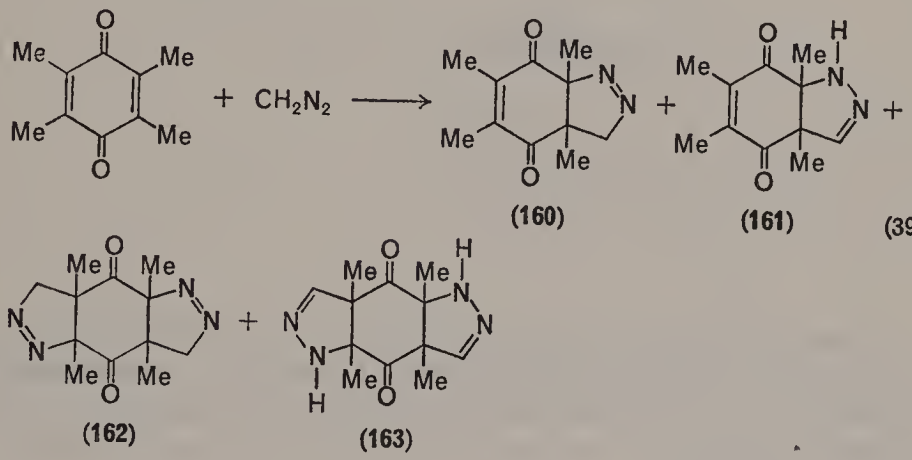
(158)

(392)



(159)

The logical extreme case of a blocked quinone in the present sense would be 2,3,5,6-tetramethyl-1,4-benzoquinone (duroquinone). A re-investigation of the report that diazomethane adds to the carbonyl group showed that quite normal cycloaddition takes place[454,455]. Four products were isolated under the reaction conditions given earlier (equation 393). The conversion of **160** to **161** and **162** to **163** can be achieved under mild conditions. Pyrolysis leads to fused cyclopropane systems.

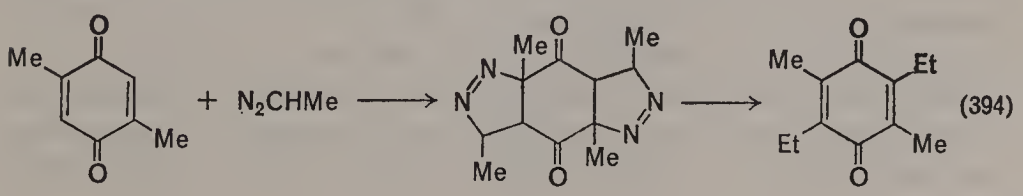


(160) (161)

(393)

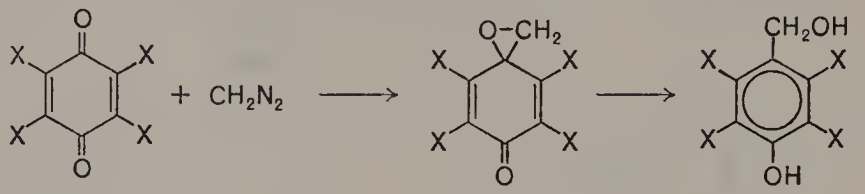
(162) (163)

Simpler quinones have also been employed in these reactions and the cycloaddition product can lose nitrogen to produce alkylated product as well as fused cyclopropyl derivatives (equation 394)[456].



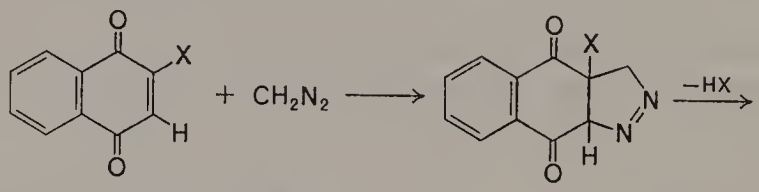
(394)

It has been shown recently that diazomethane adds to a carbonyl group in quinones with all of the hydrogens replaced by electronegative groups (equation 395)[457]. The epoxy product **164** is useful for the synthesis

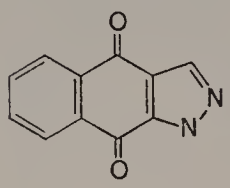


X = F, Cl, Br, I, OMe, O_2CMe **(164)** (395)

of certain types of benzyl alcohols. The 1,4-naphthoquinones bearing similar 2,3-substituents also show this chemistry. When one of the substituents is hydrogen, ring addition takes place and subsequent elimination occurs readily (equation 396).



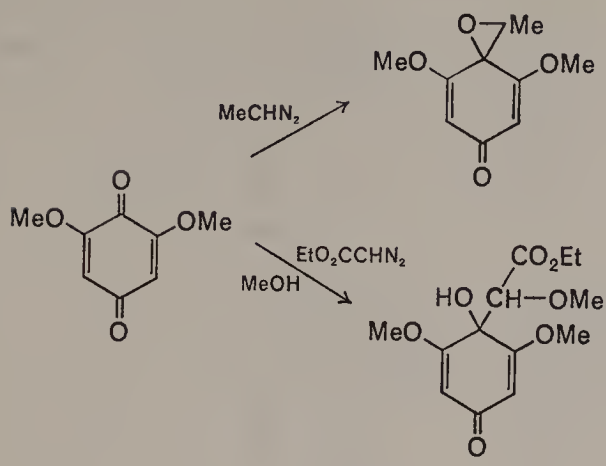
X = Cl, Br, SMe, SOMe, SO_2Me (396)



A later and closely related study showed that carbonyl addition of diazomethane and diazoethane also occurs with 2,6-dimethoxy-1,4-benzoquinone[458]. The exact nature of the product depends on the substitution pattern of the quinone and the diazo compound employed (e.g. equations 397–400).

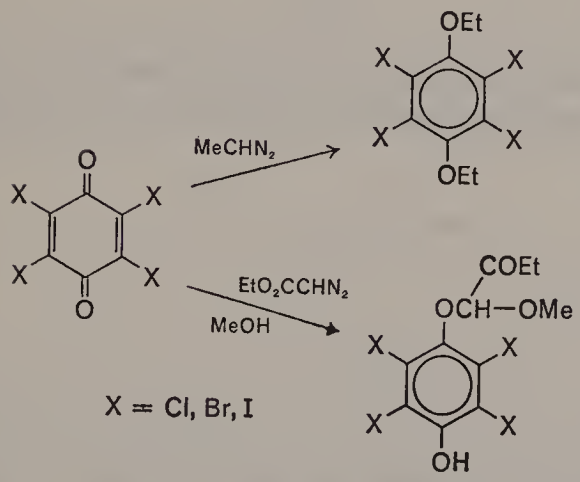
Earlier reports of the addition of diazomethane to 1,4-naphthoquinone have been re-examined, the structure of the adduct revised and a new product identified (equation 401)[459]. The general structure of **166** was consistent with its spectra and formation from **165** and dimethyl sulphate or diazomethane. The alternative structure **167** was not ruled out.

Awad and collaborators have expanded their studies to include the 1,4-benzoquinones[460]. With 2-methyl-1,4-benzoquinone, diazomethane and diazoethane each produced a single product (**168** in equation 402).



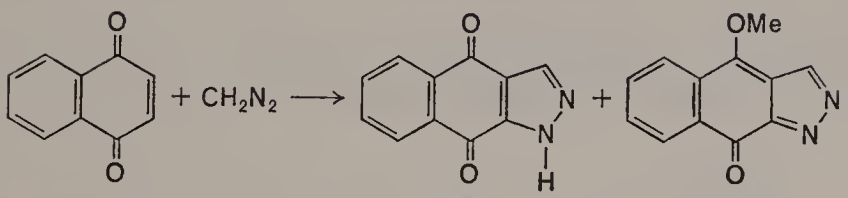
(397)

(398)



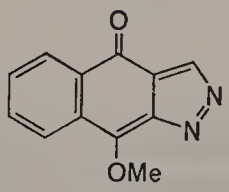
(399)

(400)

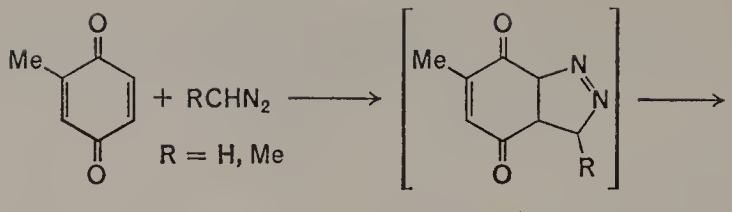


(401)

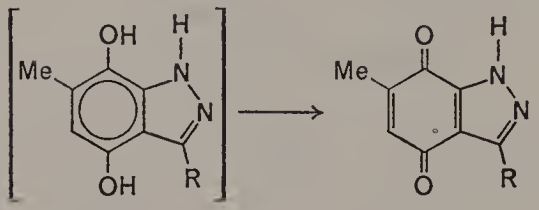
(165) (166)



(167)

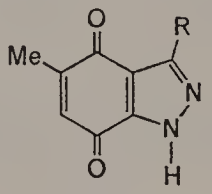


(169) (402)



(170) (168)

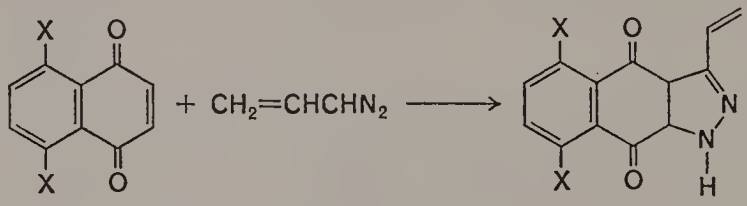
Neither of the suggested intermediates (**169** and **170**) was isolated. The possible isomeric product **171** was considered (as were the appropriate



(171)

isomeric intermediates) but no evidence favouring one or the other is presented. The oxidized state of the product **168** is attributed to atmospheric oxygen, because no 2-methylhydroquinone could be found in the reaction mixture.

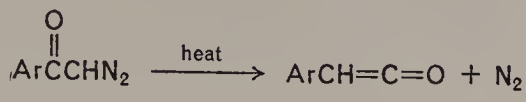
The addition of vinyldiazomethane to substituted 1,4-naphthoquinones has been reported recently (equation 403)[461].



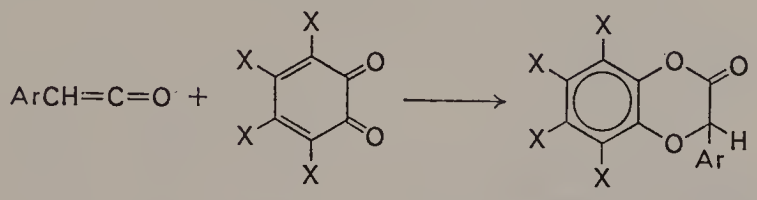
X = H, OH, OAc (403)

Until recently only a single study of the reaction 1,2-quinones with diazoalkanes had been added to the early work of Fieser and Hartwell[448,462]. Fair yields of cyclic lactones were obtained from the

ketoketenes formed in the pyrolysis of acyldiazomethanes (equations 404 and 405). A variety of aryl groups, stearoyl and two bis-diazomethanes were used.



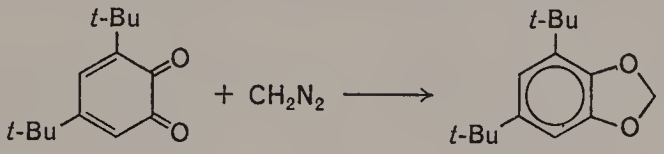
(404)



(405)

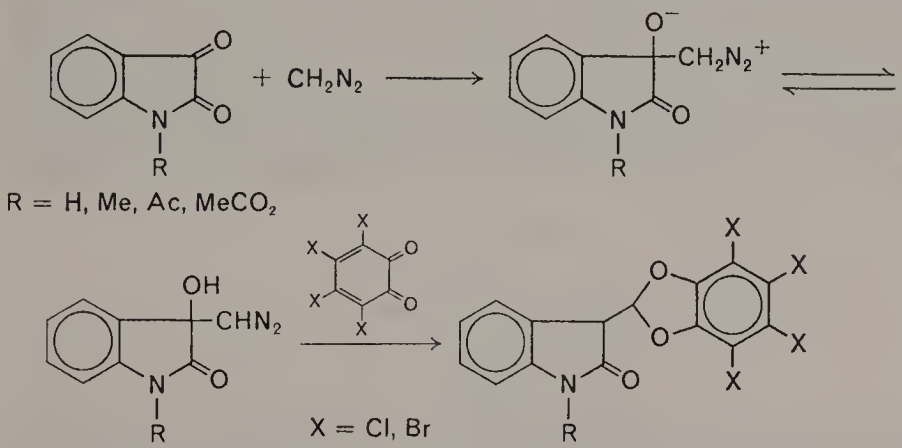
X = Cl, Br

With diazomethane itself the cyclic diether first reported is the usual product (equation 406)[463]. These products are also familiar from our earlier discussion of carbonyl hydrazone addition (see section III).



(406)

The tetrahalo-1,2-benzoquinones have been used to trap intermediate 1:1 addition products of diazomethane and α-dicarbonyl compounds (equation 407)[464]. Similar chemistry was found for a series of indanediones.

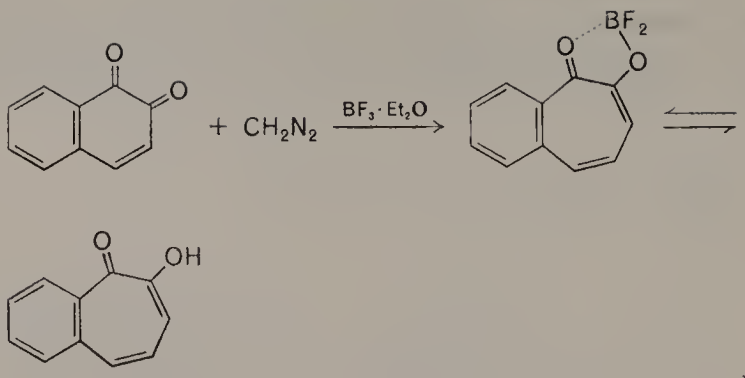


R = H, Me, Ac, $MeCO_2$

(407)

X = Cl, Br

A ring enlargement reaction starting from a 1,2-quinone has been reported (equation 408)[465]. The intermediate boron complex can be isolated and the overall yield is a respectable 24%.

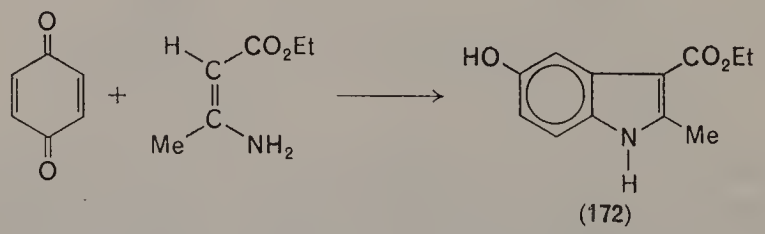


(408)

C. The Addition of Enamines

1. Nenitzescu condensation

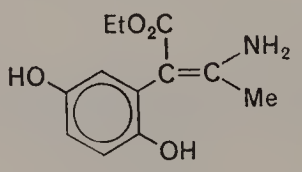
The pharmacological activity of several naturally occurring 5-hydroxyindoles has resulted in extensive study of the general method for their synthesis first published by Nenitzescu[466]. The original reaction (equation 409) has been modified extensively[467–470]. Some of this work, while



(409)

(172)

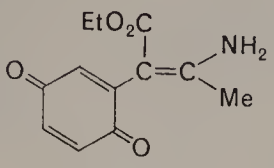
emphasizing synthetic variations, has also produced useful mechanistic information. An early proposal[468] suggested an intermediate, **173**, that cyclizes to product in some unspecified manner. A more elaborate picture of this mechanism has been presented[471], but with little solid evidence. The variation of yield with substitution seemed to these authors to be consistent with the proposed mechanism. A modification has been offered



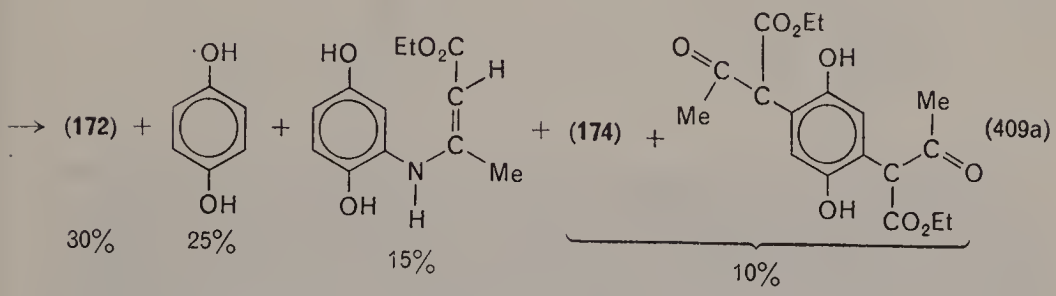
(173)

in which both the hydroquinone **173** and its oxidation product **174** are intermediates[472]. At about the same time a careful product isolation and characterization study provided a good deal of experimental support for such a path (equation 409 with some additional products)[473]. The high

total yield (some experiments were as high as 95%) is important. Similar results were found with 2-methyl-1,4-benzoquinone.

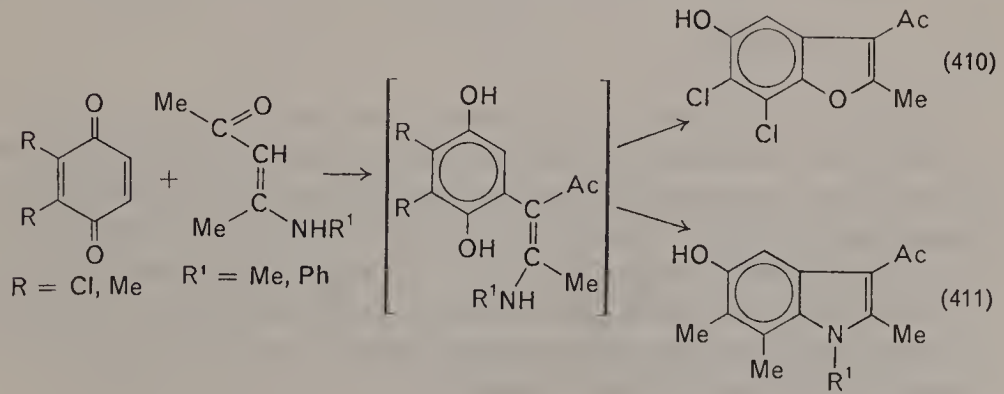


(174)



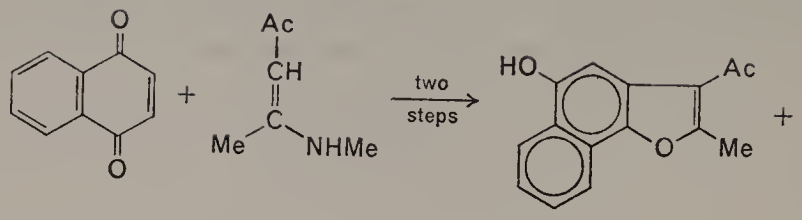
(409a)

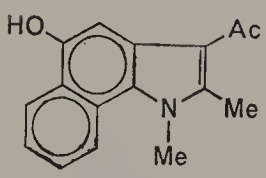
The Nenitzescu condensation can also represent a valuable method for the synthesis of substituted benzofurans. Grinev and collaborators have made an impressive contribution to our understanding of both paths. As a part of their continuing study of the addition of a monoimine of acetylacetone to 1,4-benzoquinones, the influence of substituents in the quinone was studied[474]. As indicated in equations (410) and (411) the electronic nature of substituents in the quinone has a very strong effect on the direction of the cyclization and hence on the structure of the observed product. The direction of the effect is certainly in accord with electronic expectations, but the magnitude of the effect is surprising. When 1,4-naphthoquinone is used in the reaction, the nature of the nitrogen substituent is significant in determining the product (equation 412). With acetylacetone *N*-phenylimine and 1,4-naphthoquinone only the indole was obtained (i.e. **175** with *N*-Ph rather than *N*-Me).



(410)

(411)

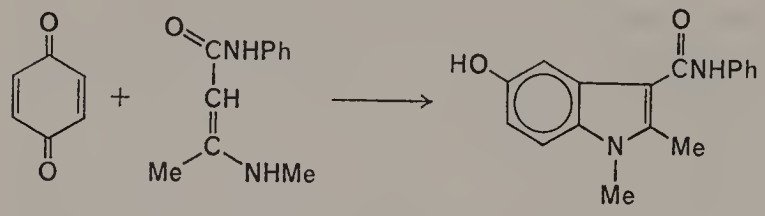




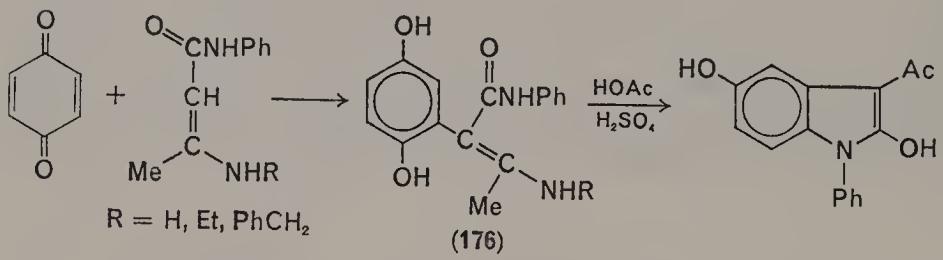
(175)

(412)

The synthesis of variously substituted indoles has been accomplished via the addition of the anilides of β-amino- and *N*-alkyl-β-aminocrotonic acids to 1,4-benzoquinone[475]. The nature of the substituent on nitrogen has a marked effect on the reaction and its outcome, as indicated by equations (413) and (414). An intermediate analogous to **176** was postulated in the *N*-Me case, but could not be isolated.



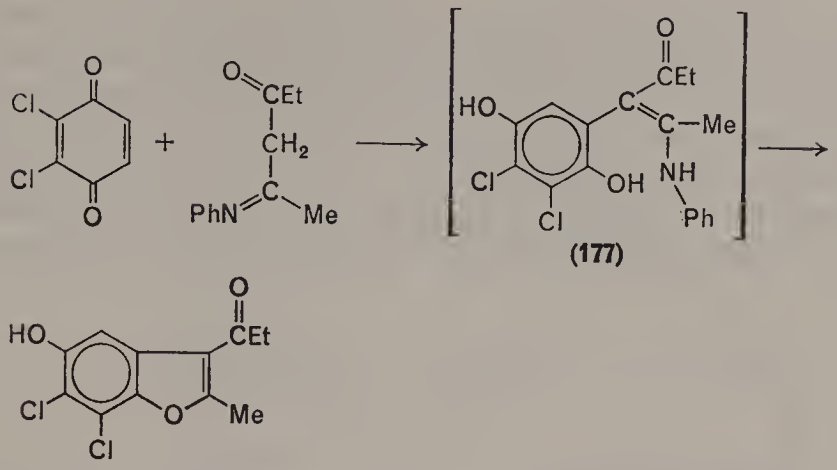
(413)



(176)

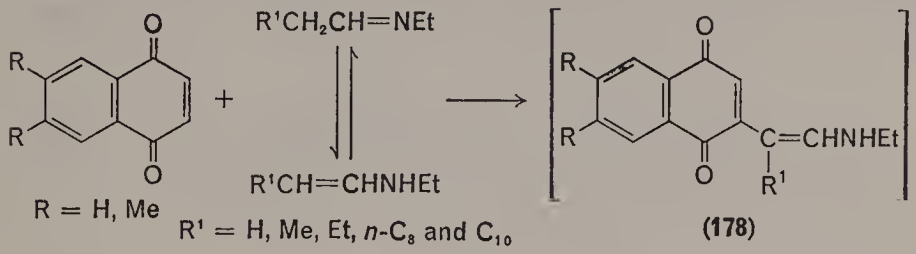
(414)

The Michael addition of 1,4-benzoquinones and the monoimines of 1,3-diketones can lead, by subsequent cyclization, to either indoles or furans. The question of whether the enamine and/or the enol system engages in the second reaction step has been studied (equation 415)[476]. The intermediate **177** was not isolated and none of the isomeric 2-ethyl-3-acetyl-5-hydroxy-6,7-dichlorobenzofuran was obtained. Thus, it may be suggested that the carbonyl imino group is always involved and the molecule eliminated (H_2O or $PhNH_2$) is significant.

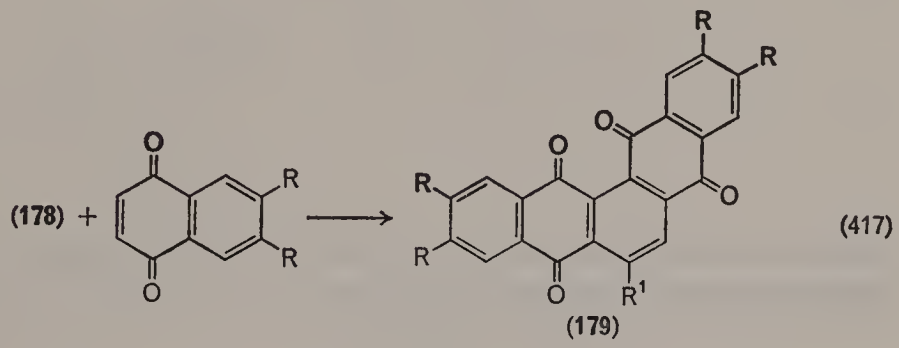


(415)

An interesting combination of the Michael and Diels–Alder reactions of enamines and quinones occurs when the Michael product reacts with additional quinone. This sequence leads to polycyclic compounds in quite reasonable yields (equations 416 and 417)[477]. Both the intermediate **178**



(416)



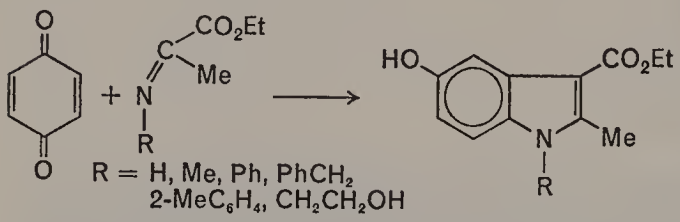
(417)

and the isolated product **179** presumably require the oxidation of an intermediate by the excess of quinone present. The significant intermediate, **178**, was not isolated and the overall yield is strongly dependent on the nature of R^1; i.e. the aldehyde from which the enamine is prepared. Finally, the presence of acid seems to be required.

A continuation of these studies showed that both 5- and 6-methyl-1,4-naphthoquinones react but the product mixture could only be

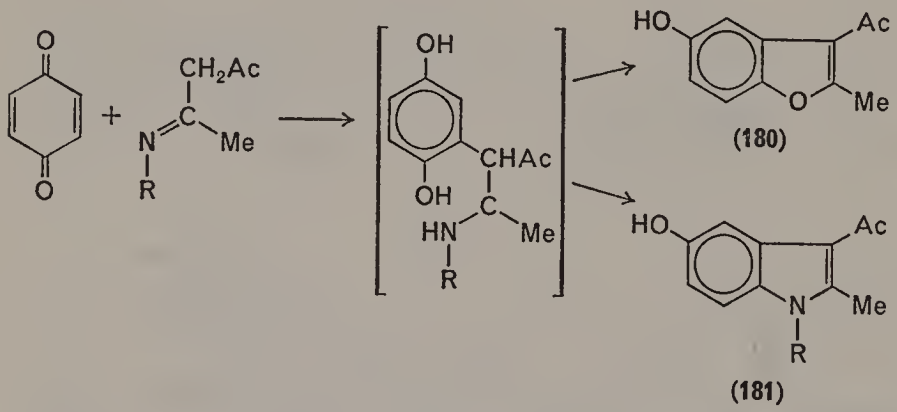
separated by paper chromatography[478]. The condensation of 1,4-anthraquinone occurred but less readily; 5,8-quinolinoquinone did not react.

In some cases the yields of indole in these reactions is quite small and methods have been sought to improve the outcome. One beneficial approach is the azeotropic distillation of the water formed in the reaction (equation 418)[479]. It appears that the water reacts with the enamine to release ammonia or amines that cause the polymerization of the quinone.



(418)

A somewhat more detailed study of the effect of imino nitrogen substituents has been made[480]. Several *N*-substituted monoimines of acetylacetone were allowed to react with 1,4-benzoquinone under the same conditions and the product(s) determined (equations 419 and 420).



(419)

(420)

The product distribution is given in Table 16. The relationship between product and basicity of amine is striking; i.e.

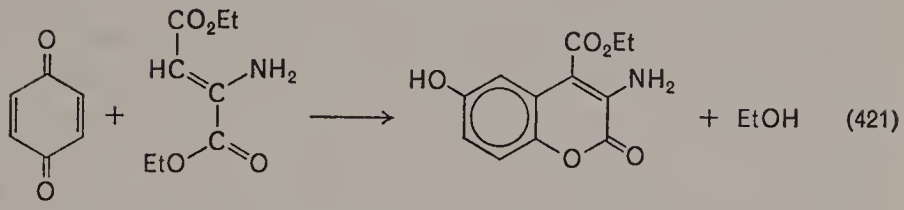
p*K* 3·3–4	benzofurans
p*K* 4·6–5	mixture
p*K* 8–10	indoles
still weaker bases	no reaction

The synthetic utility of the Nenitzescu condensation has been greatly expanded by Domschke and collaborators[481]. Much of this work deals with benzofuran synthesis, but coumarins (equation 421)[482] have also been prepared.

TABLE 16. Product distribution in the reactions of monoimines of acetylacetone with 1,4-benzoquinone (equations 419 and 420)[480]

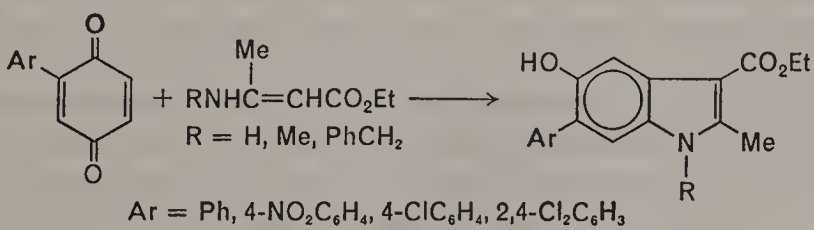
R	Product (180) %	(181) %
n-Bu	39	
CH_2CO_2Et[a]	×	×
CH_2CH_2OH[a]	×	×
CH_2Ph[a]	×	×
Ar(XC_6H_4)		
4-Me		37
4-MeO		50
2-MeO		12
4-Me_2N		58
4-AcNH		57
4-Br	0	0
4-NO_2	0	0

[a] Total yields are in the range 20–49%. Both products are present, but individual yields were not recorded.



(421)

Finally, aryl-substituted quinones have been used in the synthesis of indoles by the Nenitzescu route, but the yields have been very disappointing (equation 422)[483].

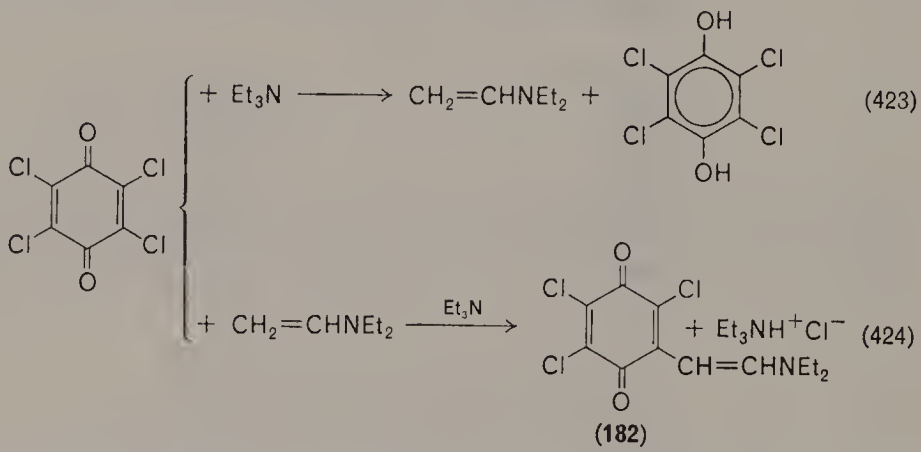


(422)

Ar = Ph, 4-$NO_2C_6H_4$, 4-ClC_6H_4, 2,4-$Cl_2C_6H_3$

2. The oxidation of tertiary amines

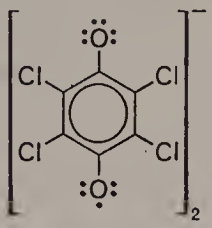
While examining the oxidation of tertiary amines with quinones, the following important reaction was discovered[484]: a solution of triethylamine and chloranil in benzene turned green, then blue, and finally a colourless crystalline product precipitated. The colourless compound was shown to be triethylamine hydrochloride and tetrachlorohydroquinone was isolated from the reaction mixture. The blue compound was also obtained in a crystalline form and shown to have the molecular formula $C_{12}H_{12}O_2NCl_3$. These data and i.r. spectra suggested the structure **182** and the following reactions were proposed (equations 423 and 424).



A thorough evaluation of the scope of the reaction revealed that for practical synthetic applications it is rather limited. Aside from chloranil and bromanil, only the 2,5- and 2,6-dichloro (and presumably the trichloro, di- and tribromo quinones) give any useful product. A wide variety of tertiary amines was tried, with few giving satisfactory results (*N*-ethylpiperidine is an exception). Some of the amines that did react in both steps (e.g. tri-*n*-butylamine) gave products that were quite reactive and consequently difficult to purify. Some speculations concerning the mechanistic details are given; for example, the available evidence suggests that the formation of a sufficient concentration of suitably activated molecular complexes is as important to the reaction's success as is a suitable redox potential.

A more detailed study of the absorption spectra of chloranil and aliphatic amines has revealed some useful facts about enamine formation[485]. As expected, solutions of ethylamine or diethylamine and chloranil show changing u.v. spectra with time and shortly produce the corresponding *N*-substituted 2,5-diamino-3,6-dichloro-1,4-benzoquinone (see section VIII). However, when a suspension of chloranil is shaken with pure triethylamine, a dark-green precipitate forms. This dark-green solid shows u.v.

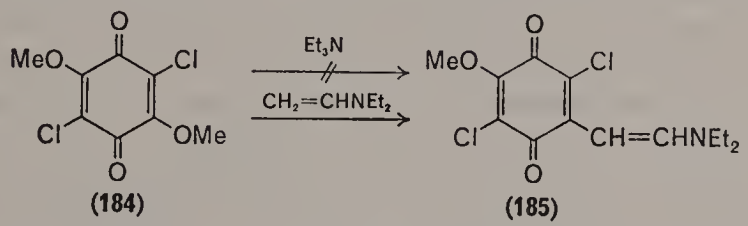
and e.s.r. spectra that are very similar to those of the product of sodium iodide and chloranil. This latter material is generally accepted as the sodium salt of chloranil semiquinone. The spectra of both products in methanol, ethanol and triethylamine are very similar, their i.r. spectra being virtually identical. There seems little doubt that the dark-green solid contains the chloranil semiquinone anion **183**. The detailed nature of the cation was not determined, but on the basis of preliminary data, it may have the structure shown. The addition of acid to this salt, **183**, regenerates



(183)

pure chloranil, showing that no substitution has taken place at this stage. The salt appears to be quite stable in the absence of solvent, but in acetone its spectrum changes with time until 2,3,5-trichloro-6-(2′-diethylaminovinyl)-1,4-benzoquinone (**182**) is produced. Foster argues against a charge-transfer complex and suggests **183** as the first phase of the reaction described by Henbest and collaborators.

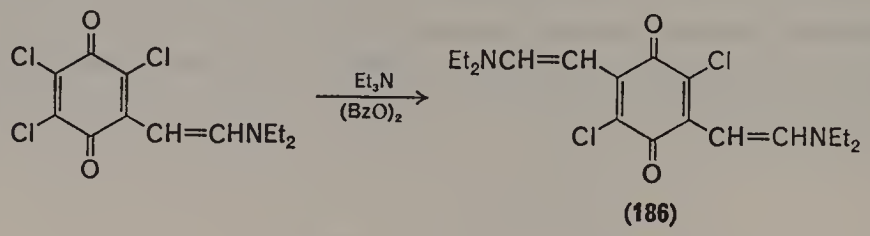
In the further study of the reactions of quinones and tertiary amines, a useful example has been found in 2,5-dichloro-3,6-dimethoxy-1,4-benzoquinone[486]. This quinone, **184**, does not oxidize triethylamine to an enamine, but if the enamine is formed it undergoes the substitution reaction readily (equation 425). Such a reaction, with its deep-blue



(184) **(185)** (425)

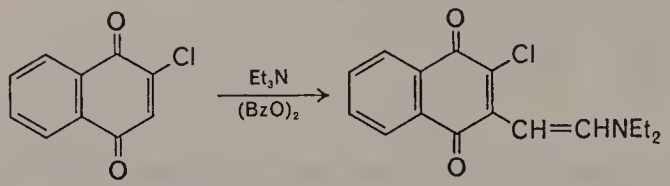
product **185**, represents a very useful test for the presence of enamines. Using quinone **184**, a number of oxidizing agents were tried with triethylamine; for example, enamines were formed with benzoyl peroxide and with *N*-bromosuccinimide, but were not formed either with MnO_2 or with 1,4-benzoquinone. The enamine used in equation (425) was generated by added benzoyl peroxide and it was found that the amount of blue quinone **185** formed is proportional to the peroxide added up to a peroxide : quinone ratio of 1 : 1.

The use of an added oxidant, like benzoyl peroxide or *N*-bromosuccinimide, provides a useful synthetic route. In several instances a reaction failed because the quinone failed to generate the enamine, not because of the substitution step (for example, equations 426–428).

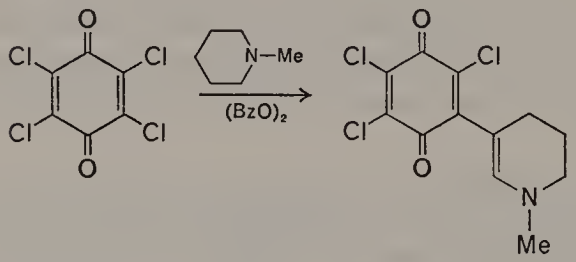


(426)

(186)

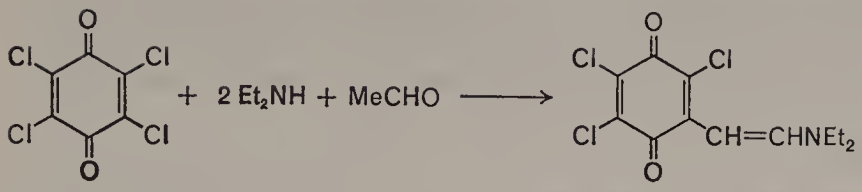


(427)

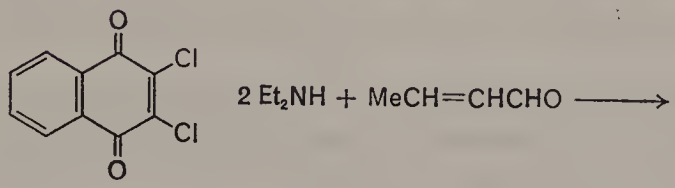


(428)

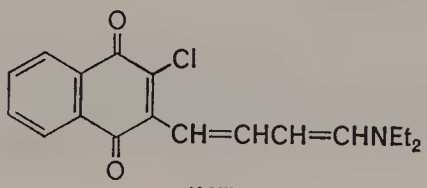
In an effort to confirm the structure of the chloranil–triethylamine adduct, another useful new synthetic approach was developed[487]. Upon simply mixing chloranil, diethylamine and acetaldehyde, a rapid reaction took place and the desired product was obtained in excellent yield (equation 429). The disubstituted product **186** can also be prepared by further additions of acetaldehyde and diethylamine. A wide variety of secondary amines is useful in this reaction and those quinones that react well with primary amines generally react with acetaldehyde and secondary amines as shown in equation (429). A complication is found with dimethylamine in that a substantial amount of direct substitution takes place and the yield of desired vinylamino compound decreases. It appears that acetaldehyde may be the only practical carbonyl reactant. Higher aldehydes gave blue solutions, but the products were difficult to purify. A reaction mixture of chloranil, acetone and morpholine led only to substitution of morpholine for chlorine. One interesting exceptional case was crotonaldehyde (equation 430). The yield of **187** was only 20%, but it could be



(429)



(430)



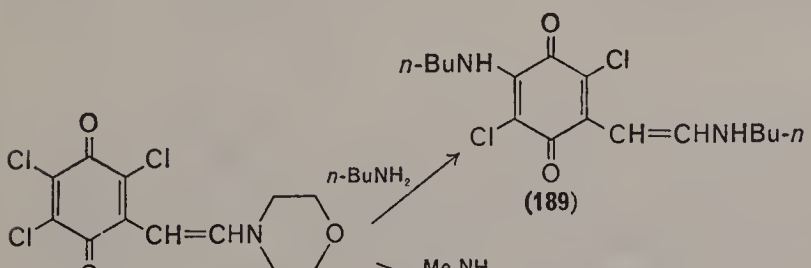
(187)

increased to 80% when the presumed intermediate **188** was prepared externally.

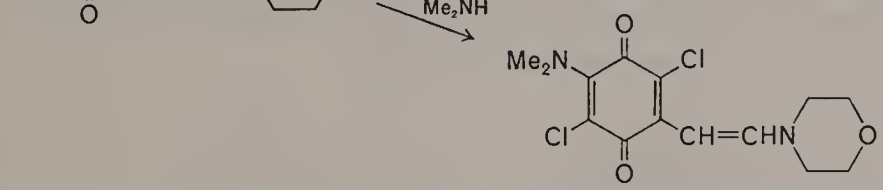
$CH_2{=}CHCH{=}CHNEt_2$

(188)

The dialkylaminovinylquinones undergo the usual nucleophilic substitution reactions of quinones (see section VIII). An interesting and exceptional reaction is illustrated in equations (431) and (432). It appears



(431)



(432)

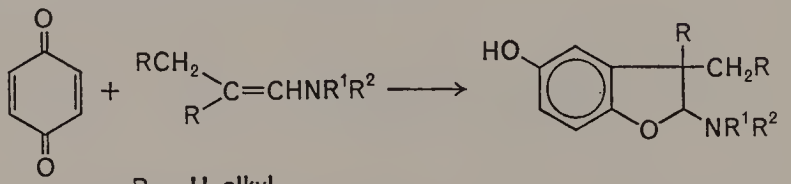
that the disubstitution product **189** arises from the preliminary substitution of the 2-chloro group by butylamine. This presumed intermediate has been thought to allow an *ortho* quinoneimine form that can lead to the

second substitution. Some comparison experiments were carried out in the substitution of chloro and methoxy quinones by primary and secondary amines. This aspect of quinone chemistry will be treated in section VIII.

3. Brief notes

Enamines and quinones have been shown to undergo several interesting reactions that deserve our notice, but have not been studied in much detail.

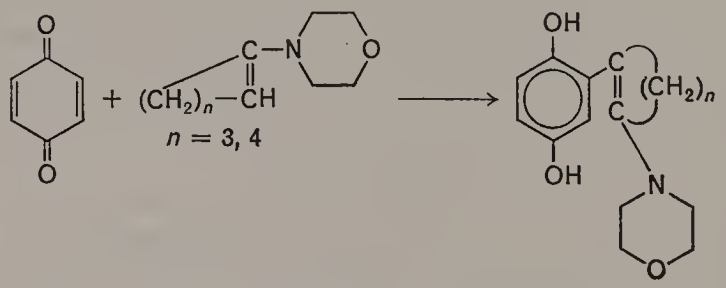
(1) A group under the direction of Brannock has made a number of contributions to our knowledge of enamine chemistry. As a part of their general survey of the enamine–carbonyl reaction, they prepared several dihydrobenzofuranols (equation 433)[488].



(433)

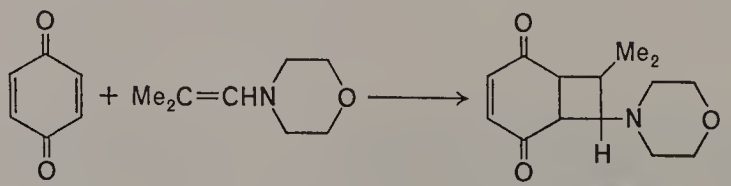
$R = H$, alkyl
$R^1 = R^2 =$ alkyl

(2) A study similar to that just cited has been carried out by Shvedov and Grinev[489]. They found that excellent yields of the initial addition product of 1,4-benzoquinone and certain enamines can be obtained by working in benzene at ice temperature (equation 434). In addition to the



(434)

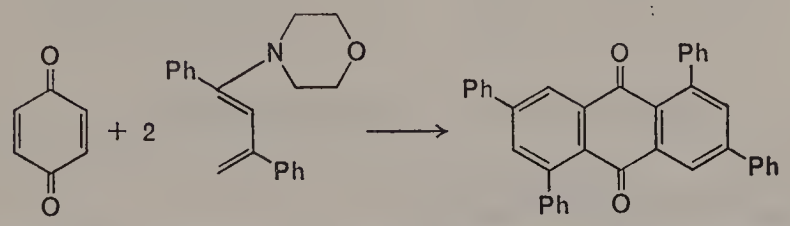
enamines of cyclic ketones, some aliphatic aldehydes gave similar results. The morpholine enamines seemed to be very superior. One exceptional case was found in the isobutyraldehyde enamine (equation 435). The structure of product **190** was assigned tentatively.



(435)

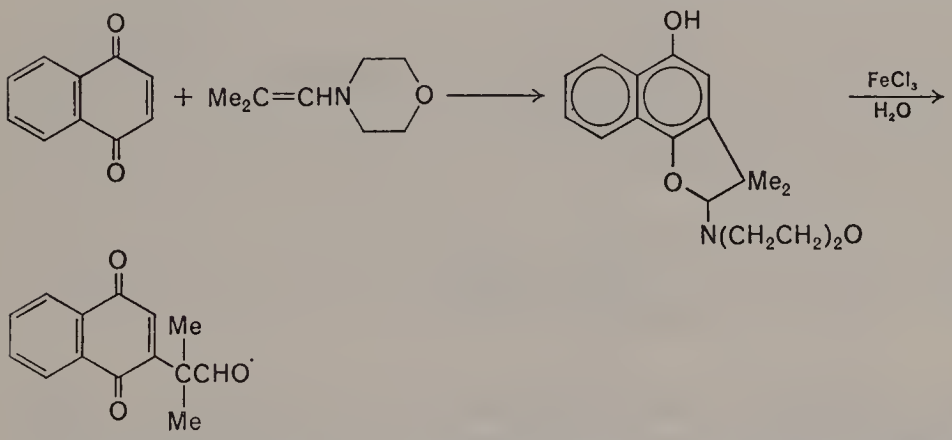
(190)

(3) Domschke has shown that 1,4-benzoquinone and enamines can undergo a Diels–Alder reaction and produce substituted anthraquinones (equation 436)[490]. The required dienamines were prepared by the condensation of two moles of morpholine–acetophenone enamine with the loss of one imino group. The expected intermediate (initial adduct) was not isolated.



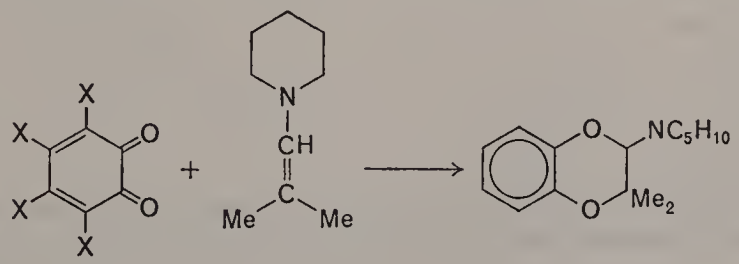
(436)

(4) It has been shown that a variety of oxidants will convert certain coumarins to quinones bearing a formylalkyl substituent (equation 437)[491]. The yields are better than 70%, but to be successful at least one of the positions *ortho* to the phenolic hydroxy group must be substituted.



(437)

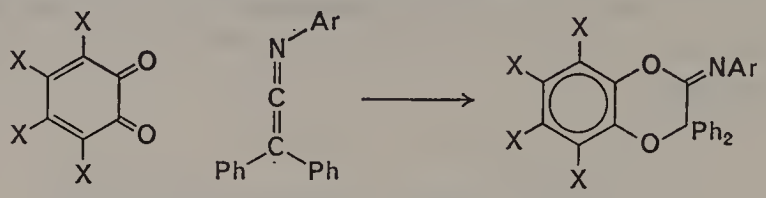
(5) Enamines will react with 1,2-quinones in a fashion reminiscent of the Diels–Alder reaction (equation 438)[492,493]. The yields are, with a few exceptions, good or excellent. Several other 1,2-quinones were used and the enamine can involve cycloalkenes and other secondary amines.



(438)

X = Cl, Br

(6) Diphenylketenimines with *N*-aryl substituents also react with 1,2-quinones to provide an interesting series of aryliminolactones (equation 439)[494]. The yields are uniformly high.

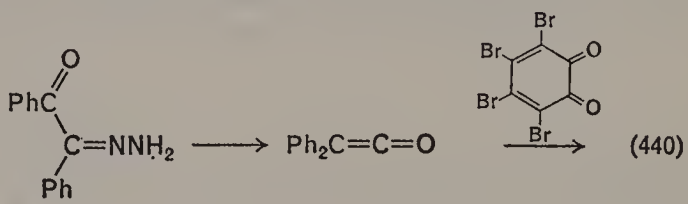


(439)

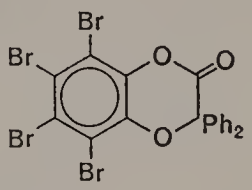
X = Cl, Br; Ar = Ph, 2- or 4-MeC_6H_4, 4-$MeOC_6H_4$

D. Related Cycloaddition Reactions

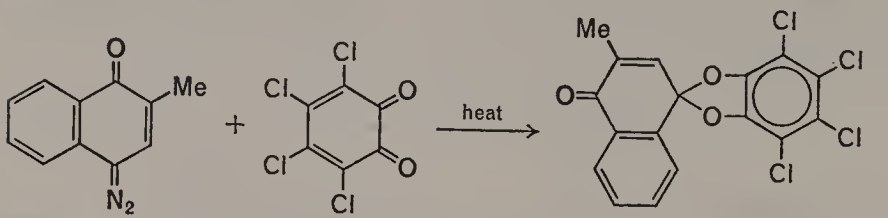
The 1,2-quinones undergo cycloaddition reactions with ketenes to form cyclic lactones[495,496]. The reaction (equation 440) allows capture of



(440)



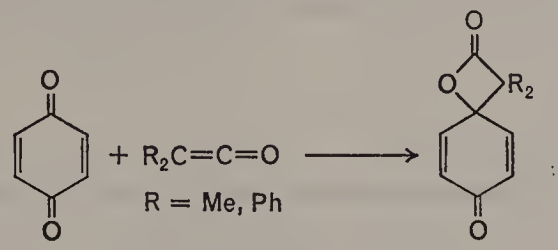
ketenes formed as unstable intermediates in the thermolysis of diazo ketones. In cases where no Wolff rearrangement takes place (e.g. 2-methyl-1,4-naphthoquinone diazide), the carbene forms a monoacetal with the quinone (equation 441).



(441)

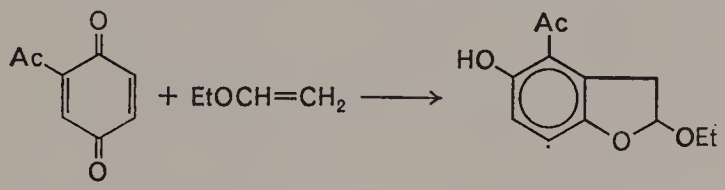
The reaction of diphenylketene with 1,4-benzoquinone was reported in 1907[497] and recently the analogous chemistry of dimethylketene was investigated[498]. Both ketenes gave a spirolactone when one equivalent was

used (equation 442). Two equivalents of the ketene led to a low yield of the bis-spirolactone when R = Ph, but R = Me gave only polymer.



(442)

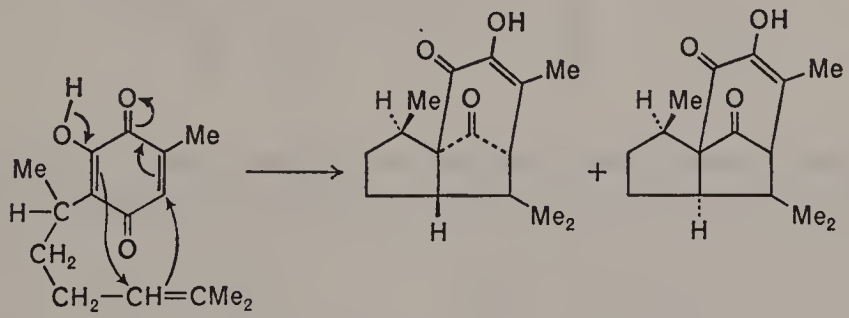
A variety of α,β-unsaturated ethers undergo cycloaddition reactions with 2-acetyl-1,4-benzoquinone to form derivatives of benzofuran (equation 443)[499]. This study has been greatly expanded recently and a



(443)

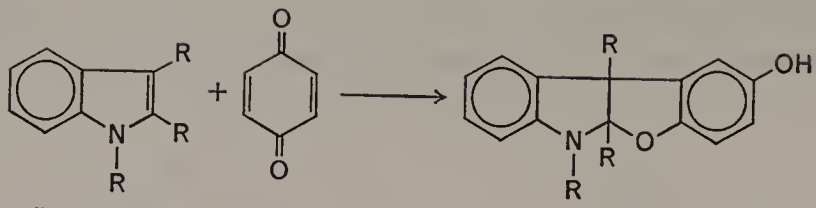
number of additional enols examined[500, 501]. Enol esters and cyclic enol ethers can be used and 2-carbomethoxy-1,4-benzoquinone is also a suitable reactant. The nitrogen heterocycles, pyrrole and imidazole, are also capable of similar addition reactions when strong electron-withdrawing groups are present in the quinone.

An interesting 1,3-cycloaddition of a hydroxy 1,4-benzoquinone has been invoked to explain the relationship of the observed products and the newly characterized parent compound perezone (equation 444)[502].



(444)

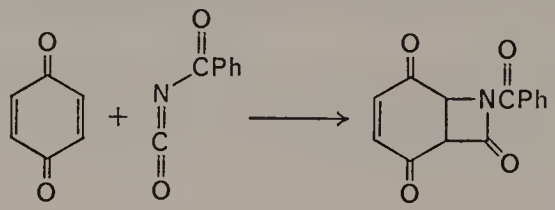
The indoles with alkyl substituents in the 3-position are known to undergo cycloaddition reactions with 1,4- and 1,2-quinones (equation 445)[503, 504]. The reaction is known to be strongly acid-catalysed, quite general and subject to some steric hindrance. The more recent study has investigated in some detail the mechanism and especially the formation of 2:1 adducts.



R = H, Me

(445)

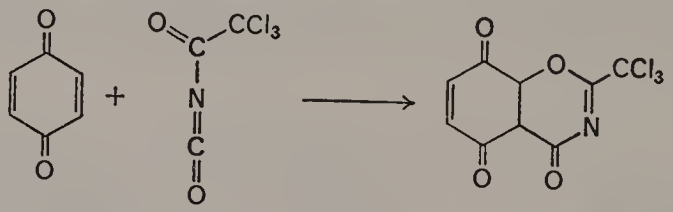
The number of 2,3-cycloadditions found in quinone chemistry is somewhat limited, but a potentially useful example has been reported in isocyanate chemistry[505]. Both 1,4-benzo- and 1,4-naphthoquinone react with benzoyl isocyanate (equation 446). The product **191** can undergo



(191)

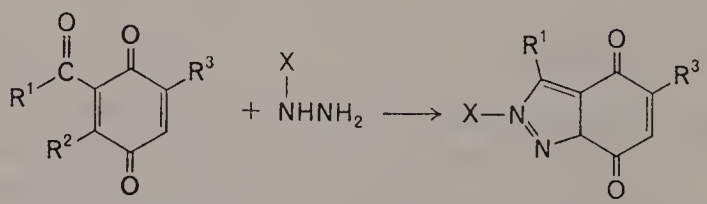
(446)

epoxidation and saponification. In the case of 1,4-naphthoquinone, the latter reaction provides a reasonable route to the fairly stable 2-carboxy-1,4-naphthoquinone. The reaction between 1,4-benzoquinone and trichloroacetyl isocyanate takes the Diels–Alder route (equation 447). No product was obtained with 1,4-naphthoquinone and this isocyanate.



(447)

Several five-membered nitrogen heterocycles fused to dihydro-1,4-benzoquinones have been prepared in good yield (equation 448)[506].

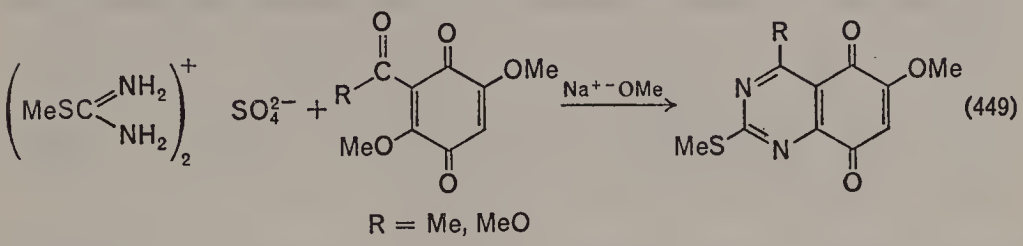


R^1 = Me, MeO
R^2, R^3 = Cl, MeO, NH_2, NHR, NHAr

X = Me, Ph, 4-$NO_2C_6H_4$, Ac, PhCO, 4-Me or 4-$NO_2C_6H_4SO_2$, OH (O in product)

(448)

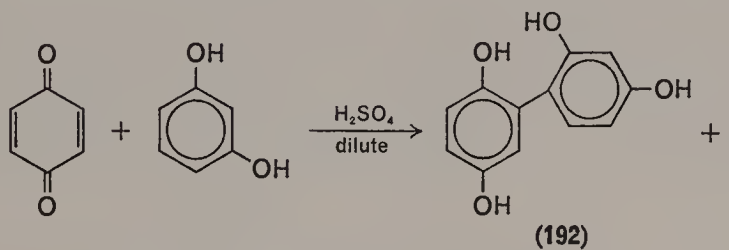
Once again a strong electron-withdrawing group in the quinone is needed. A similar reaction with *S*-methylthiuronium sulphate leads to six-membered heterocycles (equation 449).



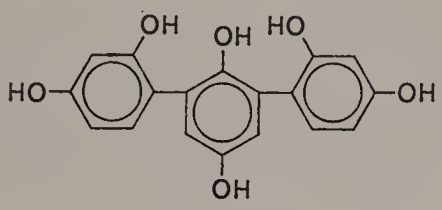
(449)

VI. ELECTROPHILIC ARYLATION OF QUINONES

The preparation of quinonoid compounds bearing aryl substituents is an important synthetic goal for both practical and theoretical reasons. An early experimental effort in this area consisted of the acid-catalysed reactions of phenols with quinones (e.g. equation 450)[507]. The mono-substitution product **192** was not correctly named and the orientation of



(192)



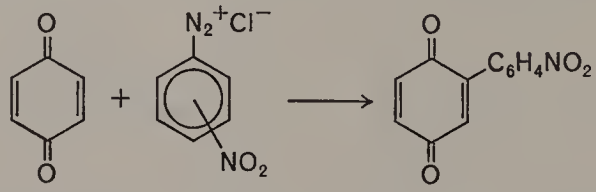
(193)

(450)

the disubstitution product **193** was not specified, but the chemistry and the gross structures have recently been verified[508]. The latter work has included a re-investigation of pyrogallol and 1,4-benzoquinone[509]. The same coupling products were obtained, along with self-condensation products.

In recent years it has become clear that the preferred route to aryl-substituted quinones is via diazonium intermediates. The first efforts in this area involved *p*-nitrosophenol or the 1,4-benzoquinone monoxime[510,511]. Several experimental difficulties caused very low yields. The patent literature provided a very important improvement by showing

the efficacy of sodium acetate in an alcoholic reaction medium. This lead was developed by Marini-Bettolo and collaborators who prepared *m*- and *p*-nitrophenyl-substituted 1,4-benzoquinones (equation 451) and studied their conversion to other derivatives[512]. In later papers it was shown that



(451)

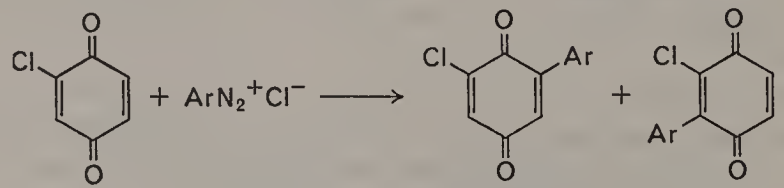
copper powder could increase the yield very sharply, at least for 1,4-naphthoquinone[513]. The range of anilines that could be used was expanded and it was found that hydroquinone is also a suitable starting material for arylation[514].

Over the last forty years the synthesis of a large number of aryl-substituted quinones using this route, with major and minor variations, has been reported[145, 186, 327g, 331, 514a–517]. However, in 1958 L'Écuyer and his students (notably Brassard) began publishing a series of detailed synthetic and mechanistic studies of quinone arylation with diazonium salts. In the first paper of the series, a careful search for optimum reaction conditions was made[518]. The following conclusions were reached:

Solvent: water	Buffer: 2 mole Na^+–OAc/mole reactant
Concentration: 0·1M	Temperature: gradually rising from 10–15°C to ambient
pH: 5	Anion: Cl^-, Br^-, PO_4^{3-}, SO_4^{2-}, but not NO_3^-

Excellent yields of product were obtained using these general principles with a wide variety of substituted anilines. These monosubstituted quinones can be converted to 2,5-diarylated-1,4-benzoquinones (symmetrical or unsymmetrical) in lower, but still satisfactory yields, by simply repeating the diazonium salt procedure[519]. While only the one product was reported in each case, the modest yields suggest that the isomeric products may also be formed.

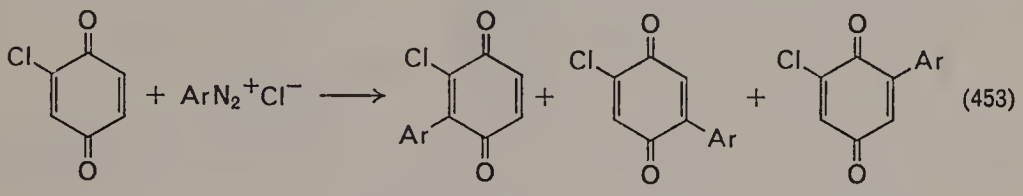
The study of the influence of substituents in the quinonoid ring began with 2-chloro-1,4-benzoquinone (equation 452)[520]. The structures of both



(452)

Ar = Ph; 81% not isolated
4-ClC$_6$H$_4$; 66% 18%

the products found and the missing isomer were demonstrated by the synthesis of more highly chlorinated derivatives by unambiguous routes. This product distribution study has been re-examined and expanded to include the *p*-nitrophenyl case[521]. The earlier discussion of nucleophilic addition showed the effect of quinone substitution, but not of nucleophile substitution (see sections II.B.2 and II.D.2). However, our own observations show that for thiol addition, *para* substituents have only minor effect on the product ratio[522]. In the current study, of electrophilic addition, all three isomers were found in significant yield (equation 453). Clearly

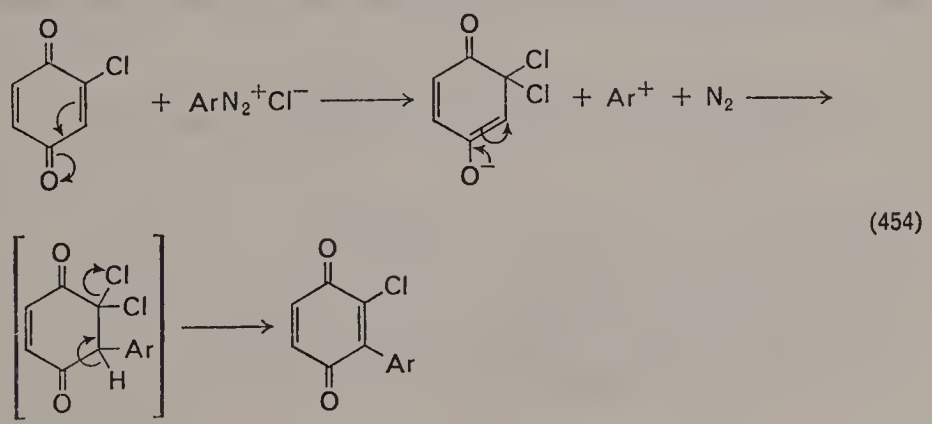


Ar = Ph;	8%	75%	17%
4-ClC_6H_4;	28%	35%	37%
4-$NO_2C_6H_4$;	41%	19%	40%

(453)

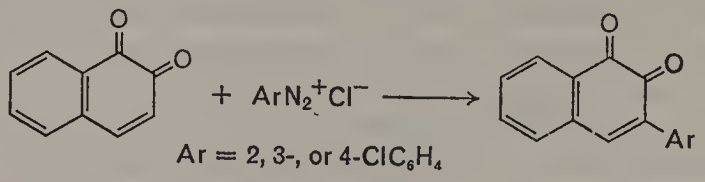
the substituent in the diazonium salt plays an important role in product determination. An earlier report of the addition of a wide variety of substituted aryldiazonium salts to 2-methyl-1,4-benzoquinone also produced only the 2,5-disubstituted product[523]. The yields varied over a very broad range, but this was attributed to the difficulty of isolation, rather than to the substituent. The structure of the product obtained was verified by a careful independent synthesis of all three possible isomeric products[524]. Certain of these studies make contributions to our understanding of the synthetic applications of hydrogen chloride addition to aryl-substituted quinones[520, 521].

On the basis of these studies, an ionic mechanism is presented (equation 454)[521]. A later study of the arylation of 1,2-naphthoquinone produced

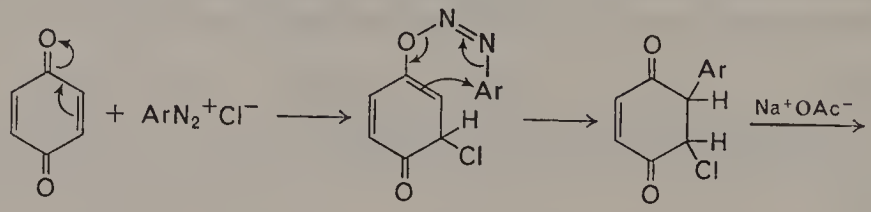


(454)

only the 3-aryl isomer (equation 455)[525]. The yields were poor, but the results prompted the consideration of a modified reaction mechanism (equation 456).



(455)



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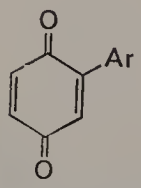
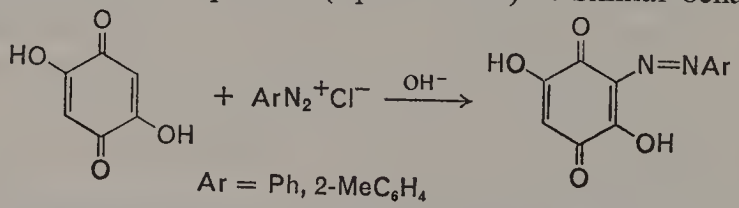
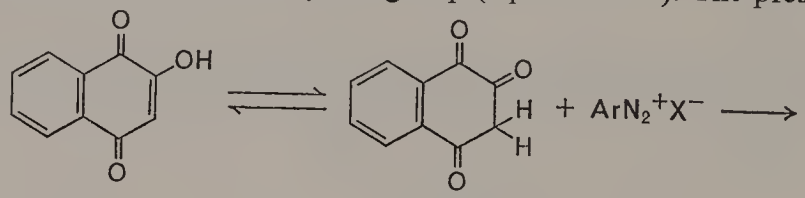


The reaction of diazonium salts with certain quinones can result in coupling rather than arylation. This competing reaction is observed with 2,5-dihydroxy-1,4-benzoquinone (equation 457)[526]. Similar behaviour has



(457)

been observed with 2-hydroxy-1,4-naphthoquinone[327g, 527]. The success of the coupling reaction may be attributed to the tautomeric triketo form **194** which has an active methylene group (equation 458). The presence of



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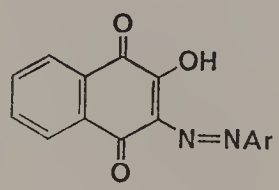
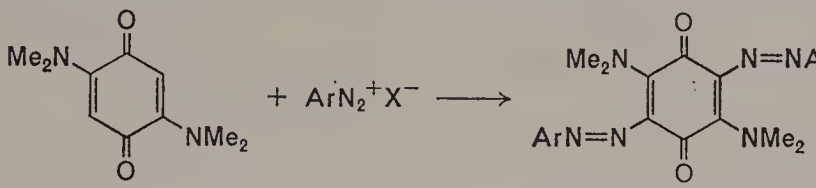


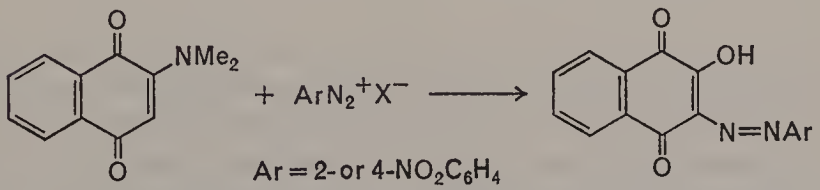
(458)

other electron-donating substituents on the quinone also promotes diazo coupling (equation 459). In the case of 2-dimethylamino-1,4-naphthoquinone the product isolated, in excellent yield, is 2-hydroxy-3-arylazo-1,4-naphthoquinone (equation 460). It was shown that under the same



(459)

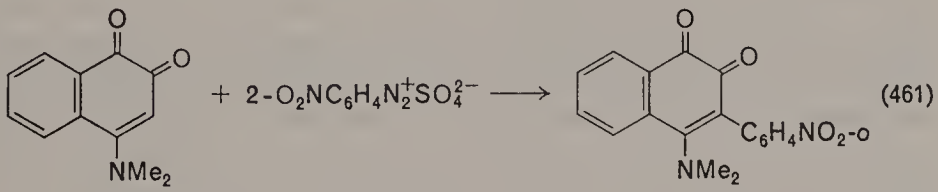
Ar = 2- or 4-$NO_2C_6H_4$, 2,5-$Cl_2C_6H_3$



(460)

Ar = 2- or 4-$NO_2C_6H_4$

conditions, but in the absence of the diazonium salt, the dimethylamino group is very readily hydrolysed. The isomeric starting material, 4-dimethylamino-1,2-naphthoquinone, has been prepared and its reactions with diazonium salts studied[528]. The only example of arylation found with this new substrate was with *o*-nitrobenzenediazonium sulphate in the presence of an excess of quinone (equation 461).



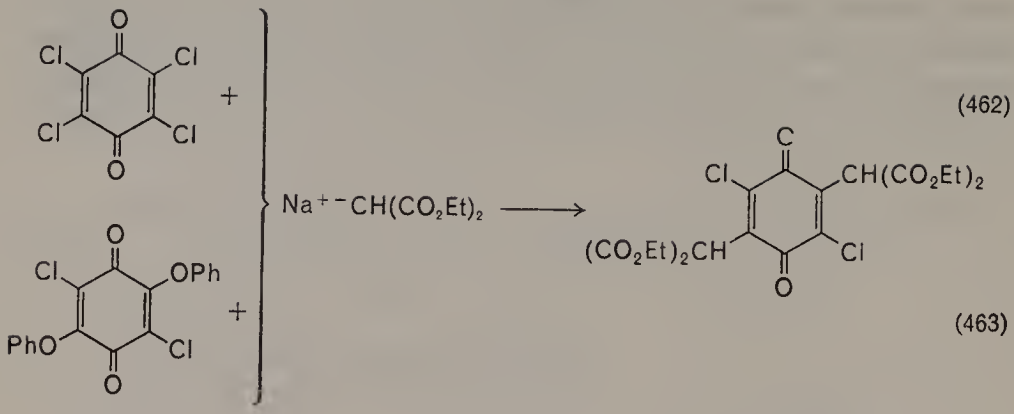
(461)

In acidic media both quinones gave the same diazonium coupling products (equation 460) and in acetate buffer 2-dimethylamino-1,4-naphthoquinone gave the 3-aryl derivatives.

VII. ACTIVE METHYLENE ANIONS AND QUINONES

A. Historical Introduction

The α,β-unsaturated carbonyl system of quinones should provide interesting examples of the Michael condensation of active methylene compounds. However, the strongly basic conditions associated with these reactions produce chiefly tars, and the early workers found very poor yields of products even with completely halogenated quinones (equations 462 and 463)[529,530].



(462)

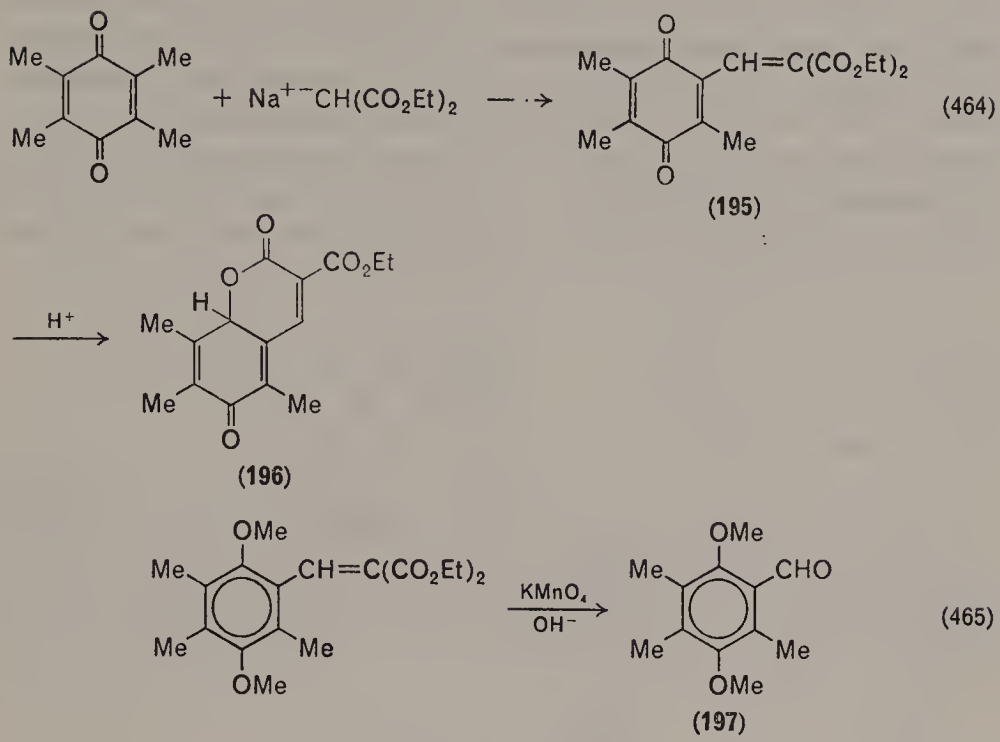
(463)

In 1926 Smith reported the first results of what was to become for him and his students a very detailed study of quinones and metal enolates[531]. Bamberger and Blangey had already reported their discouraging results with another organometallic reagent and quinones[532]. When the Grignard reagent, methylmagnesium iodide, was added to simple quinones, very large numbers of products were formed. Even though they succeeded in isolating and identifying six solid reaction products in the case of 2,5-dimethyl-1,4-benzoquinone, less than half the starting material was accounted for and the general outlook was very unpromising.

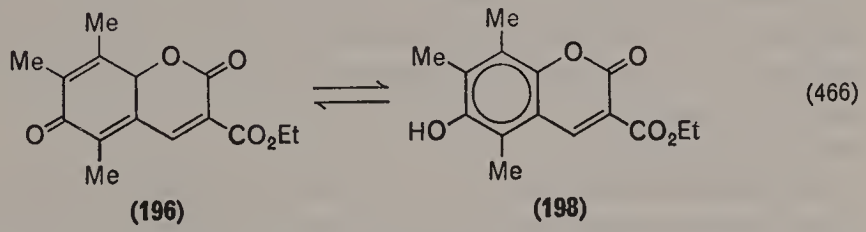
B. *The Work of Lee Irvin Smith*

Smith began his work feeling that the presence of hydrogen on the quinonoid ring was responsible for the large number of products and he also wished to avoid the ambiguity of the Würtz–Fittig path for halogenated quinones. Thus, he chose to study first the reaction of diethyl sodiomalonate with duroquinone. The reaction was carried out in dry benzene to avoid the formation of diduroquinone. When an inert atmosphere is used, one of the products is durohydroquinone, accompanied by equivalent amounts of a red sodium salt of **195** that resists further purification. When this salt is treated with acid, a yellow compound, **196**, is obtained. An extensive series of chemical reactions of **196** led Smith and Dobrovolny[531] to suggest the following structures (equation 464).

One especially interesting point in the experimental evidence concerning the structure of **195** is the oxidation of a hydroquinone diacid dimethyl ether related to it (equation 465). All of the evidence clearly requires the highly substituted benzaldehyde shown, but **197** could not be oxidized to a benzoic acid derivative. While this seems strange, some other examples are cited and Smith later synthesized **197** by a completely independent route[533].



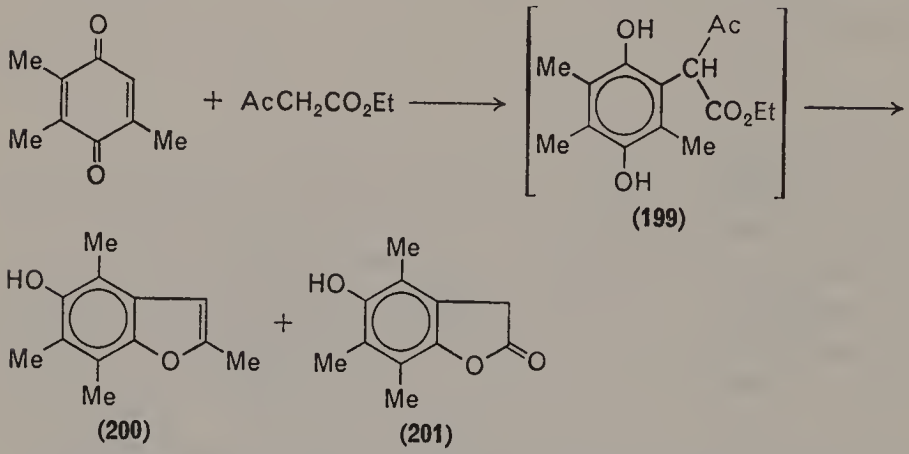
The yellow colour of the lactone **196** caused Smith and Dobrovolny to use the structure shown, but their use of the tautomeric structure (**198** in equation 466) for all of the methylation and acetylation products clearly showed they felt the latter better described the chemical nature of the product (equation 464). In a later study, Smith and Denyes showed that a



large number of chemical transformations were best explained on the basis of 3-carbethoxy-5,7,8-trimethyl-6-hydroxycoumarin (**198**) and that none required the tautomeric form **196**[534]. Some other examples of yellow coumarins are given.

The single reaction described thus far, using duroquinone as the substrate, is quite different from the usual quinonoid addition reaction in that a methyl group attached to the quinone is the reactive site. Smith and MacMullen wished to remove the particular limitation of duroquinone without returning to the state described in an earlier paper; 'It may be

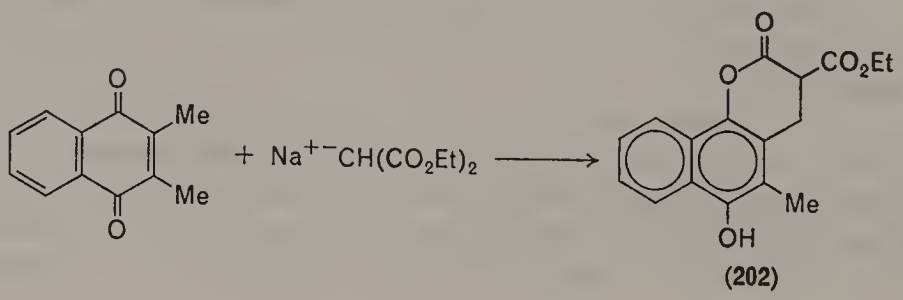
noted, however, that benzoquinone, when treated with malonic ester in exactly the same way as duroquinone, gives only a hopeless tar'[535]. They cite some earlier reports of the addition of acetoacetic ester to quinone; however, the structures of the products were not satisfactorily demonstrated. The reaction between 2,3,5-trimethyl-1,4-benzoquinone and acetoacetic ester allows both the methyl group reaction, observed earlier, and the more usual 1,4-addition. Actually, only the latter reaction was observed and this produced two products (**200** and **201** in equation 467).



(467)

The most reasonable way to explain the products is simply 1,4-addition to yield the intermediate **199** (not isolated) which then undergoes ring closure and the usual two cleavages of β-keto esters. When diethyl sodiomalonate was used, only **201** was produced, offering additional evidence of the correctness of the proposed reaction scheme. The chemical properties of both **200** and **201** were entirely consistent with the structures assigned and the latter was synthesized by an independent route. It is especially significant that no coumarin derivatives were obtained, even when the reaction was run under exactly the same conditions applied earlier to duroquinone.

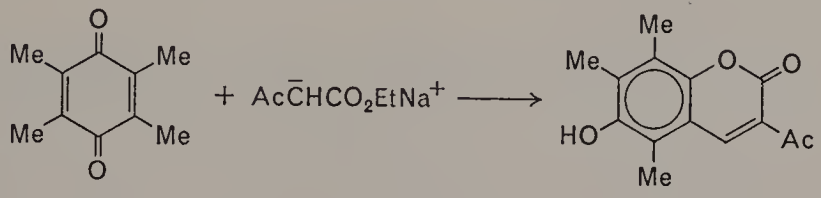
An obvious extension of the work with duroquinone would be 2,3-dimethyl-1,4-naphthoquinone and its reaction with diethyl sodiomalonate has been studied (equation 468)[536]. Two facts about this work are of



(468)

interest in view of the obvious similarity to the earlier work: (i) the naphthoquinone proved to be very much more difficult to work with than duroquinone, and (ii) the α-naphthocoumarin (7,8-benzocoumarin, **202**) product was very resistant to ring opening.

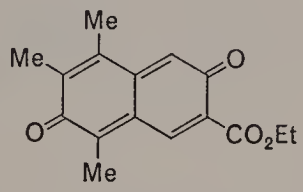
Another logical extension is the reaction of ethyl sodioacetoacetate with duroquinone (equation 469)[537]. The product, 5,7,8-trimethyl-3-acetyl-6-



(469)

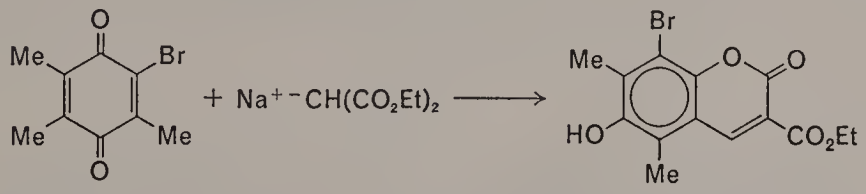
(203)

hydroxycoumarin (**203**), showed chemical properties similar to the compounds reported previously. The structure **203** was demonstrated in the usual manner including independent synthesis. The hope of finding the *amphi*-naphthoquinone **204** that might result from a reasonable alternate pathway was not realized.



(204)

The next step in the exploration of the active methylene chemistry of quinones by Smith and his students involved offering a substitution pathway for the reaction[538]. Again, the earlier literature was reviewed and found to be intriguing, but sketchy. The reaction between diethyl sodiomalonate and 2-bromo-3,5,6-trimethyl-1,4-benzoquinone did not follow the substitution path and produced only one of the three possible isomeric coumarins (equation 470). The coumarin ring proved to be very difficult



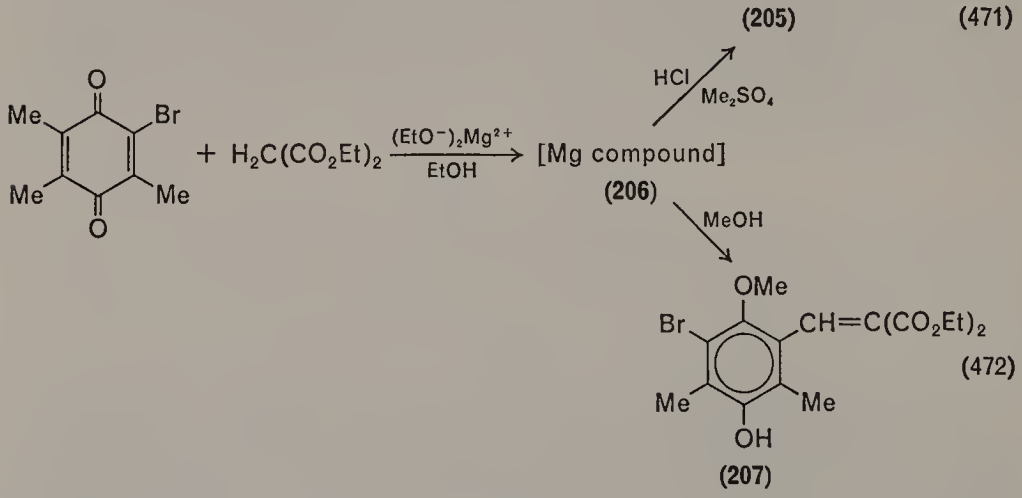
(470)

(205)

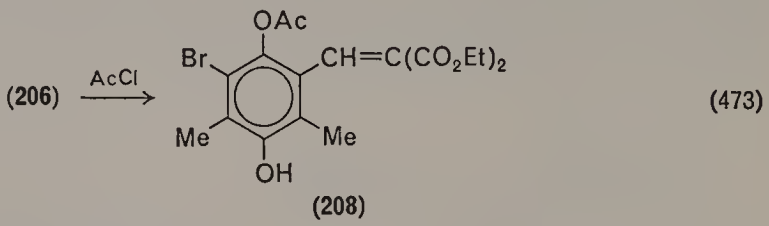
to open and thus synthesis appeared to be the best approach to structure determination. In a very pleasant display of candour, Smith and Johnson

reported that their selection of the first route was made because 2,5-dimethyl-1,4-benzoquinone was the most available starting material. The synthesis was carried far enough to offer good evidence that the actual product **205** did not have the *para*-dimethyl structure. The use of 2,6-dimethyl-1,4-benzoquinone in a similar synthesis led, after some difficulties, to a derivative of **205** and was considered to demonstrate the correctness of that structure.

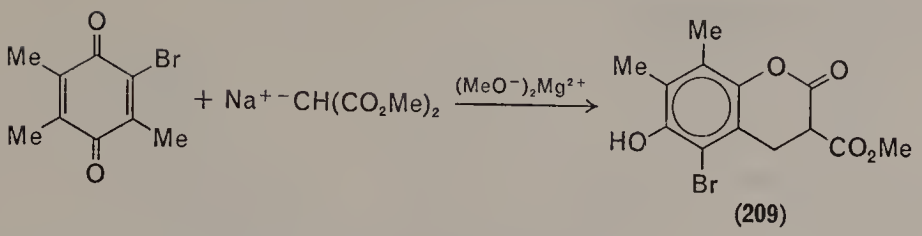
The reaction of the bromoquinone just described did not produce very good yields and the material balance was also poor under the usual conditions. A method was found under which not only could the yield of **205** be greatly improved, but a new series of related compounds could be prepared from a common intermediate, **206**. A very tentative structure assignment was made for the first member of the new series (**207** in equation 472). It was also found that freshly distilled acetyl chloride



converted the magnesium compound into a new derivative, tentatively assigned structure **208** in equation (473).



A thorough re-investigation of the reaction between 2-bromo-3,5,6-trimethyl-1,4-benzoquinone and dimethyl sodiomalonate revealed that, in the presence of magnesium methoxide, the hydrocoumarin **209** is produced (equation 474)[539]. It should be noted that the structure of **209**

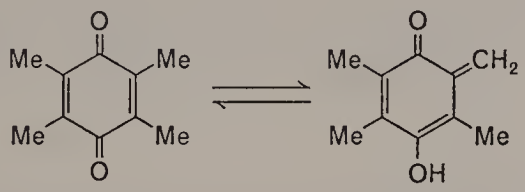


(474)

(209)

is that of the third isomeric possibility; i.e. the *ortho*-dimethyl derivative. This structure was demonstrated by two independent syntheses and comparison of X-ray powder diagrams of the product with those of authentic 3-carbomethoxy-5-bromo-6-hydroxy-7,8-dimethylcoumarin. This demonstration of the correct structure of the chief reaction product and its derivatives allowed Smith and Wiley to show that the 'new series' of compounds obtained from the magnesium compound **206** were, in fact, identical with them.

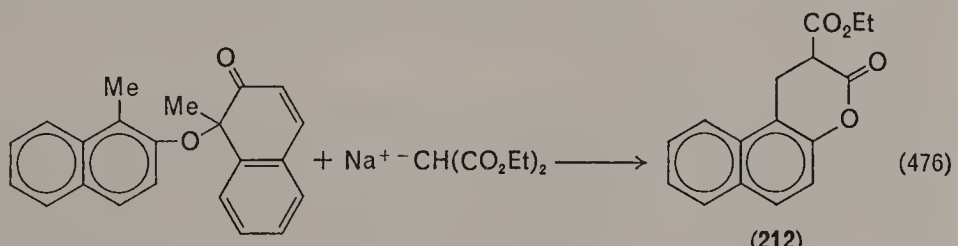
It had been felt for some time in Smith's laboratory that the addition of active methylene compounds to the methyl groups of quinones probably involved the methylene tautomer (**210** in equation 475). A trapping



(475)

(210)

experiment provided the first experimental evidence for this mechanism[540]. Evidence had been presented earlier for the existence of an *ortho*-methylene quinone as a transitory intermediate[541]. Smith and Horner reasoned that, if such intermediates were formed, and if they reacted with diethyl sodiomalonate more rapidly than with each other, a dihydrocoumarin would be formed. When dehydro-α-methyl-β-naphthol (**211**) was warmed with diethyl sodiomalonate, the hydrocoumarin **212** was isolated (equation 476). The yield of **212** was not good because of the difficulty of isolating it

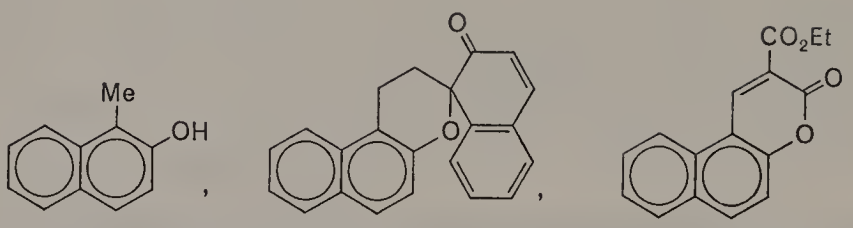


(476)

(211)

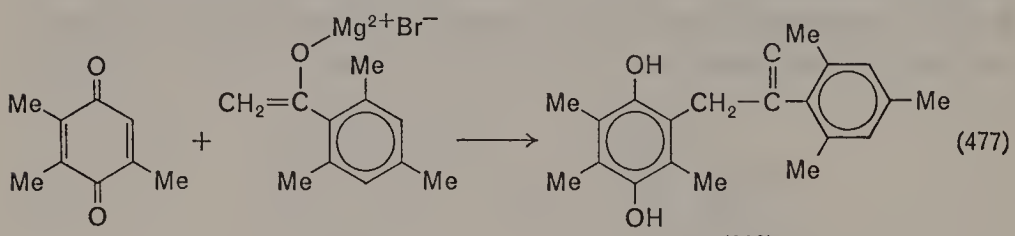
(212)

from the other products; e.g.:



However, the evidence of an *ortho*-methylene quinone intermediate is quite convincing.

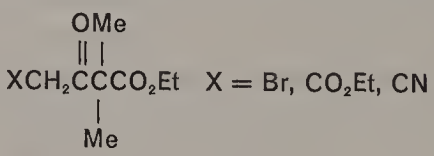
A class of weakly basic metallic enolates, that offer attractive possibilities for addition to quinones, are the bromomagnesium compounds derived from ketones and Grignard reagents. With the enolate of acetomesitylene, addition to 2,3,5-trimethyl-1,4-benzoquinone took place smoothly (equation 477)[542]. For steric reasons, it is not surprising



(477)

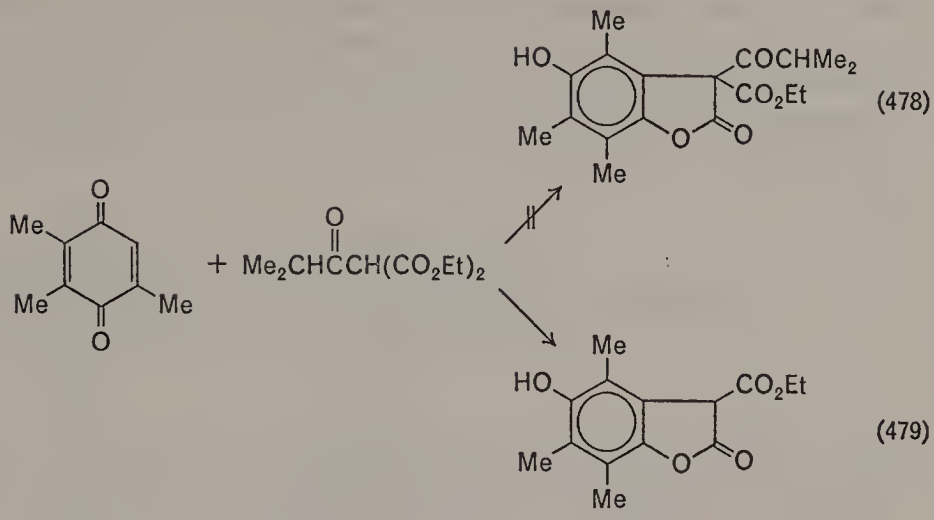
(213)

that the initial adduct **213** does not cyclize. Several other metallic enolates of this type were tried and either did not form or did not react with the quinone; for example, an acylmalonic ester did add to the quinone, but



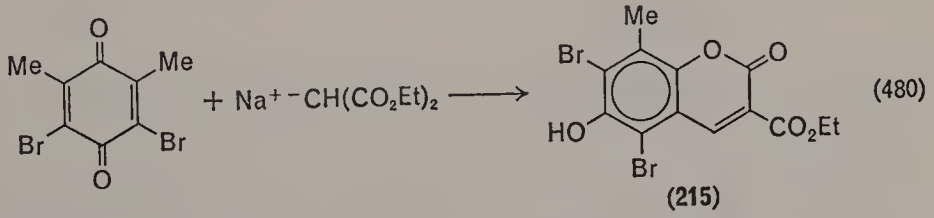
the product had lost the acyl group during formation (equations 478 and 479). Efforts to re-introduce the acyl group proved unsuccessful so, while the synthesis demonstrated additional interrelationships among previously prepared compounds, the aim of extending the scope of the reaction was not realized.

The sodium enolates of a variety of active methylene compounds were allowed to react with duroquinone and 2,3,5-trimethyl-1,4-benzoquinone[543]; Table 17 summarizes the results of these studies. It seems clear that there are quite definite limitations on the simple addition reactions, although the reasons are not so clear. In the case of addition to



a methyl group of duroquinone (or to the *ortho*-methylene tautomer) the ease of the loss of an alkoxy group and the resulting cyclization appears to be an essential aspect of the reaction.

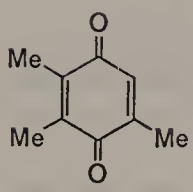
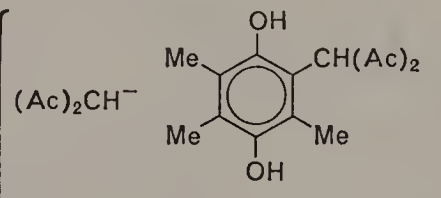
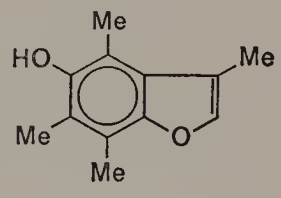
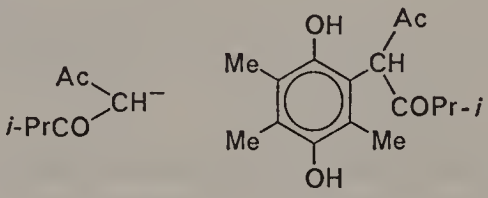
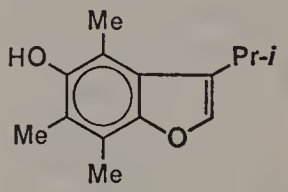
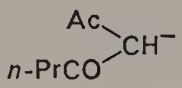
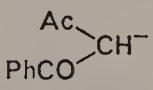
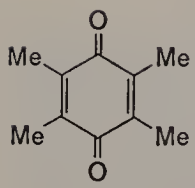
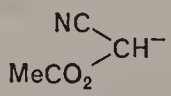
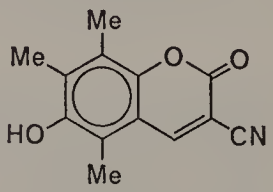
The compound, 3,5-dibromo-2,6-dimethyl-1,4-benzoquinone, appeared to offer an entirely new system with respect to the arrangement of alkyl and halogen groups; thus, its reaction with diethyl sodiomalonate was examined (equation 480)[544]. The additional bromine on the quinonoid



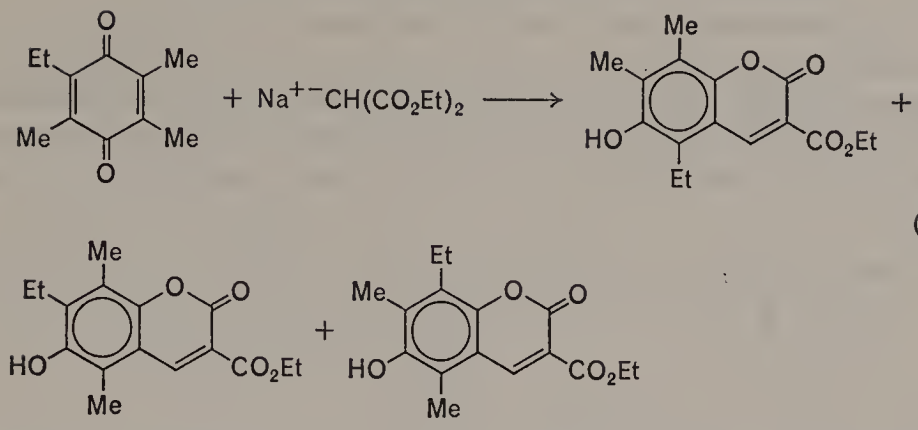
ring made the selection of solvent and other experimental conditions much more critical and, at best, substantially increased the effect of side-reactions. Unlike the earlier example of a coumarin with a single ring bromine, this product **215** underwent ring-opening reactions with great ease. The structure of **215** was demonstrated by a consideration of its chemical behaviour and an independent synthesis of the dimethyl ether of its ring-opened derivative.

The very strong directive effect of the bromine in 2-bromo-3,5,6-trimethyl-1,4-benzoquinone[538] promoted interest in the range of such effects. Therefore, the reaction of diethyl sodiomalonate with 2-ethyl-3,5,6-trimethyl-1,4-benzoquinone was carried out[545] after it was demonstrated that 2,3,5,6-tetraethyl-1,4-benzoquinone is inert. It was expected

TABLE 17. Some additions of active methylene enolates to methylated 1,4-benzoquinones[543]

1,4-Benzoquinones	Enolate	Products
		 (214)
		(214) + 
		None
		None
	$(PhCO)_2CH^-$	None
		
	$(Ac)_2CH^-$	None
	$(PhCO)_2CH^-$	None

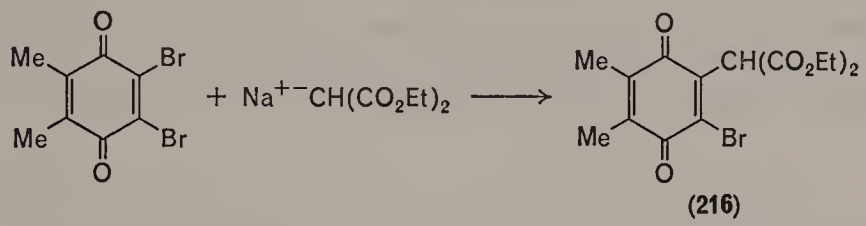
that three isomeric coumarins should be formed upon acid treatment of the initial adduct (equation 481). The yields of products in both steps are excellent but the separations extremely tedious. It was felt that two pure materials had been obtained, but so little material was available that the synthesis of the three expected products was undertaken. When the three



(481)

isomeric coumarins, of known structure, were in hand, thermal analysis showed that both of the isolated fractions were mixtures. The effect of the ethyl group on orientation in active methylene addition is negligible[546].

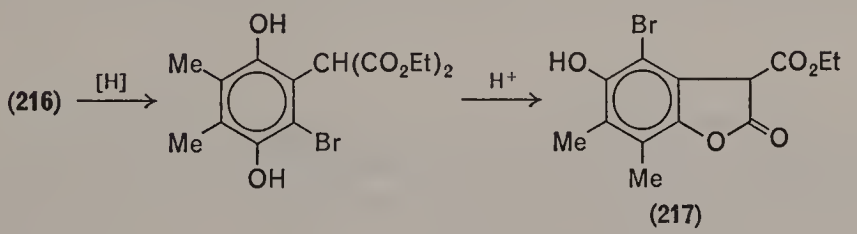
The reaction of 5,6-dibromo-2,3-dimethyl-1,4-benzoquinone with diethyl sodiomalonate has been studied (equation 482)[547]. Unlike the



(482)

(216)

brominated quinones reported previously, the *ortho*-dibromo arrangement leads to substitution of one or, after longer reaction times, two bromine atoms. The quinonoid product **216** is easily reduced to the corresponding hydroquinone which in turn is cyclized with acid to the isocoumaranone (**217** in equation 483). The synthesis of a key derivative of **217**, together

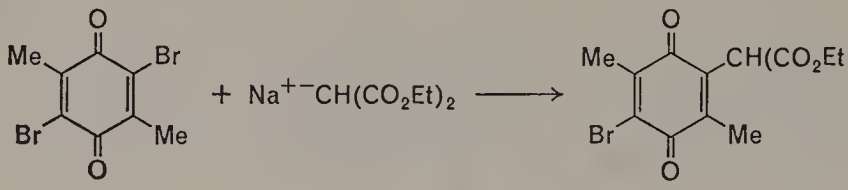


(483)

(217)

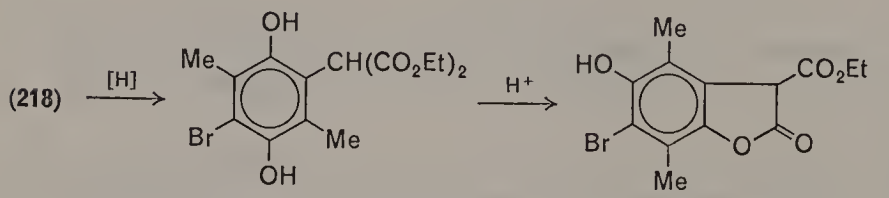
with the usual chemical evidence, determined the structure. These findings clearly require that the *ortho*-dibromo grouping exert a stronger mutual influence in these reactions than that directed toward the *meta*-methyl groups.

The reactions of *ortho*- and *meta*-dibromodimethyl quinones with active methylene compounds proved sufficiently interesting that the *para* isomer was also treated with diethyl sodiomalonate[548]. The chemistry observed exactly followed that of the *ortho*-dibromo isomer[547] (equations 484 and 485). The disubstituted product is also obtained, but in poor



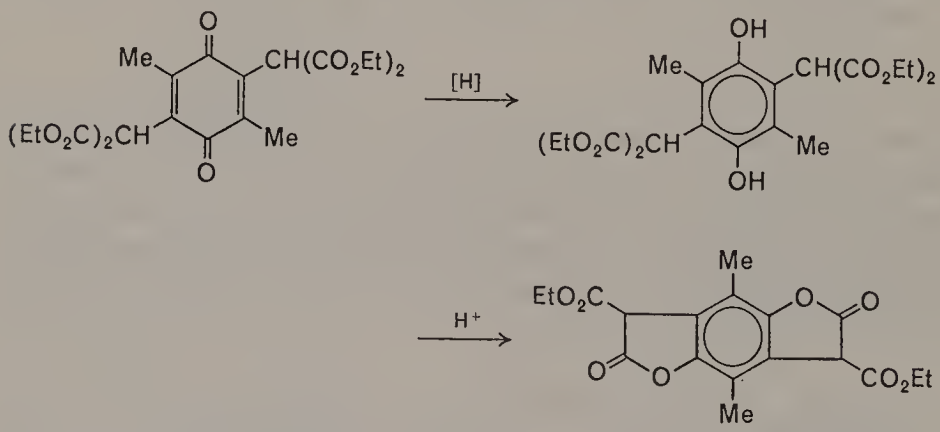
(484)

(218)



(485)

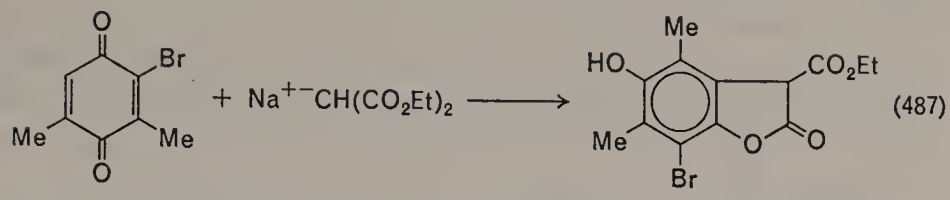
yield and under much more strenuous conditions. This disubstitution product can be converted to a difurano compound (equation 486). In neither the *ortho*- nor the *para*-dibromo case could any evidence of a coumarin be found; i.e. only substitution for bromine took place.



(486)

The observed reactions of the three isomeric dibromo-dimethyl-1,4-benzoquinones and 2-bromo-3,5,6-trimethyl-1,4-benzoquinone can be rationalized in terms of the principal resonance contributors. A description of this analysis has been presented and its application to the more general case of anionic reagents and hetero conjugated systems pointed out[549].

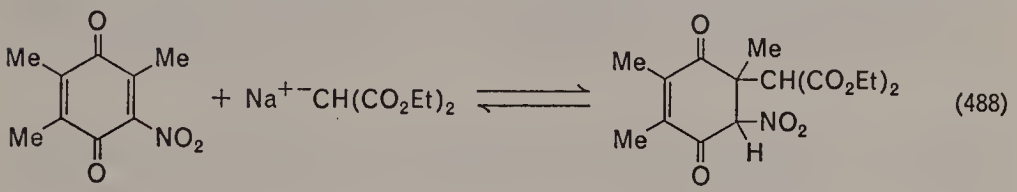
An interesting combination experiment was carried out by Smith and Wiley when they reacted 2-bromo-3,5-dimethyl-1,4-benzoquinone with diethyl sodiomalonate (equation 487)[550]. In principle, this quinone can



(487)

undergo three different modes of reaction: (i) bromine substitution, (ii) methyl group addition, or (iii) Michael (1,4-) addition. As shown in equation (487), only the third option is taken, shedding some light on the relative energetics of the three paths.

The reactions of active methylene enolates with replaceable groups other than bromine are of interest in considering the electronic influence of substituents on the course of the reaction. The very strong electron-withdrawing nitro group and electron-donating amino group were selected for study[551]. The results were indeed very different; 2-nitro-3,5,6-trimethyl-1,4-benzoquinone undergoes simple 1,2-addition of diethyl sodiomalonate at the double bond bearing the nitro group; i.e. behaves like a nitroalkene (equation 488). The properties of **219** are quite consistent with the proposed

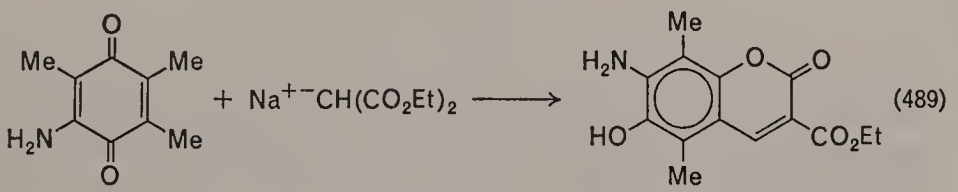


(488)

(219)

structure; e.g. formed reversibly, acidic, colourless, *cis* and *trans* forms, etc. Dimethyl sodiomalonate formed a completely analogous adduct, but ethyl sodioacetoacetate and the bromomagnesium enolate of aceto-mesitylene produced only oils and resins.

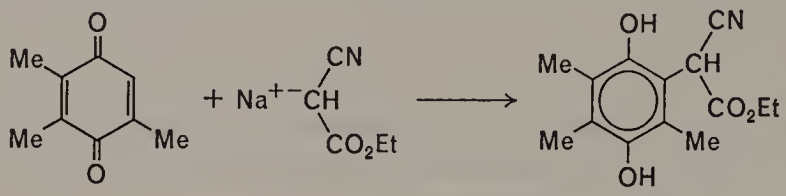
The reaction of 2-amino-3,5,6-trimethyl-1,4-benzoquinone with diethyl sodiomalonate followed a course related to the corresponding bromo-quinone (equation 489). The high yield suggests that once again only a



(489)

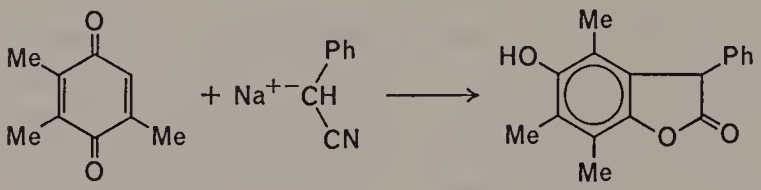
single isomer is formed, but the methyl group *para* to the amino group is attacked. This is in contrast to the earlier observation of attack at the methyl group *ortho* to the bromine atom. The structure of the product was demonstrated by the synthesis of a derivative.

In an attempt to study the range of active methylene enolates that can successfully react with quinones, Smith and Dale carried out the following reactions with 2,3,5-trimethyl-1,4-benzoquinone (equations 490–492)[552].

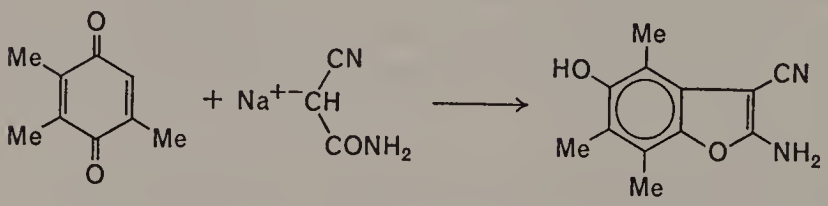


(490)

(220)



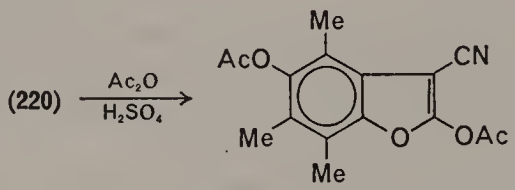
(491)



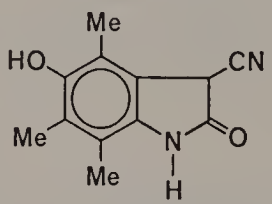
(492)

(221)

Treatment of **220** with acetic anhydride and sulphuric acid produced cyclization (equation 493). Structure **222** was not rigorously excluded as a

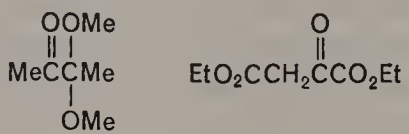


(493)



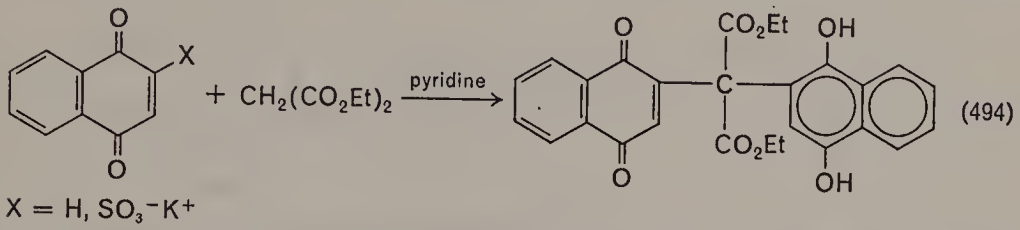
(222)

possible alternative for **221**. Determined efforts were made to add two other enolates to this quinone, but without success:



C. Recent Studies

With the conclusions of Smith's efforts, others have continued to explore these condensations of quinones with active methylene compounds. One area, relatively unexplored so far, concerns the reactions of 1,4-naphthoquinones. Pratt and his students began with a not too surprising result (equation 494)[553]. The yield was markedly improved by

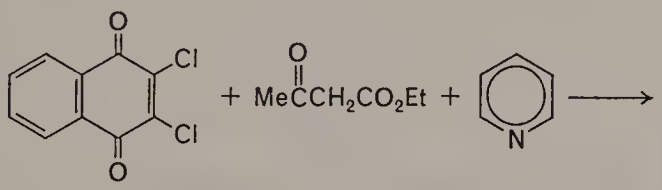


(494)

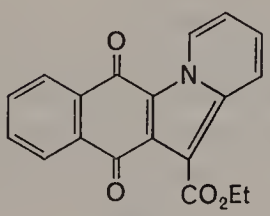
X = H, $SO_3^-K^+$

using the potassium sulphonate salt in a substitution reaction (15–40%). Diethyl malonate does not appear to be a typical reagent as Pratt's further work suggests.

The reaction of 2,3-dichloro-1,4-naphthoquinone with ethyl acetoacetate and pyridine provides an interesting heterocyclic quinone **223** in good yield (equation 495)[554]. Related active methylene compounds give



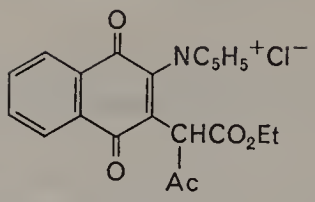
(495)



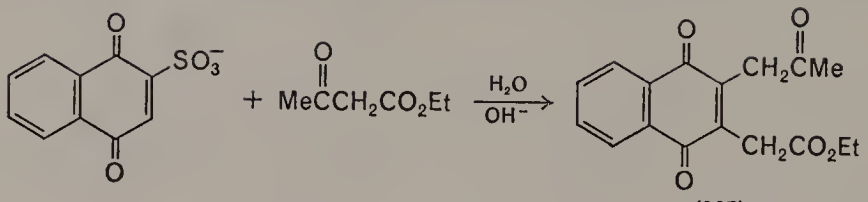
(223)

the same or analogous products; e.g. ethyl benzoylacetate yields **223** and methyl acetoacetate yields the corresponding methyl ester. Quinoline will take the place of pyridine in the reaction. The possible mechanisms presented depend on the logical intermediate **224**, but no experimental evidence is given.

An interesting sidelight on these studies is the reaction of 1,4-naphthoquinone-2-sulphonate with ethyl acetoacetate in aqueous alkali (equation 496). The two different modes of cleavage are not explained. The same



(224)

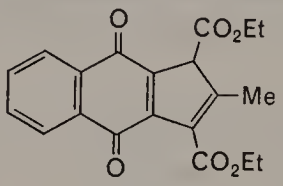


(496)

(225)

reaction takes place with 2-bromo-1,4-naphthoquinone and the unsubstituted quinone.

Ten years later Reynolds and his collaborators undertook a careful re-investigation of this unexpected chemistry[555]. Actually, the structure **225** had been questioned much earlier and the alternative structure **226**



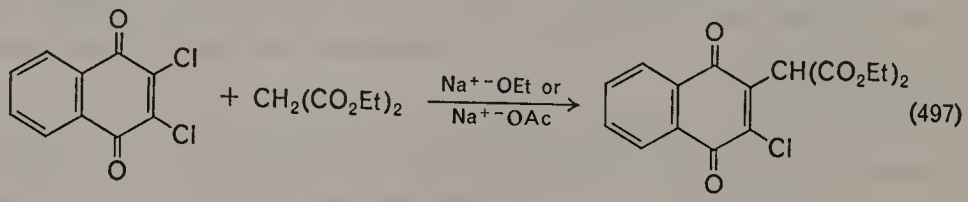
(226)

proposed[556]. The twofold objective of this study was:

(1) To improve the yield of product (**225**, **226** or **?**).

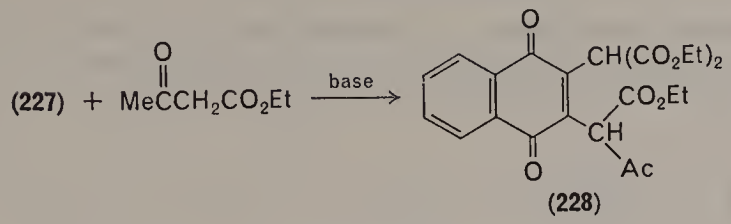
(2) To use modern instrumentation to determine the correct structure.

A careful product study, in which reactant concentration, base and time were varied, revealed that competing cyclization of the initial adduct was the cause of low yields of the desired cleavage product. The following synthesis was devised to avoid the cyclization (equations 497–499). Both of the intermediates (**227** and **228**) could be isolated, but the preferred method used them *in situ*. A massive instrumental attack was made on the final product structure. The results of mass spectra, molecular weight

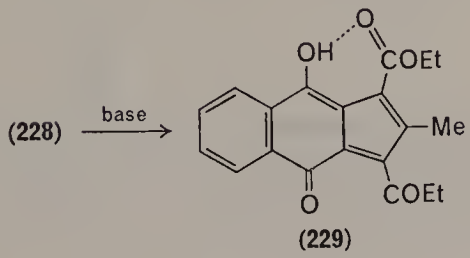


(497)

(227)



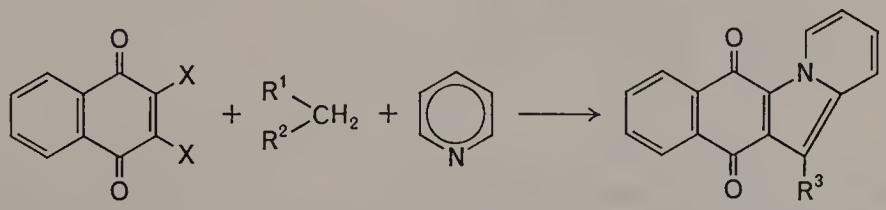
(498)



(499)

determination (vapour pressure osmometry), absorption spectra (i.r., u.v., visible and n.m.r.), polarography and non-aqueous titration were strikingly consistent with structure **229**.

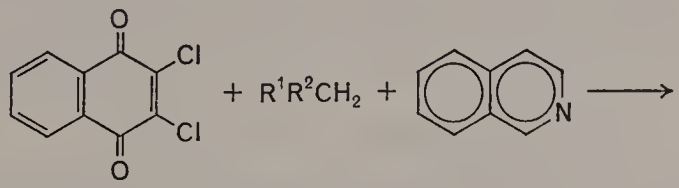
The range of active methylene compounds that exhibit quinonoid addition and substitution reactions involving heterocyclic bases is quite large (equation 500)[557]. The yields vary from trace to very good for



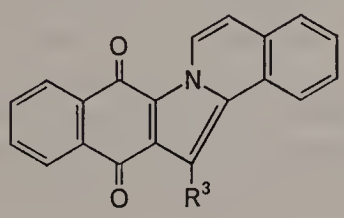
(500)

X = H, Cl
R^1, R^2 = Ac, CN, CO_2R, Ph, EtCO, Me, NO_2, PhCO
R^3 = CO_2R, Ac, PhCO, CN, Ph, Me

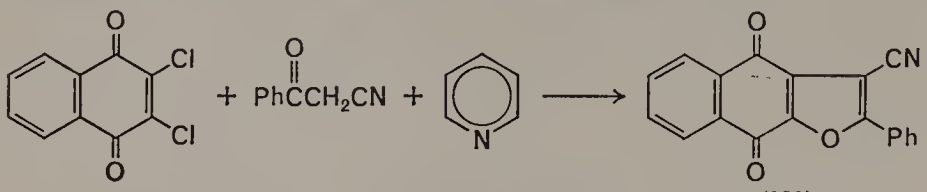
pyridine, but when isoquinoline is used, the yields are generally superior (equation 501).



(501)



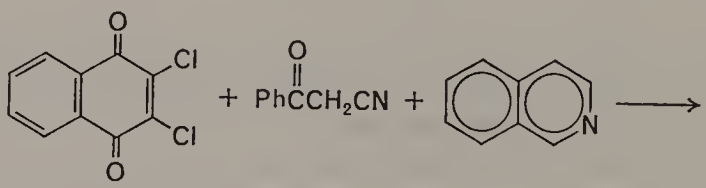
An exception to the entry of nitrogen bases into these reactions was found in the case of benzoylacetonitrile (equation 502)[558]. This example



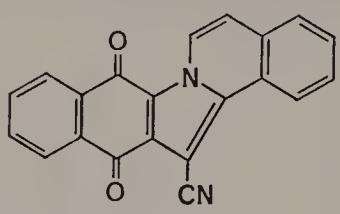
(502)

(230)

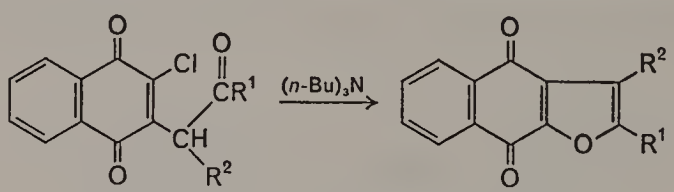
is very surprising because when isoquinoline is used in place of pyridine the more usual product, including the base in its structure, is found (equation 503). The same furan **230** is produced if 2-hydroxy-3-bromo-



(503)



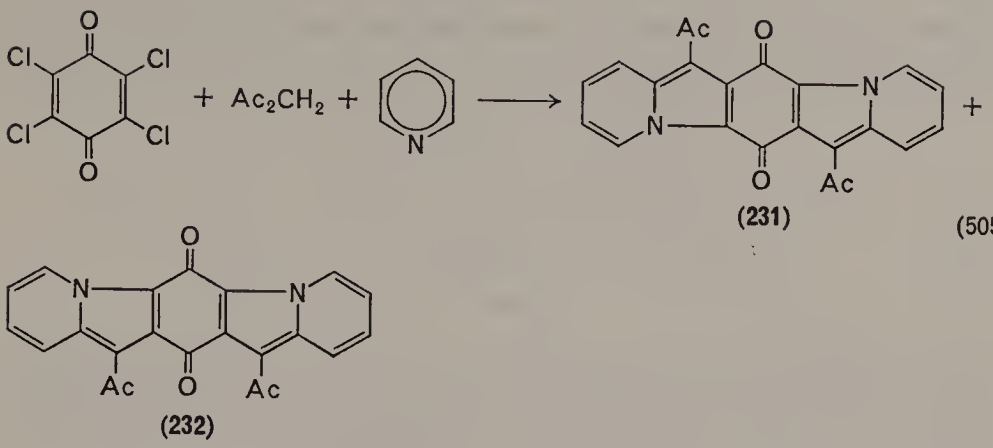
1,4-naphthoquinone is used, but the yield drops substantially. A series of active methylene enolates displaced one chlorine of 2,3-dichloro-1,4-naphthoquinone and these intermediates could be cyclized to 2,3-di-substituted-4,5-phthaloylfurans (equation 504).



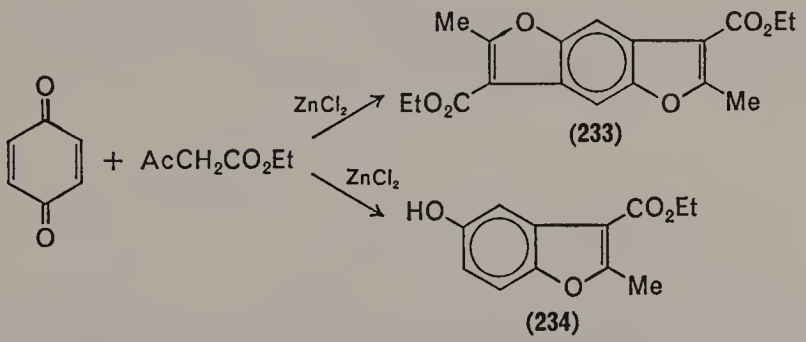
(504)

R^1 = Ph, Me R^2 = CN, Ac, PhCO, CO_2Et, H

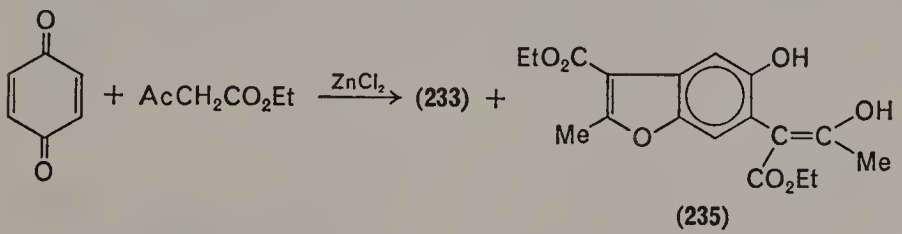
Condensations of active methylene compounds and chloranil in the presence of pyridine have also been conducted with analogous results (equation 505)[559]. It was also found that with a limited amount of pyridine a single displacement–cyclization sequence can be achieved, thus opening the way for the synthesis of unsymmetrical compounds related to **231** and **232**.



A detailed study of the reactions of ethyl acetoacetate with 1,4-benzoquinone in the presence of Lewis acids has shown that the relative amounts of mono- and diaddition can be controlled by regulating the concentration of quinone[560–563]. The slow addition of quinone can produce the monofuran in 80% yield (equations 506 and 507). Similar control can be achieved in the addition of ethyl benzoylacetate.

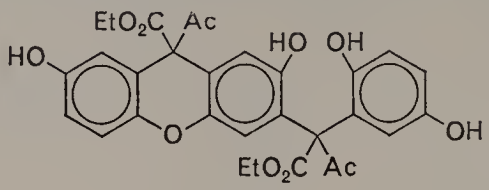


In another study of this addition, the effect of lower reaction temperature was investigated[564]. When the reaction is carried out at 80–85°C and with very low concentration of quinone, only the benzofuran (**234**) is obtained. At 41–45°C, and a low quinone concentration, the difuran (**233**) and a new product (**235**) are formed (equation 508). At 38°C only **235** is produced;



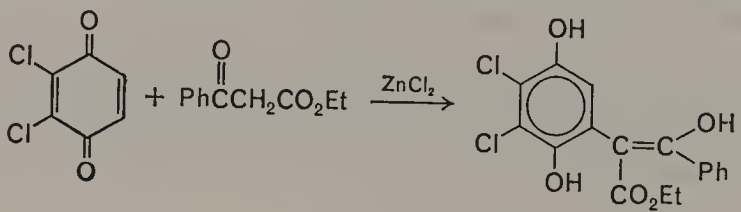
the same result can be achieved by lowering the zinc chloride concentration. If the concentration of quinone is increased at the lowest temperatures

studied, a new product (**236**) is formed. This material shows chemical and physical properties that indicate a dibenzopyran derivative.



(236)

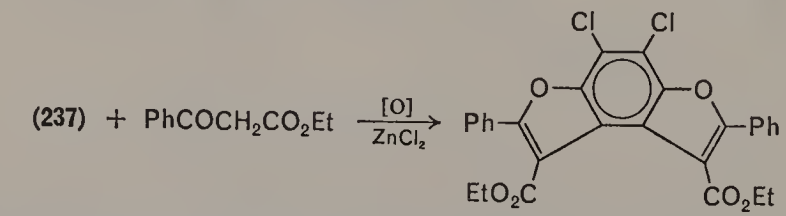
With 2,3-dichloro-1,4-benzoquinone and ethyl benzoylacetate, it was possible to isolate the proposed intermediate **237** in good yield by working at less than 60°C (equation 509). The intermediate could be oxidized to the



(509)

(237)

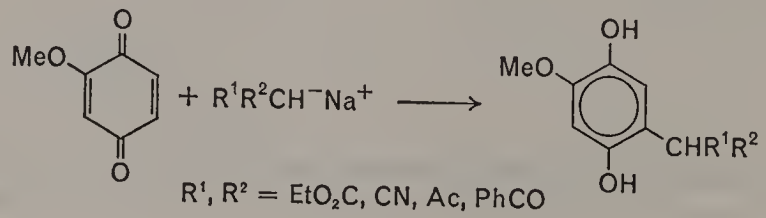
corresponding quinone, which underwent further reaction with ethyl benzoylacetate to form the previously prepared difuran (equation 510).



(510)

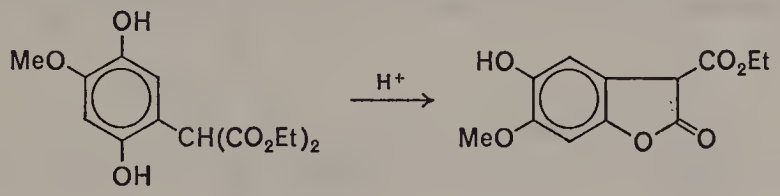
The several stable enols suggested need additional experimental verification, but the general situation is clear. The outcome of these reactions depends heavily on: (i) the concentration of quinone, (ii) the concentration of Lewis acid, (iii) the temperature and (iv) the nature of the active methylene compound.

A series of active methylene compounds have been added to 2-methoxy-1,4-benzoquinone (equation 511)[565]. All the primary adducts were isolated, but that from ethyl acetoacetate was unstable. Subsequent

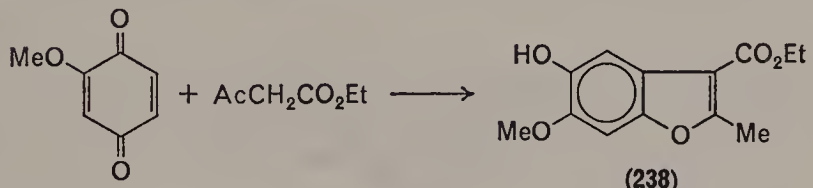


(511)

treatment with acid caused ring closure of the usual kinds (e.g. equation 512). The major product isolated from the reaction of ethyl acetoacetate was the benzofuran (**238** in equation 513).



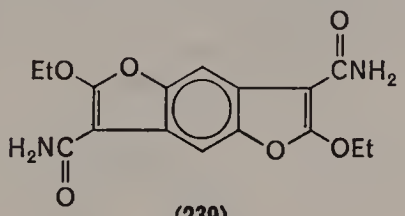
(512)



(513)

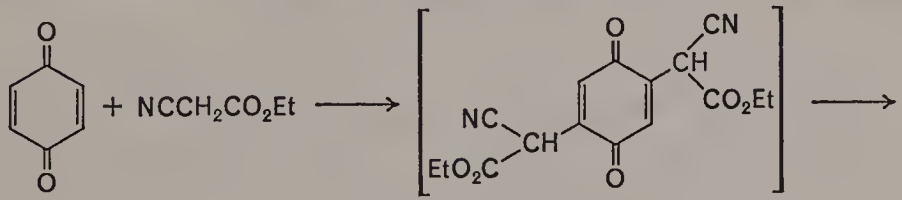
(238)

Jeffreys found several minor products in the preparation of the adduct with ethyl cyanoacetate. One of these, **239**, was the same as that found, but given a different structure, in an earlier re-investigation of the Craven

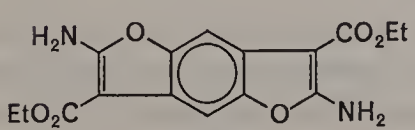


(239)

reaction[566, 567]. Still another re-investigation of this particular example has been reported[568]. On the basis of spectral data, especially comparisons with compounds known to contain certain structural features, it now appears that the elusive structure is **240** in equation (514).

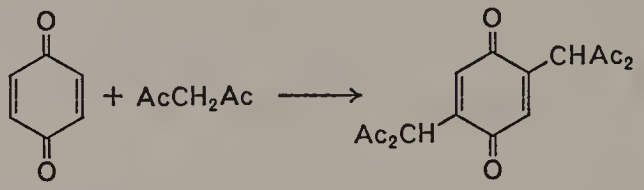


(514)

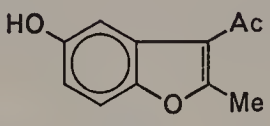


(240)

Some earlier reports also bear on the most probable pathway for these reactions[569,570]. The reaction of 1,4-benzoquinone with acetylacetone produced a quinone with the characteristics of a simple bisaddition product (equation 515). An n.m.r. study strongly suggests that these

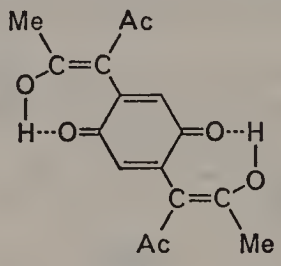


(515)



(242)

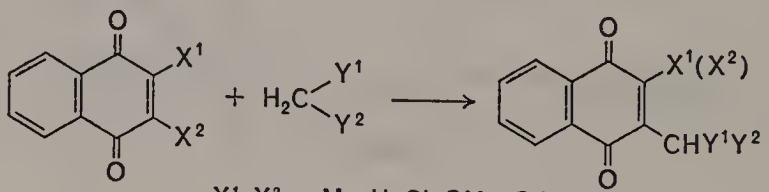
simple adducts exist in the doubly enolized form **241** [571]. However, when the excess acetylacetone, used as the solvent, was recovered, a new crystalline



(241)

product, **242**, was obtained. All of the chemical and physical data are consistent with the proposed structure **242**.

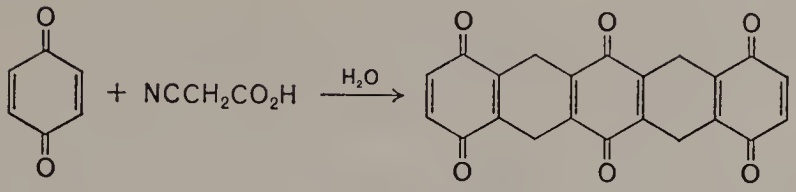
Interest in the Craven reaction continues and a recent report has made its synthetic range somewhat clearer (equation 516)[572]. When 1,2-naphthoquinone is used, the 4-substituted product is obtained.



(516)

X^1, X^2 = Me, H, Cl, OMe, OAc
Y^1, Y^2 = CN, CO_2Et

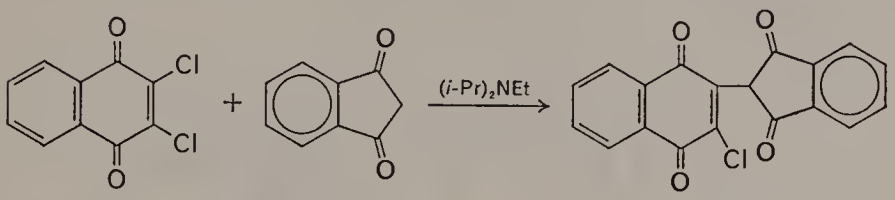
In 1960, Junek reported that in aqueous solution without excess base, cyanoacetic acid and 1,4-benzoquinone form a surprising triquinone (**243** in equation 517)[573]. With more highly substituted quinones, normal addition products are obtained.



(517)

(243)

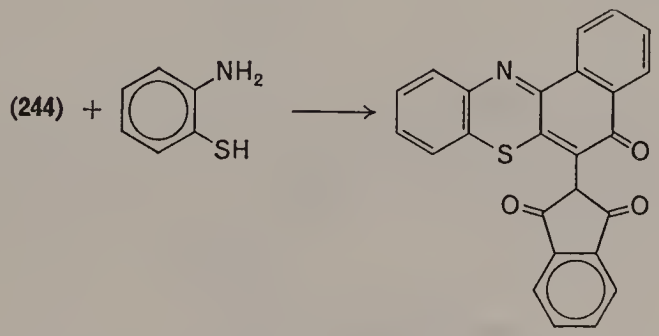
A less usual active methylene compound, 1,3-indandione, also reacts with 2,3-dichloro-1,4-naphthoquinone (equation 518)[574]. The product



(518)

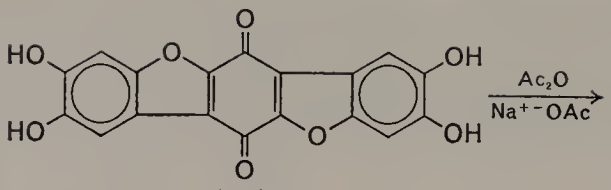
(244)

244 is obtained in excellent yield and undergoes additional substitution reactions including the formation of a phenothiazine with *o*-aminobenzenethiol (equation 519). This reaction is closely related to the furan and lactone cyclizations described earlier in the Nenitzescu condensation.

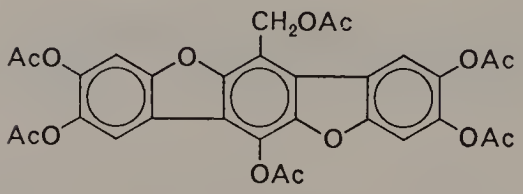


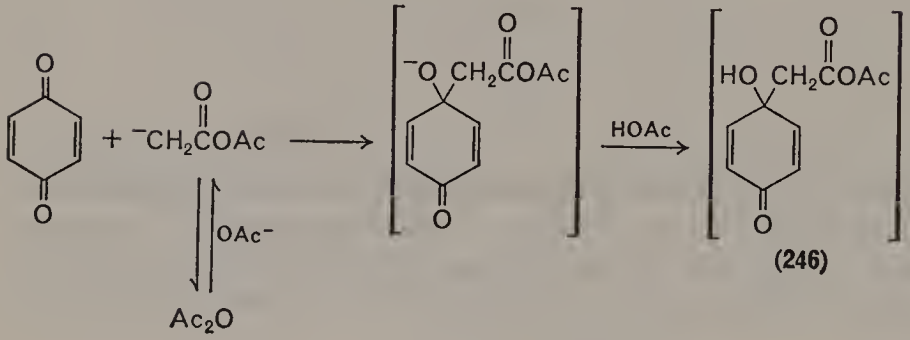
(519)

In attempting to prepare the hexaacetate of thelephoric acid **245**, it was discovered that an intermediate Perkin condensation has taken place (equation 520)[575]. This route only became clear after rather extensive studies of simpler quinones (especially 2,5- and 2,6-dimethoxy-1,4-benzoquinones) by Lounasmaa[576]. The mechanism is essentially that proposed earlier by Bloom for the reaction of 9,10-phenanthrenequinone with acetic anhydride in the presence of sodium acetate[577]. The initial addition of the α-carbanion of acetic anhydride to the quinone (equation 521) is followed by dehydration and hydrolysis (equation 522). After this fairly normal Perkin condensation, decarboxylation and the reductive addition of acetic anhydride occur (equation 523)[578]. The decarboxylation

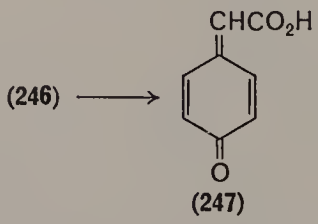


(245) (520)

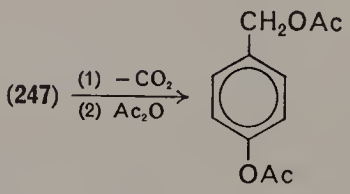




(246) (521)

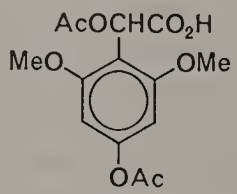


(247) (522)

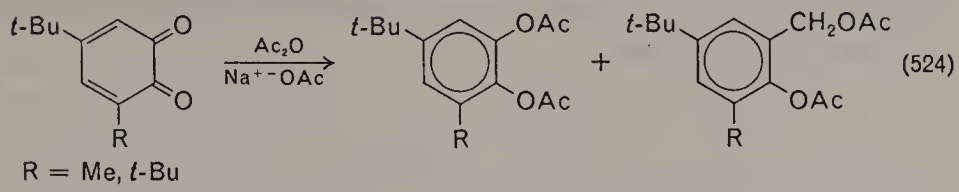


(523)

reaction did not occur spontaneously and it was possible to isolate the key intermediate (**248**)[579]. This reaction also takes place with 1,2-benzoquinones (equation 524), but in very low yield[580].

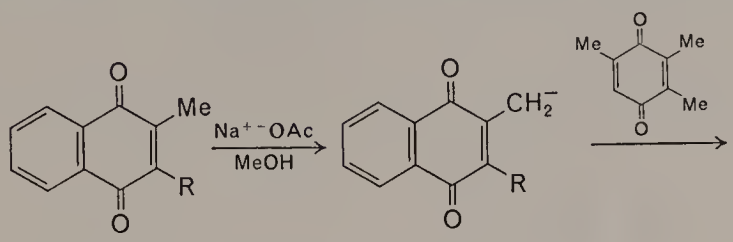


(248)

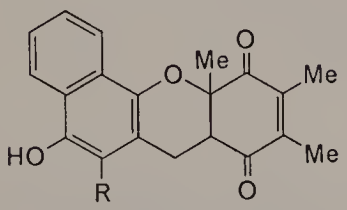


R = Me, *t*-Bu (524)

Recently the reactions of carbanions derived from alkyl quinones with a second quinone have been examined. The use of mildly basic conditions makes it possible to control subsequent reactions and isolate an initial 1,4-cycloaddition product (**249** in equation 525)[581]. With stronger base,

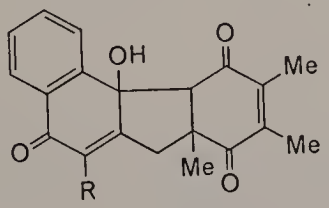


R = H, Me (525)



(249)

ring opening and oxidation are rapid and an unsymmetrical methylenediquinone forms. A previously unreported competing reaction leads to a 1,3-cycloaddition product containing a fluorene ring structure (equation 525 with additional product **250**). It is interesting that the isomeric

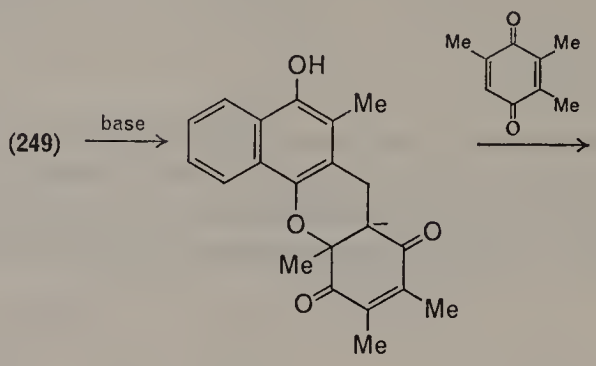


(250)

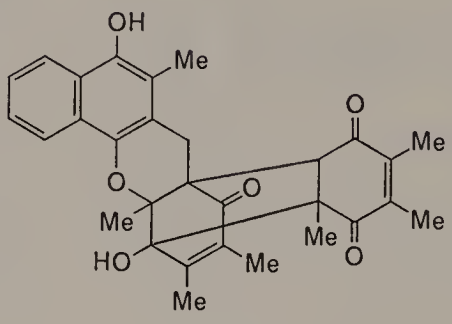
structures of **249** and **250** (where R = H) are not present in these reactions and it is possible to account directly for as much as 70% of the carbanion produced.

In a later study it was found that **249** (R = Me) in weak base also forms a carbanion that will react with a second molecule of 2,3,5-trimethyl-1,4-benzoquinone (equation 526)[582]. Only the single isomer (**251**) is

produced and both the structures and stereochemistry of the addition have been demonstrated.

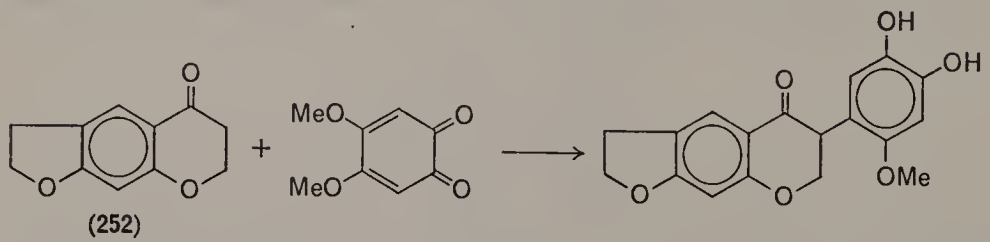


(526)

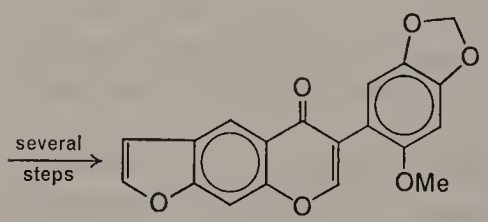


(251)

A final recent example of the use of carbanion–quinone reactions comes from the synthesis of natural products[583]. The total synthesis of dehydroneotenone (**253**) has been accomplished by the condensation of the furobenzopyran (**252**) with 4,5-dimethoxy-1,2-benzoquinone (equation 527).



(527)



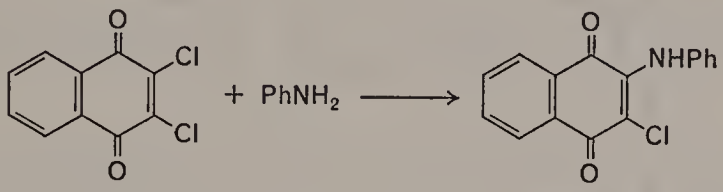
(253)

VIII. THE SUBSTITUTION CHEMISTRY OF QUINONES

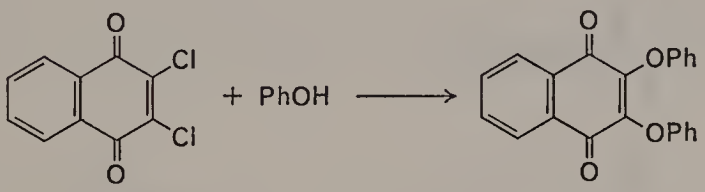
A. Historical Introduction

A large number of substituted quinones can be conveniently prepared via a suitable nucleophilic substitution reaction of a quinone bearing some relatively labile group. The vast majority of these reactions are displacements by amines offering a complement to the nitrogen addition studies previously discussed (see section II.C).

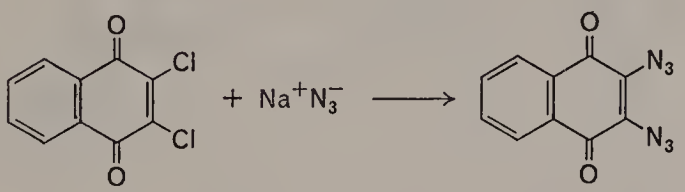
From the earliest days, a key synthetic intermediate in quinonoid chemistry has been 2,3-dichloro-1,4-naphthoquinone (see section VII.C). Among the first reports of syntheses involving this substrate are those that suggest the broad potential scope of quinone substitution chemistry. The following will provide some typical examples (equations 528–530)[584–586]. Furthermore, the sequential introduction of 2,3-nitrogen



(528)



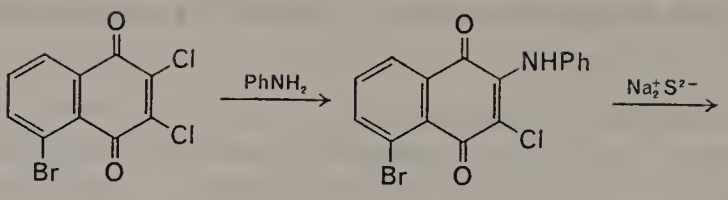
(529)



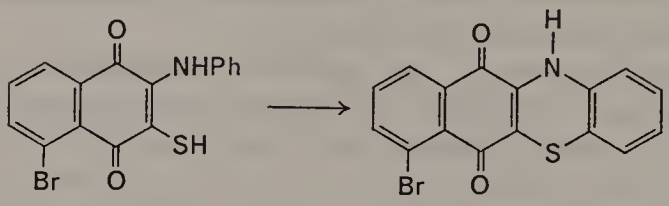
(530)

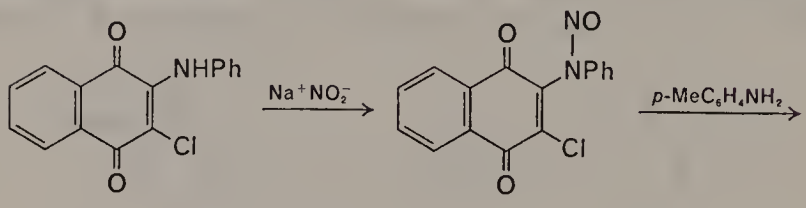
substituents makes it possible to prepare a large number of additional interesting compounds (equations 531 and 532)[587,588]. Diamines generally react with the two chlorine atoms in 2,3-dichloro-1,4-naphthoquinone, one amino group at a time. An interesting exception is *o*-phenylenediamine (equation 533)[589]. As the introduction to a synthetic report, Buu-Hoï has given a fine brief review of these early studies[590].

The massive study of aryl-nitrogen addition chemistry already mentioned (see section II.C.1) suggested the importance of competitive substitution in certain cases[5]. For example, depending on the relative

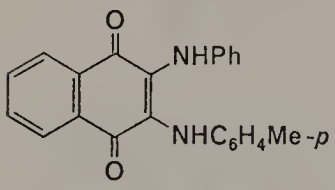


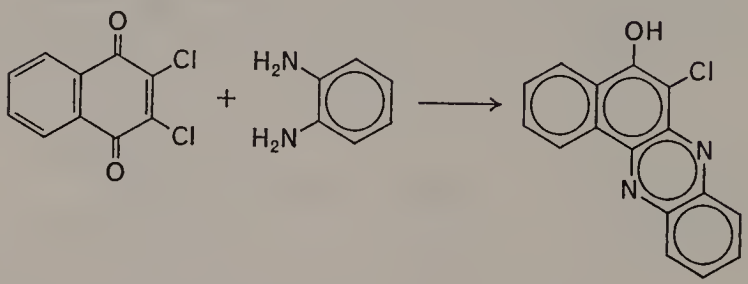
(531)





(532)

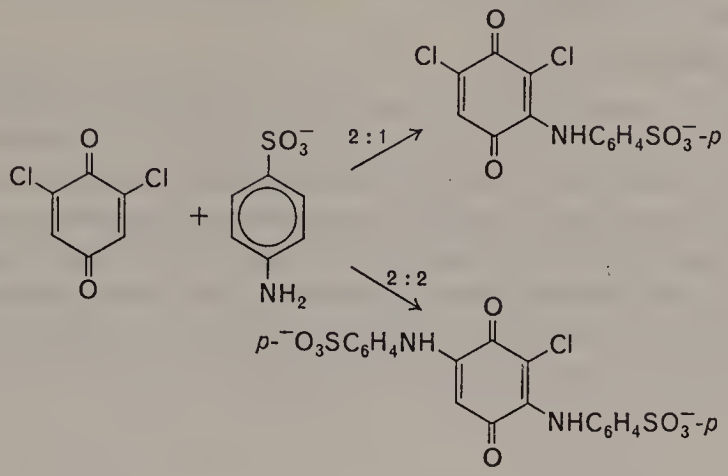




(533)

proportions of reactants, the following reactions occur (equations 534 and 535). An equivalent amount of 2,6-dichlorohydroquinone is also found in both reaction product mixtures.

Some of the early substitution chemistry of quinones involved nucleophiles other than nitrogen. Before the turn of the century, a number of studies of oxygen substitution had been made[591–593] (e.g. equation 536[530]). It was also found that the phenoxy groups could be displaced by aniline and that under slightly more severe conditions all four chlorine atoms can be replaced.



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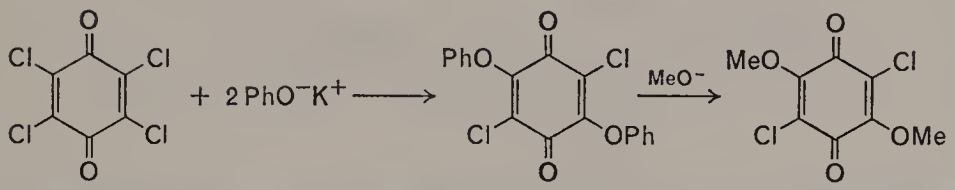
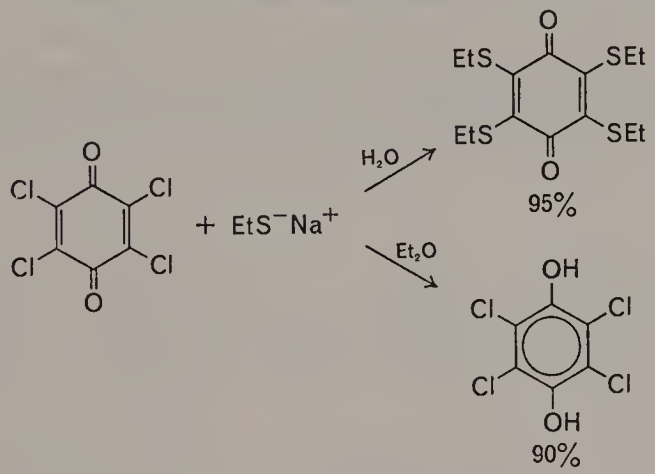
(535)



(536)

Several early reports of the substitution of quinones by sulphur nucleophiles have been recorded[594, 595]. The most important outcome of these studies was an appreciation of the importance of solvent in determining the reaction outcome (equations 537 and 538). While substitution and



(537)

(538)

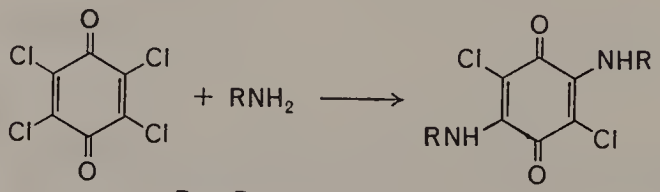
reduction were not the only reactions observed in water and ether respectively, the yields change in such a dramatic manner that the significance of the observation cannot be doubted.

Numerous additional contributions to the synthetic literature of quinonoid substitution chemistry were made in the late 19th and early 20th centuries[68, 596–599].

B. Nitrogen Substitution

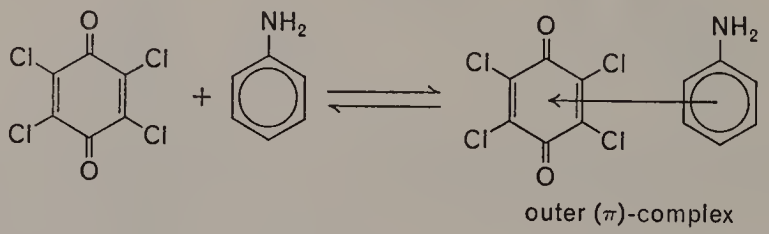
1. Mechanistic studies

While the application of nitrogen substitution chemistry to the synthesis of quinonoid compounds has a long and abundant history, the serious mechanistic study of these reactions is a recent activity of the physical-organic chemist. The question of the importance of charge-transfer complexes as intermediates in such substitution reactions is a central concern. In 1968 Das and Majee claimed that, for simple amines (equation 539), the observed spectra are those of product rather than

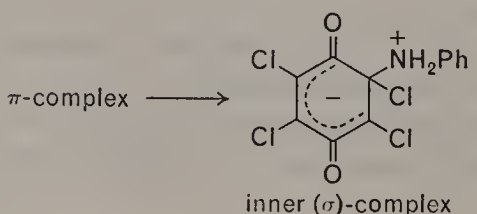


R = Et, n-C_6H_{13}, C_6H_{11} (539)

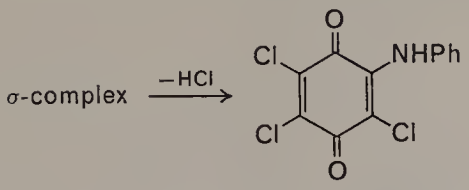
charge-transfer[600]. The experimental evidence is unconvincing and a later, detailed study has been presented[601]. For the system of chloranil and various substituted anilines evidence for both outer- and inner-complex formation was obtained. It was not possible to state positively that the outer-complex actually takes part in the reaction, but the inner-complex is certainly an intermediate in the substitution reaction. The following reaction mechanism is suggested (equations 540–542). The details of the second substitution are not as clear and two alternatives are presented. Still, the essential characteristics of the reaction mechanism are clear.



outer (π)-complex (540)

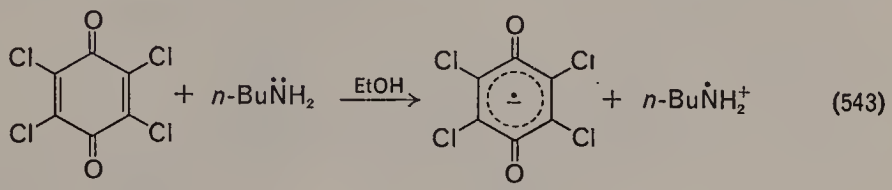


inner (σ)-complex (541)



(542)

In a recent study by Tamaoka and Nagakura[91] (see section II.C.2) using rapid scan spectrophotometry, the occurrence of electron transfer, prior to the substitution itself, was demonstrated (equation 543). Spectra of the chloranil–butylamine system and related kinetics suggest the following sequence of steps (equation 544). The monoaminated intermediate was not detected in this particular reaction, but was in other quite



(543)

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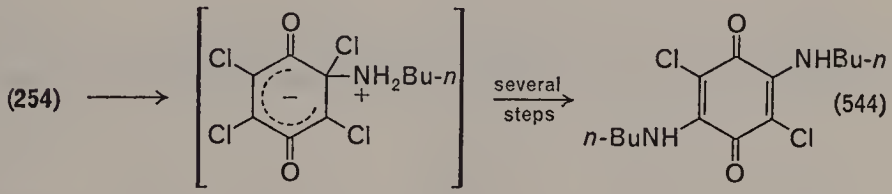
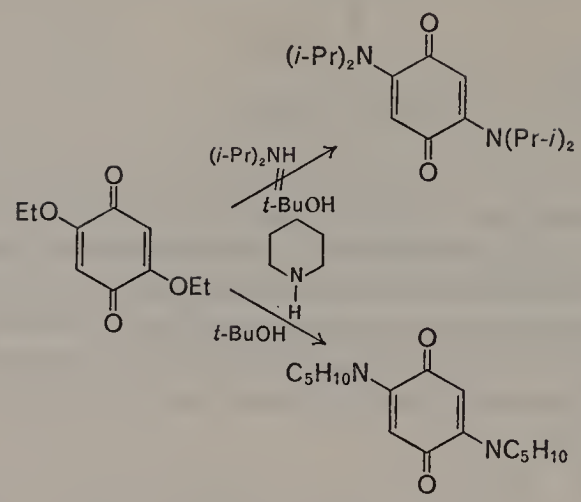


(544)

similar systems. The general outline of the above mechanistic scheme was applied to a broad range of quinones and amines. With the less polar solvent ethyl ether, the quinone anion radical was not observed in systems that clearly showed this step in ethanol.

A number of synthetic papers record observations bearing on nitrogen substitution mechanisms in quinonoid compounds. An interesting observation relative to the substitution of alkoxy groups by amines was made during a study of the steric limitations of diisopropylamine in addition reactions (see section II.C.3)[105]. When 2,5-diethoxy-1,4-benzoquinone is treated with diisopropylamine in refluxing *t*-butyl alcohol no reaction takes place in three days, while under these conditions piperidine readily replaces the ethoxy groups (equations 545 and 546). However, when methanol is used as the solvent, a quantitative conversion to 2,5-dimethoxy-1,4-benzoquinone is achieved, if diisopropylamine is present (equation 547).

The striking effect of cerous ion on the addition products formed between anilines and 5,8-quinolinequinone has already been discussed (see section II.C.3)[109]. Pratt included some significant substitution



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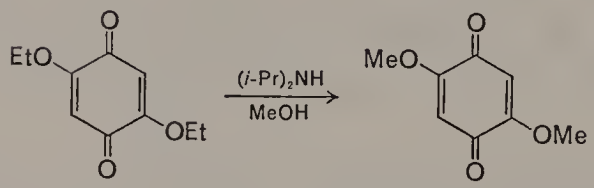
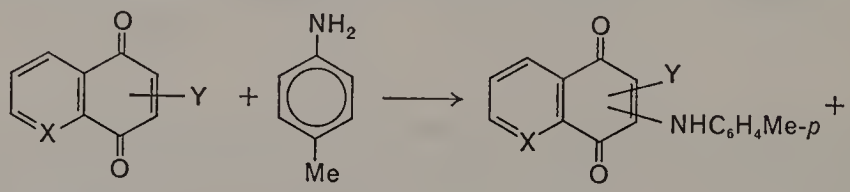
(546)



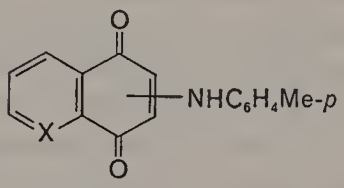
(547)

reactions in his study. Halogen and methoxy groups were examined in both the heterocyclic quinone and 1,4-naphthoquinone (equation 548).



X = CH, N
Y = Cl, Br, OMe

(255)



(256)

(548)

The approach used (i.e. monosubstituted quinone substrates) allows a discussion of the competition between addition and substitution. Some typical results are presented in Table 18. As would be expected, the halogenated quinones react mostly by addition. The low reactivity of the 7-position in 5,8-quinolinequinone is re-emphasized by the complete absence of substitution in the 7-chloro derivative. The addition of cerous

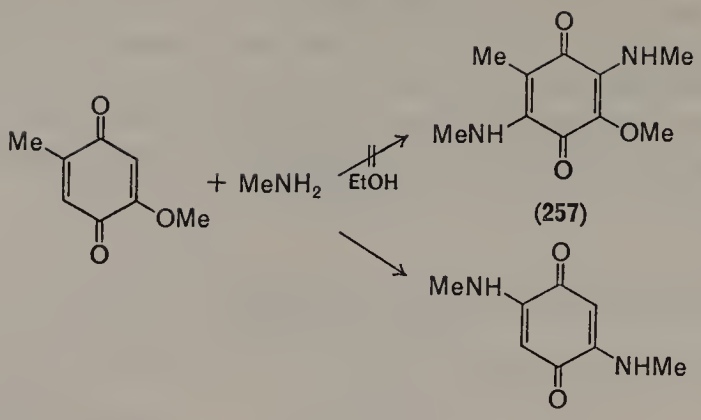
ion again exerts its strong catalytic effect on the 6-position of the heterocyclic quinone. Not only do the overall yields increase, but substitution becomes essentially the only reaction with 6-chloro-5,8-quinolinequinone. With 2-halo-1,4-naphthoquinones the effect of cerous ion is not very great. The low reactivity of the methoxy group is clearly demonstrated as is the powerful catalysis of the cerous ion.

TABLE 18. Addition versus substitution products of *p*-toluidine and quinones (equation 548)[109]

	Yield, % (without $CeCl_3$)		Yield, % (with equivalent $CeCl_3$)	
	Addition (255)	Substitution (256)	Addition (255)	Substitution (256)
5,8-quinolinequinone				
6-Chloro-	76	7		94
7-Chloro-	69	0	87	0
6-Methoxy-	0	0		93
7-Methoxy-	0	0	33	22
1,4-naphthoquinone				
2-Chloro-	75	14	62	27
2-Bromo-	58	26	47	33
2-Methoxy-		<10		80[a]

[a] 0·1 equivalent $CeCl_3$.

One of the most unexpected observations in quinone chemistry is the substitution of a methyl group by nitrogen[86]. In demonstrating the structure of spinulosin, a product of mould metabolism, Anslow and Raistrick attempted the reaction of alcoholic methylamine with 2-methyl-4-methoxy-1,4-benzoquinone. Instead of the expected addition product **257** they found that both the methyl and methoxy groups had been displaced by methylamine (equations 549 and 550). The displacement of a methoxy group by an amine was already a known process. Fieser had used the reaction as part of the characterization of isomeric methoxynaphthoquinones (equations 551 and 552)[602]. Even the surprising methyl substitution reaction was not completely unknown at the time (equation 553)[597,598] but had not been explored. The case of methylamine and 3,6-dibromothymoquinone is exceptional in that the 'normal' substitution of bromine takes place and the methyl group is unaffected.



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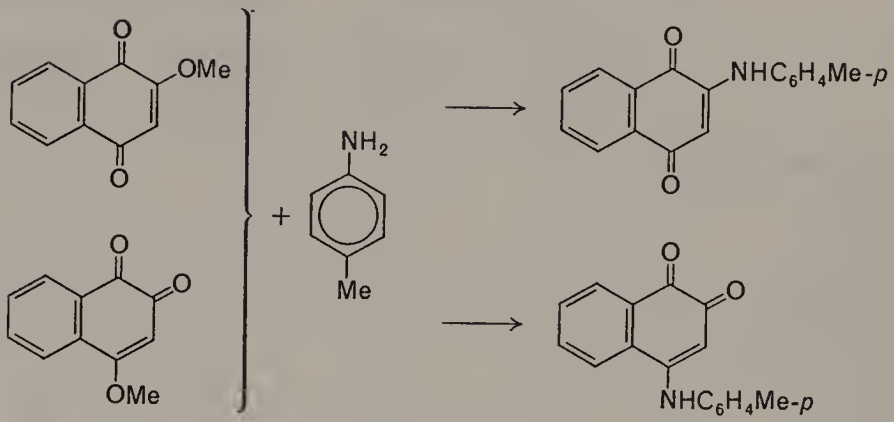
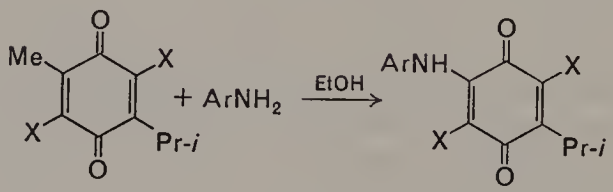
(550)



(551)

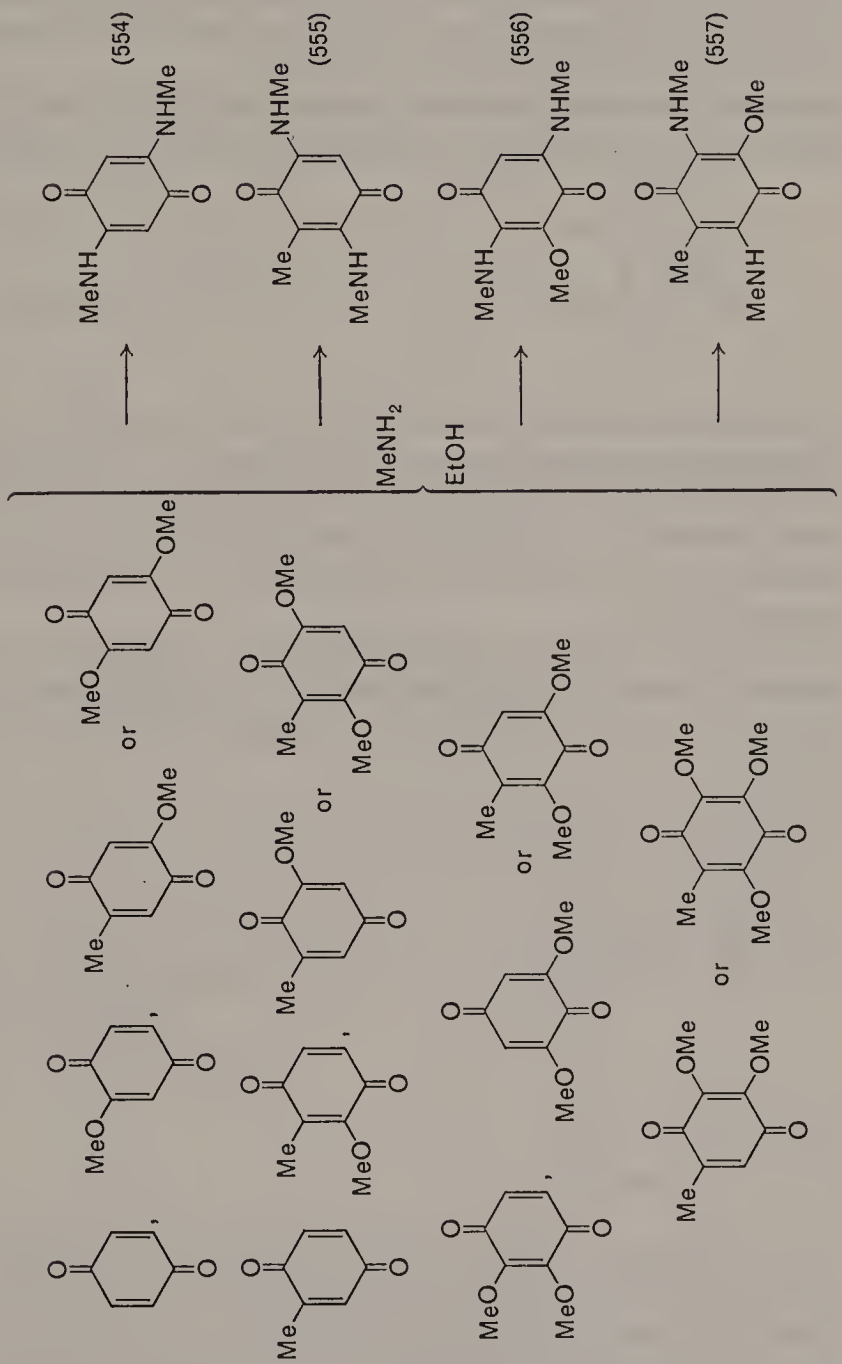
(552)



(553)

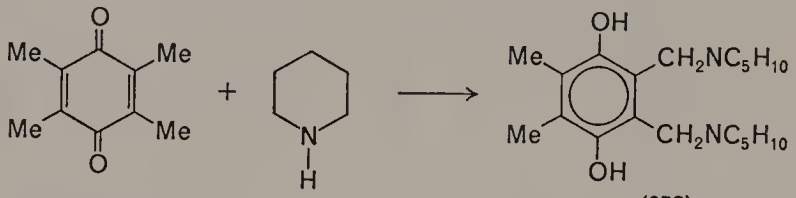
X = Cl, Br Ar = Ph, 3- or 4-MeC_6H_4, 4-$MeOC_6H_4$

Thirteen 1,4-benzoquinones, variously substituted with methyl and methoxy groups, were allowed to react with alcoholic methylamine and the products determined (equations 554–557). All of the reactions gave the bismethylamino product and the *para* orientation. The yield, in most cases, was that expected from the relative proportion of addition and substitution. It is interesting to note that addition *ortho* to a methoxy group is avoided


(554)
(555)
(556)
(557)
MeNH2
EtOH
or

(see section II.D.3) in all cases except 2,6-dimethoxy-1,4-benzoquinone. In this case the tendency toward *para* nitrogen orientation overcomes the low reactivity of the three position. A series of nine 1,4-benzoquinones containing methyl, methoxy and hydroxy groups was also examined, but no methyl group displacement was found.

Another important new quinone–amine reaction has been found in the process of side-chain amination (equation 558)[603, 604]. In addition to the

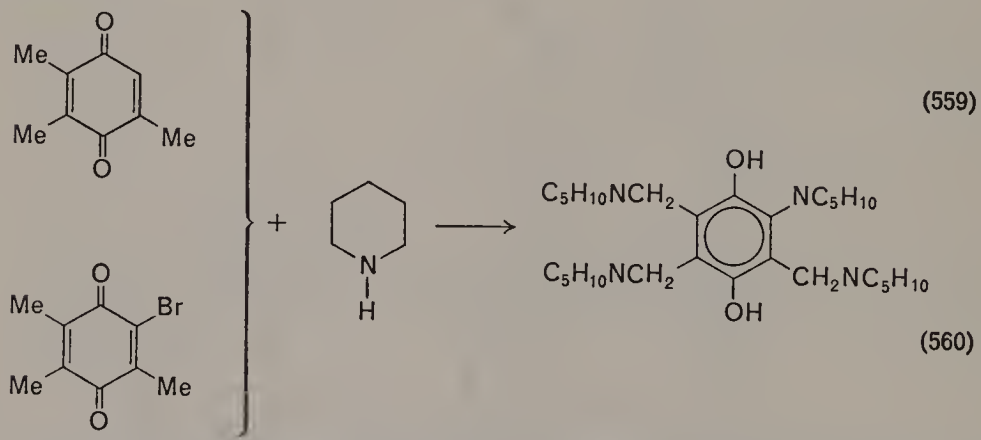


(558)

(258)

2,3-bispiperidinomethyl product **258**, a low yield of 2-methyl-3,5,6-trispiperidinomethylhydroquinone was obtained. The latter product, or duroquinone, can be converted, in low yield, to the tetrakispiperidinomethyl derivative by prolonged treatment. The structure of **258** is consistent with its spectral characteristics and it was synthesized by an independent route.

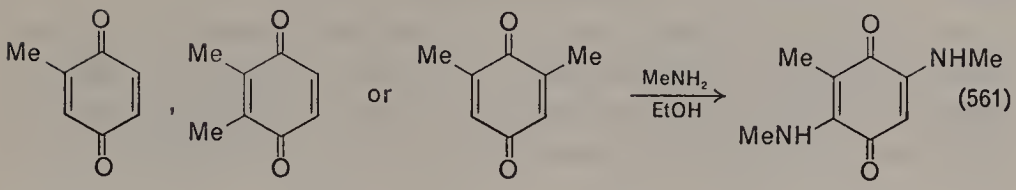
The reaction is fairly general with respect to quinones and primary or secondary amines. With quinones that are not fully alkylated, addition or substitution takes place as well as side-chain amination (equations 559 and 560).



(559)

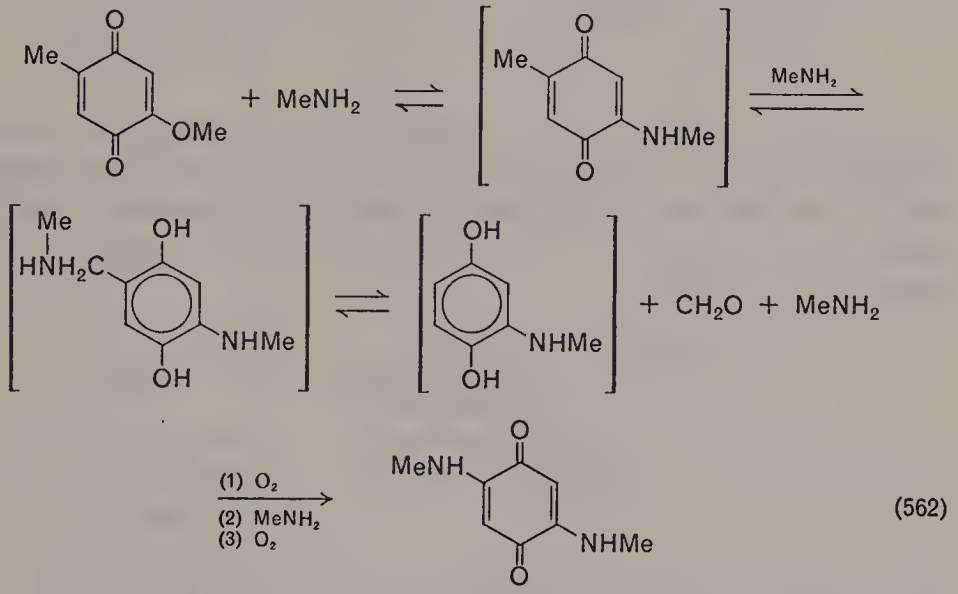
(560)

The relationship between side-chain amination and methyl group substitution by amines has been discussed[605]. The data presented earlier suggest that direct addition or substitution will take place as long as the two amino groups can be *para* to one another. However, if such an arrangement is not possible by simple routes, the displacement of a methyl group occurs (compare equation 561 with equations 559 and 560). The mechanism



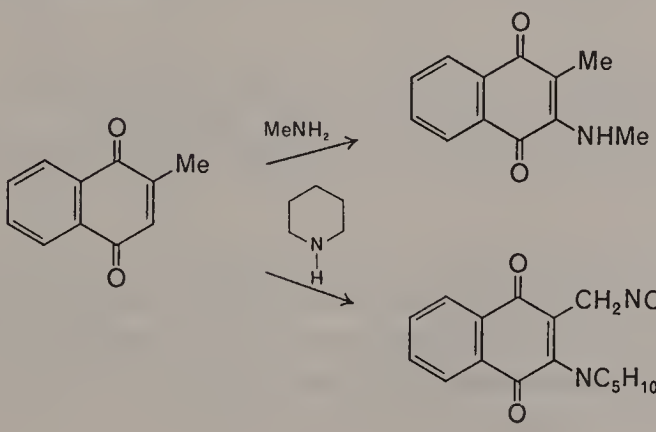
(561)

suggested for this entire reaction type takes into account the oxygen uptake and the formation of formaldehyde (equation 562). The several



(562)

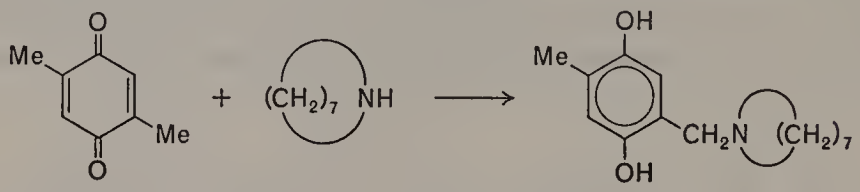
equilibria may well be unfavourable, but the final irreversible step assures the observed product. The reverse Mannich reaction is also a reasonable proposal, although attempts to isolate intermediates were not successful. It was also shown that analogous reactions occur with other amines; e.g. piperidine and cyclohexylamine. Finally, it appears that methylamine is a much weaker nucleophile for side-chain amination than is piperidine (equations 563 and 564).



(563)

(564)

The relationship between nuclear and side-chain amination has been studied with respect to both quinone and amine structure[606]. The first system in which the side-chain reaction is clearly preferred suggests the importance of steric effects (equation 565). The bis side-chain amination



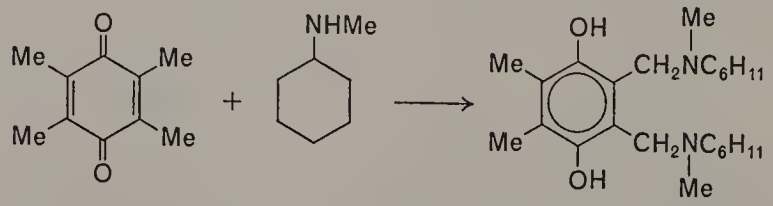
(565)

product was also formed. The reactions of the homologous series of polymethyleneimines and 2,5-dimethyl-1,4-benzoquinone were carefully re-examined and two interesting trends were found. The data in Table 19 suggest both the steric effect and the very impressive change in redox potential with ring size.

TABLE 19. Side-chain versus nuclear amination of 2,5-dimethyl-1,4-benzoquinone[606]

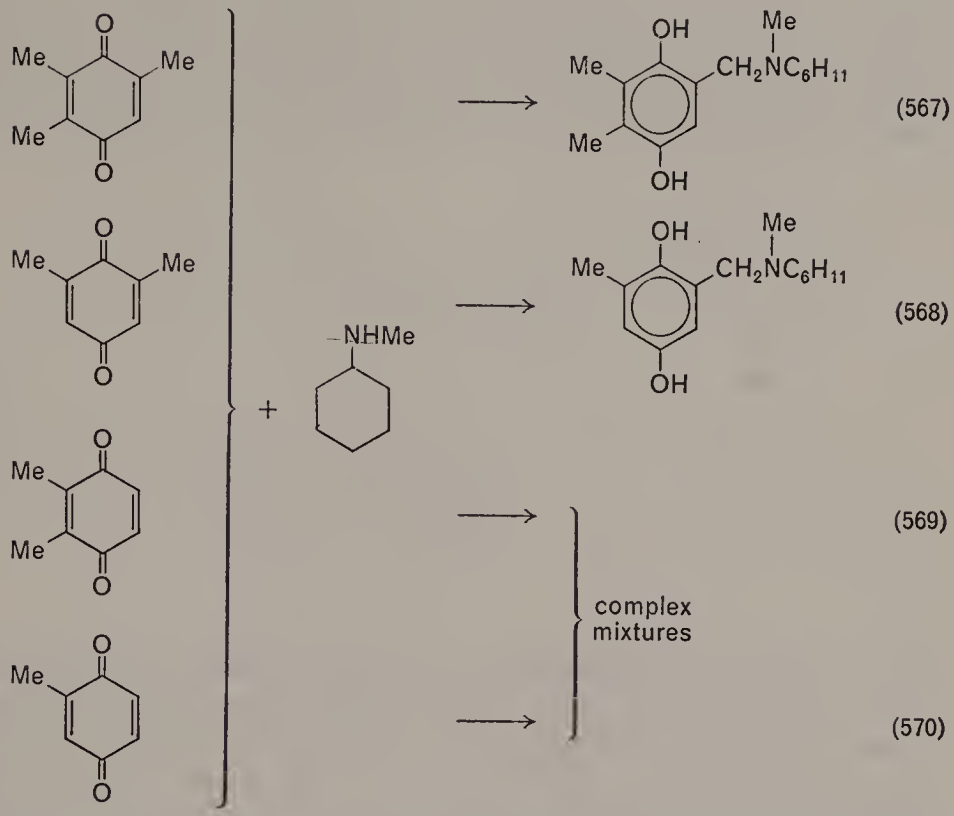
$(CH_2)_xNH$	Side-chain product (%)	Oxidation state of nuclear product
4	0	Q
5	Trace	1 : 1 Q : HQ
6	20–30	HQ
7	100	

A more detailed study was made with *N*-methylcyclohexylamine. As would be expected, this amine reacted with 2,5-dimethyl-1,4-benzoquinone to give only the side-chain amination product (equation 566). When

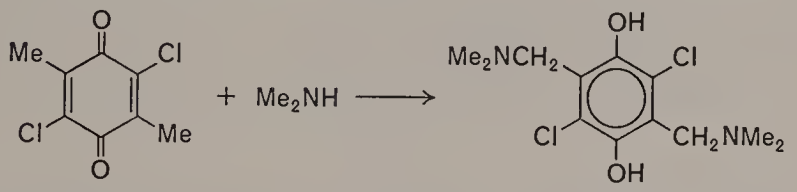


(566)

duroquinone was used, the bis side-chain amination product, analogous to those found earlier, was obtained. The remaining methylated 1,4-benzoquinones present some interesting observations (equations 567–570). The reaction with 1,4-benzoquinone itself gave a poor yield of a bis-*N*-methylcyclohexylamino adduct (probably the 2,5-isomer).



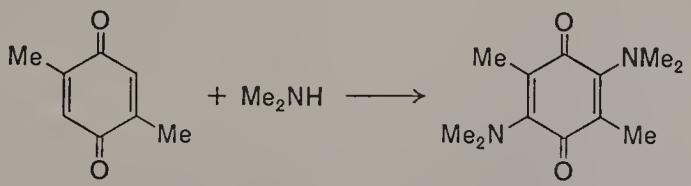
Finally, the compound 2,5-dichloro-3,6-dimethyl-1,4-benzoquinone provided an unexpected and interesting picture of side-chain amination versus nuclear substitution (equation 571). The product structure **260**



(571)

(259) **(260)**

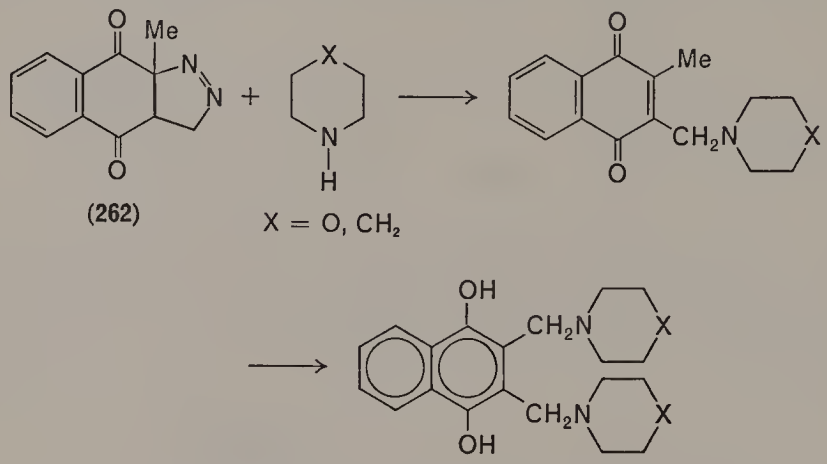
should be contrasted with that obtained from the addition of dimethylamine to 2,5-dimethyl-1,4-benzoquinone (**261** in equation 572). With methylamine the dichloro quinone **259** undergoes a trace of substitution for chlorine, but side-chain amination is by far the major process.



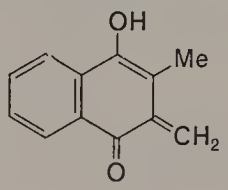
(572)

(261)

Another group of English chemists has recently published a detailed study bearing on the mechanism of side-chain amination[607]. When the quinone–diazomethane adduct (**262**) is treated with secondary amines, products clearly related to such reactions are obtained (equation 573).



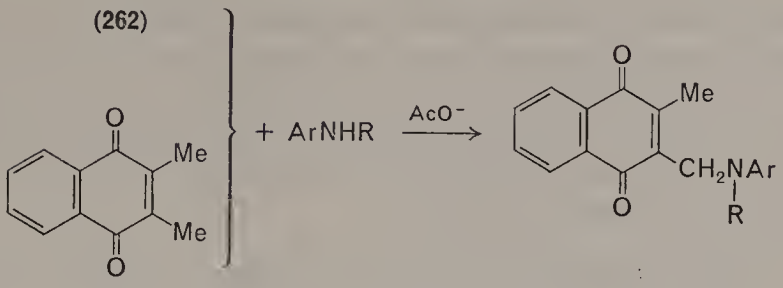
The two amines behave differently, as befits their different basicity. Only the first step was observed with morpholine, although there is no reason to doubt that the second will occur under more strenuous conditions. With piperidine, only the bisaminomethyl product was obtained unless short reaction times and lower temperatures were used. An intermediate quinone methide (**263**) was suggested for this ring opening[608] as well as



(263)

for the side-chain amination reaction[604]. It was found that a series of anilines could also participate in either of these reactions if acetate ion is present (equations 574 and 575).

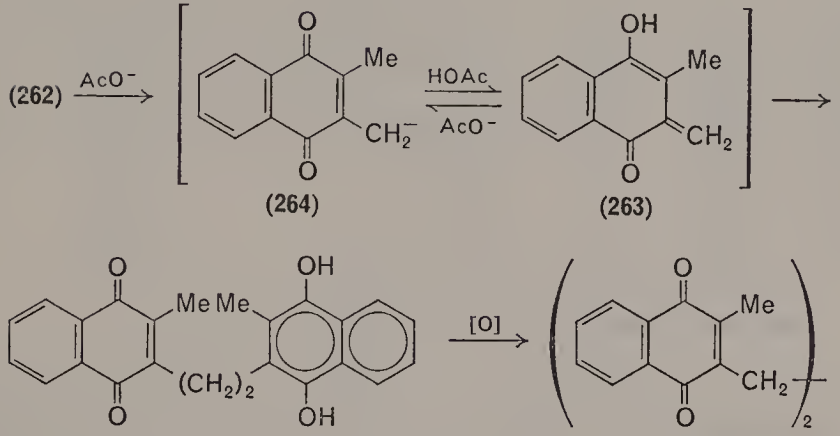
The decomposition of **262** under basic conditions, but in the absence of primary or secondary amines, leads to an ethylenediquinone (equation 576). Several different possible mechanistic paths were considered in the light of available experimental evidence. The sequence involving Michael addition of the carbanion **264** to the quinone methide **263** seems most plausible. The equilibrium between **263** and **264** is certainly a central aspect of the mechanism and competitive experiments (with limited aniline concentration) show that base concentration has strong influence. If the



(574)

(575)

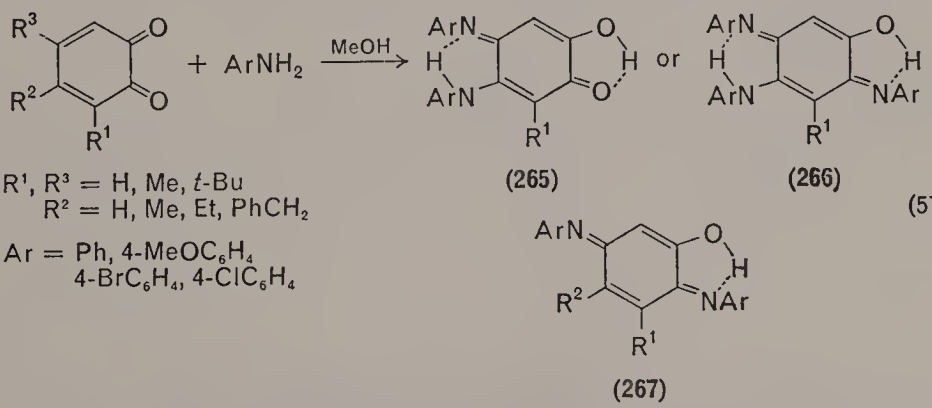
Ar = Ph, 4-MeC_6H_4, 4-$NO_2C_6H_4$, 4-ClC_6H_4, 4-$MeO_2CC_6H_4$
R = H, Me



(576)

acetate concentration is low, the arylaminomethylquinone is favoured (equation 574); at high acetate concentration, the ethylenediquinone is favoured (equation 576).

Within the past two years the displacement of alkyl groups from 1,2-quinones has been observed (equation 577*)[609]. The scope of the reaction has been expanded and the mechanism investigated[610]. The data



R^1, R^3 = H, Me, *t*-Bu
R^2 = H, Me, Et, $PhCH_2$

Ar = Ph, 4-$MeOC_6H_4$, 4-BrC_6H_4, 4-ClC_6H_4

(577)

* Other tautomeric forms are possible, but these are preferred on the basis of the expected strong intramolecular hydrogen bonding.

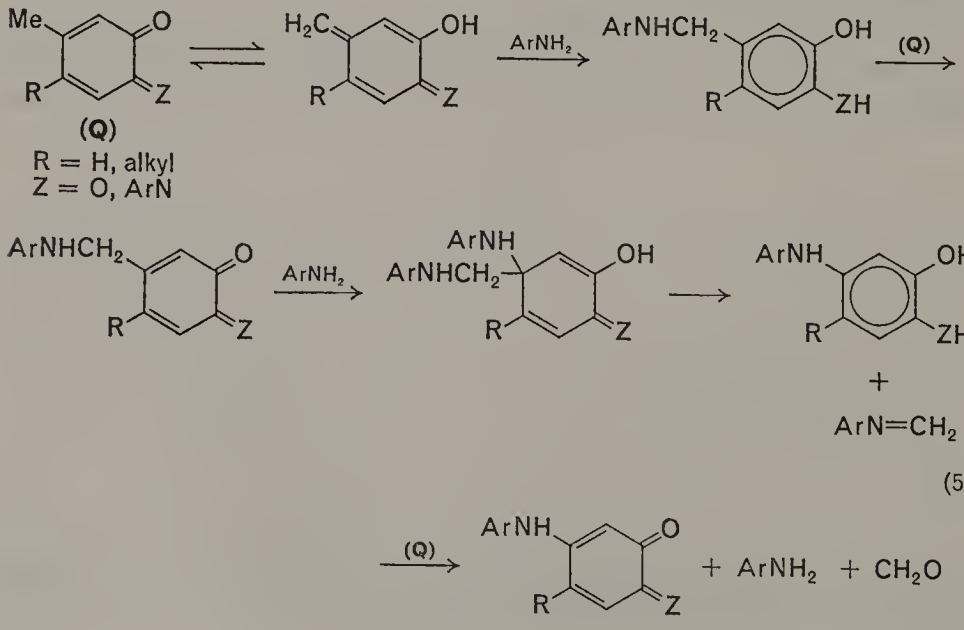
in Table 20 indicate the major product obtained with various quinone structures. Several important features of this reaction are clear: (i) ethyl or benzyl groups are displaced as well as the methyl group, (ii) alkyl groups in the three position are not displaced, (iii) when two groups are present, only one (*para* to a carbonyl group) is displaced and (iv) the product of a displacement reaction is a mono-anil.

TABLE 20. Principal product of the reaction of anilines with alkyl-substituted 1,2-benzoquinones (equation 577)[609, 610]

R^1	R^2	R^3	X in 4-XC_6H_4	Major product
H	H	H	H, MeO, Cl, Br	(265)
Me	H	H	MeO	(265)
H	Me	H	H, MeO, Cl	(266)
H	Et	H	MeO	(266)
Me	H	Me	MeO, Cl	(266)[a]
H	$PhCH_2$	H	MeO	(266)
H	Me	Me	MeO, Cl	(267)[a]

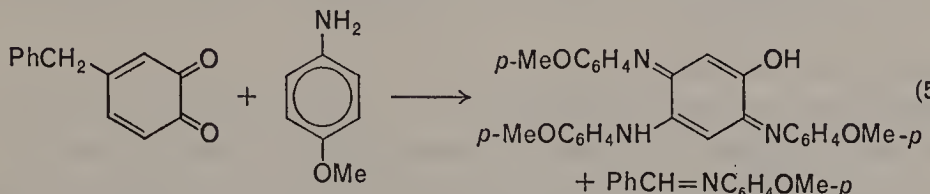
[a] One of two possible structural isomers.

The mechanism of this reaction was carefully studied. Both oxygen and solvent were ruled out as being directly involved in the reaction although the latter appears to be important in solvating the transition state. The following mechanism was proposed (equation 578). The required formaldehyde was found in the recovered solvent. The case of benzyl group



(578)

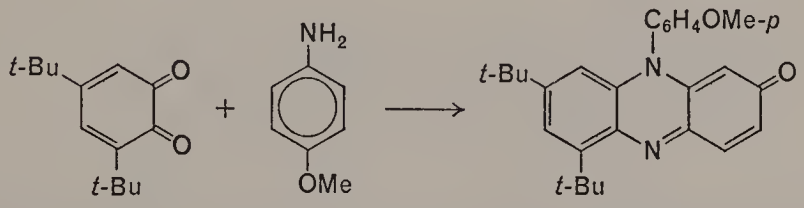
displacement is important because *N*-benzylidene-*p*-anisidine (**268**) was obtained in the same yield as the quinonoid product (equation 579).



(579)

(268)

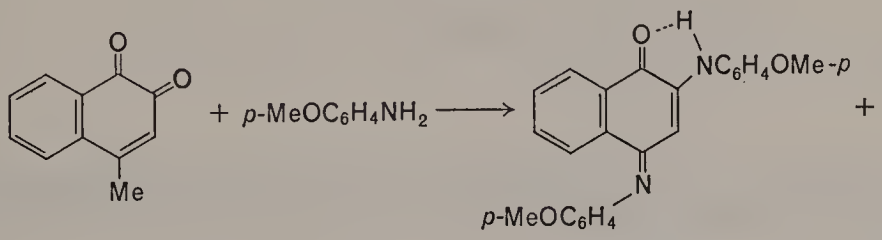
No alkyl group displacement was found in the case of 3,5-di-*t*-butyl-1,2-benzoquinone. This observation could be the result of steric hindrance, but it is also the predicted result on the basis of the suggested mechanism (equation 578). The product that does form has not been completely characterized, but appears to be **269** on several grounds (equation 580).



(580)

(269)

Finally, 4-methyl-1,2-naphthoquinone and *p*-anisidine produce two products and both involve methyl group displacement (equation 581).



(270) (581)

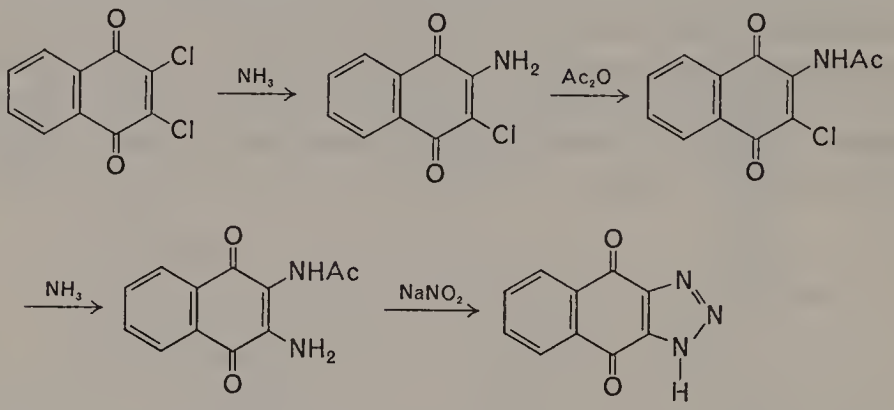
(271)

It is possible that product **271** might be formed by the hydrolysis of product **270**, but under more vigorous conditions than those of the

displacement such a hydrolysis did not occur. It follows that, at least in this case, methyl group displacement precedes or occurs concurrently with anil formation.

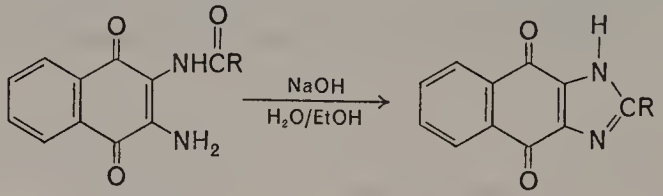
2. Synthetic survey

Fieser, in his wide-ranging studies of heterocyclic quinones electronically analogous to carbocyclic systems (see sections II.E.3 and V.B), has made interesting use of a modification of the *N*-nitroso method (equation 582)[611]. Chloranil was also used to prepare the analogous system



(582)

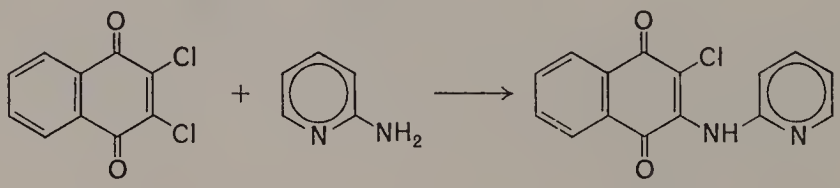
containing two triazole rings. A closely related sequence of reactions has been used to prepare imidazoles of similar structure (equation 583)[234, 612].



(583)

R = alkyl

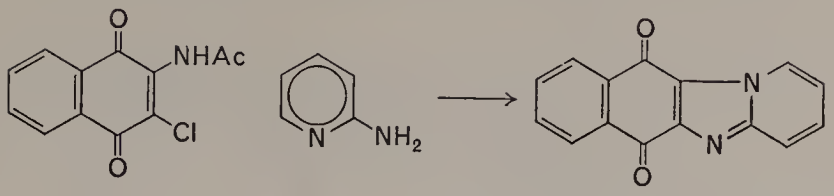
The reaction of 2-aminopyridine with 2,3-dichloro-1,4-naphthoquinone has been reported (equation 584)[613] and the structure of the product **272**



(584)

(272)

confirmed through subsequent conversion to a polycyclic benzimidazole prepared independently (**273** in equation 585)[614]. This latter preparation is a further application of the method of Fries and Billig[588]. The benzimidazole structure proposed (**273**) has now been revised.

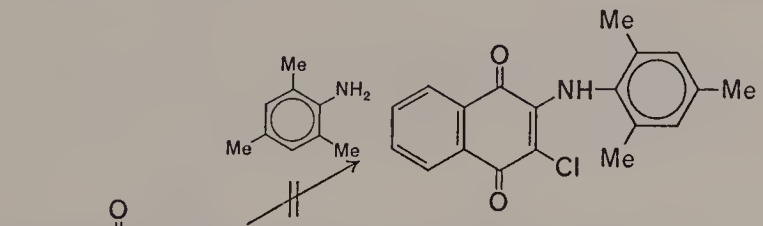


(585)

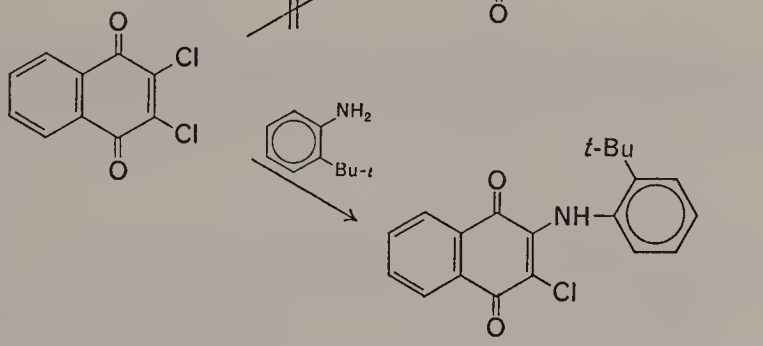
(incorrect structure, see reference 619)

(273)

The possibility that halogen displacement reactions might be useful for the qualitative identification of primary and secondary amines led Buu-Hoï to examine the question of steric limitations[615]. Not unexpectedly, the reaction of either 2,3-dichloro-1,4-naphthoquinone or chloranil took place with anilines having one *ortho* substituent, but not with both *ortho* positions occupied (equations 586 and 587). The reactions with chloranil



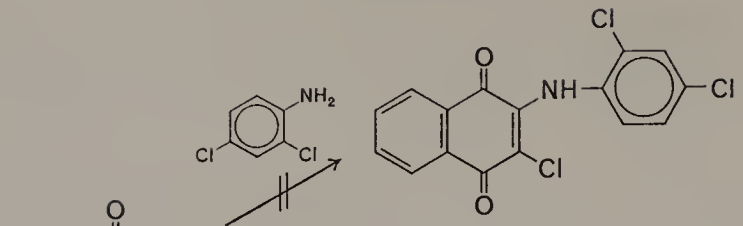
(586)



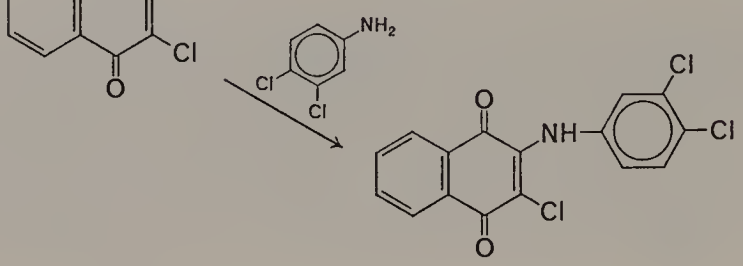
(587)

produced the 2,5-dianilino derivatives. It has been found recently that the interplay of steric and electronic effects is very strong in these reactions. For example, even a single *ortho* electron-withdrawing substituent will prevent the reaction (equations 588 and 589)[616].

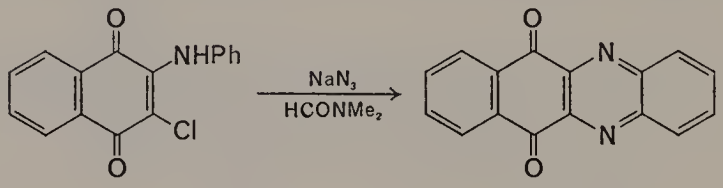
An important modification of the techniques for converting 2,3-dichloro-1,4-naphthoquinone to heterocyclic quinones has been presented by Reynolds and collaborators. In studies of the chemistry of benzo[b]-phenazine and related compounds, the 6,11-quinone (**274**) is a key intermediate[617]. The treatment of 2-anilino-3-chloro-1,4-naphthoquinone with sodium azide in dimethylformamide produced the required compound (equation 590). The presumed intermediate azide was not isolated in this case, but was in a later example (**275**).



(588)



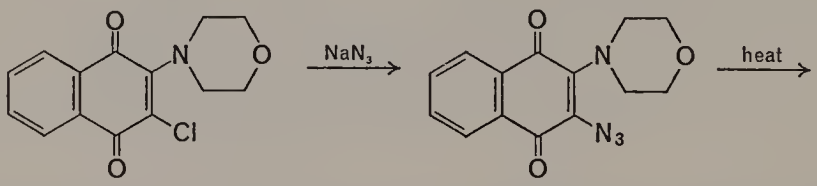
(589)



(590)

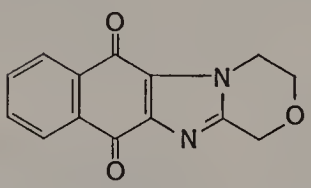
(274)

The reaction proved to be quite general both for anilines and a series of saturated heterocyclic amines (e.g. equation 591)[616]. The preparation

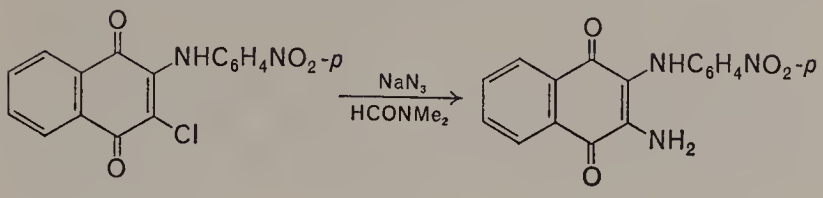


(275)

(591)



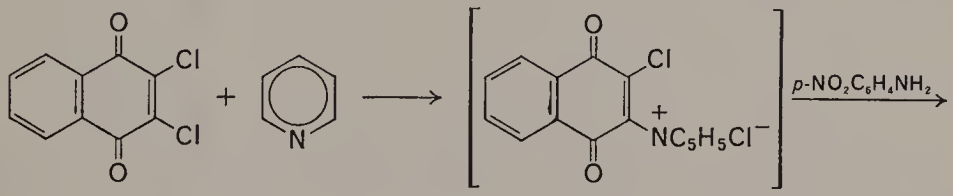
of 2-(4-nitroanilino)-3-chloro-1,4-naphthoquinone (**276**) had to be accomplished indirectly. When this compound was treated with sodium azide in dimethylformamide, the chlorine was replaced by an amino group and no cyclization took place (equation 592). On closer inspection, products analogous to **277** were found for other cyclizations involving an anilino group.



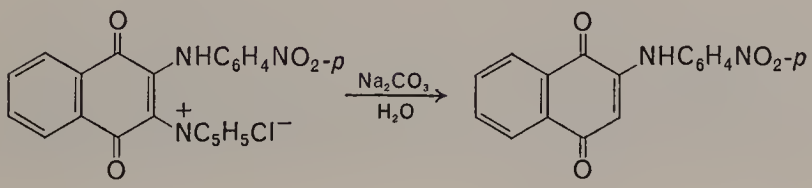
(592)

(276) (277)

While trying to prepare **276**, Reynolds and Van Allan attempted unsuccessfully to repeat the reported direct substitution of 2,3-dichloro-1,4-naphthoquinone by *p*-nitroaniline[584]. They found that under more vigorous conditions an interesting reductive loss of chlorine occurred (equation 593)[618]. The initial pyridinium salt was not isolated, because on

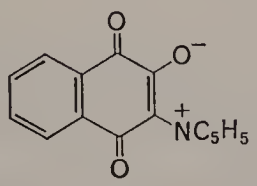


(593)



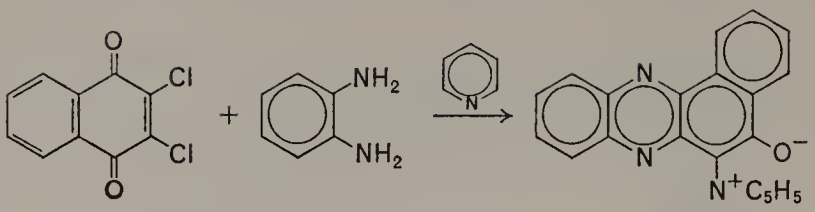
(278)

attempted recrystallization, from water or ethanol, the internal salt **279** was obtained (equation 594). The second pyridinium salt **278** was purified and its structure established.



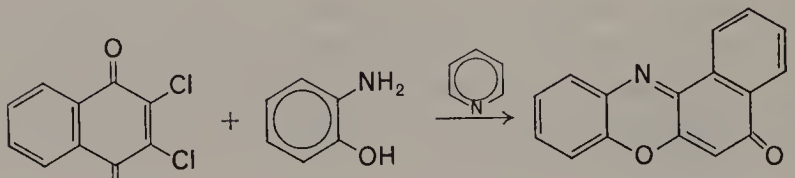
(279)

The condensation of *ortho* bifunctional aromatic amines with 2,3-dichloro-1,4-naphthoquinone in pyridine has led to some interesting new heterocyclic syntheses (equations 594–596)[618]. All three of these reactions are of interest beyond their indication of the scope of this condensation. The reaction product with *o*-phenylenediamine in pyridine (**280**) is



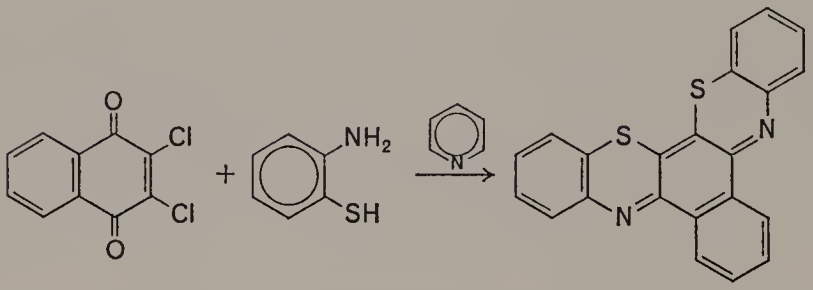
(594)

(280)



(595)

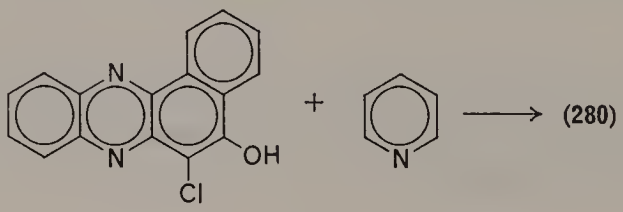
(281)



(596)

(282)

similar to that formed from the same reactants in ethanol (**283**) and can be obtained from the latter (equation 597). The reaction with *o*-aminophenol

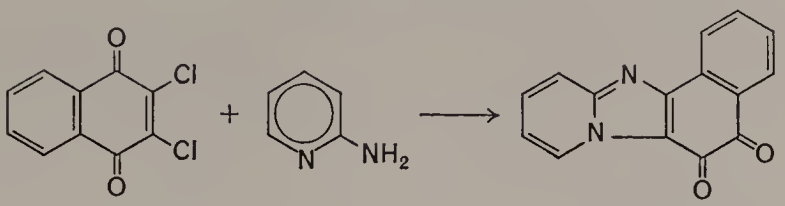


(597)

(283)

is again noteworthy for its facile reduction of the chloro group (**281**). Finally, under all conditions studied, *o*-aminobenzenethiol produced the disubstitution product (**282**).

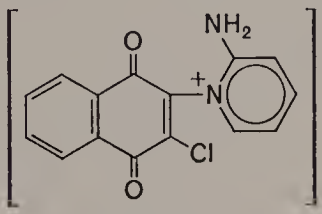
The structure of the products just described (i.e. all angular) caused Reynolds and Van Allan to re-examine the reaction of 2,3-dichloro-1,4-naphthoquinone with 2-aminopyridine (equation 598; see also equation 585)[618]. The authors of the earlier report[614] had eliminated structure **284** from consideration because they could not observe a reaction with *o*-phenylenediamine. Reynolds and Van Allan achieved this reaction as well as the conversion of **284** to an anhydride with sodium peroxide,



(598)

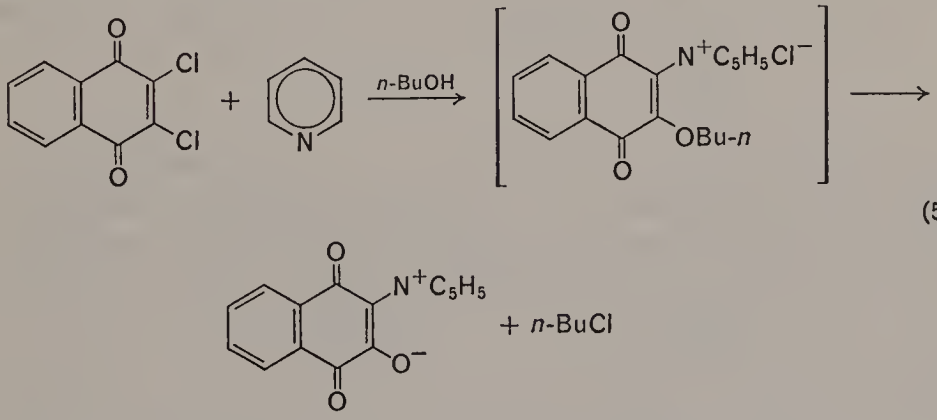
(284)

leaving no doubt of its *ortho* quinonoid structure. The alternative arrangement of nitrogen atoms was considered, but **284** was preferred because the ring nitrogen of 2-aminopyridine is known to quaternize more readily than the amino group, hence intermediate **285** is suggested.



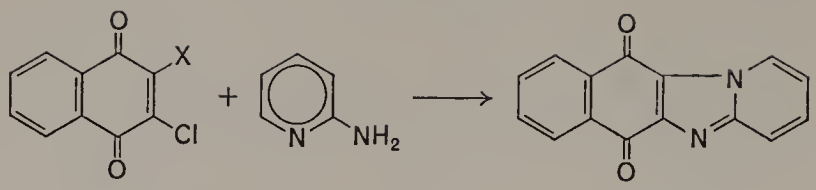
(285)

The reaction of 2,3-dichloro-1,4-naphthoquinone with two equivalents of pyridine in anhydrous butanol is interesting (equation 599)[618]. The intermediate is speculative, but seems entirely reasonable. On the basis of this experiment, it is possible to see the probable similarity of mechanism in the several examples.



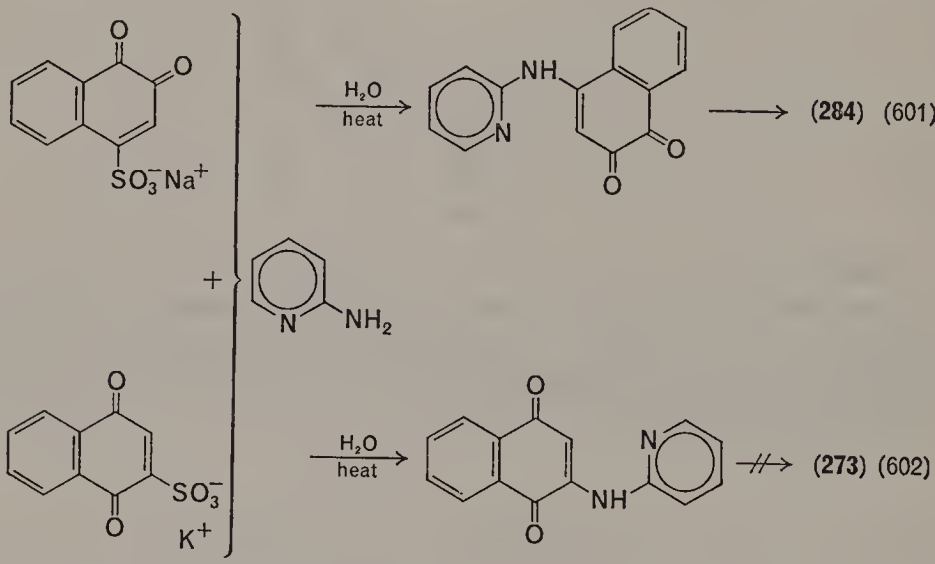
(599)

Actually another group of chemists had demonstrated the angular structure of **284** some years earlier[619]. Mosby had also shown that by using different leaving groups on the quinone it is possible to prepare the linear system **273** in equation 600[620]. Some mechanistic speculations are presented, but the subtle structure changes and the marked changes in product they bring about demand more detailed study. In a later paper, Mosby and Silva present still another curious aspect of these systems



X = OH, EtO, OAc (273) (600)

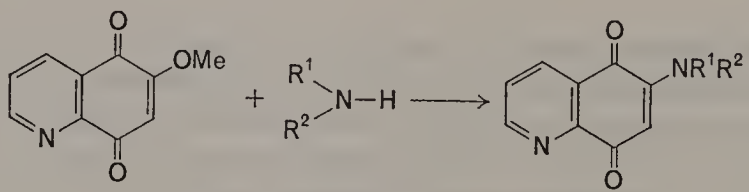
(equations 601 and 602)[621]. It should also be noted that both of the initial substitution products are formulated as *N,N*-diaryl secondary amines rather than pyridinium salts. Clearly, much work remains to be done in this important reaction series.



(284) (601)

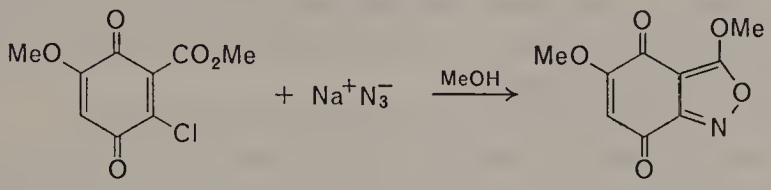
(273) (602)

The displacement of oxygen functions by nitrogen nucleophiles has also played a significant role in quinone substitution chemistry. A variety of amines have been used to displace the ether linkage of 6-methoxy-5,8-quinolinequinone (equation 603)[622]. The yield of product obtained in most cases is very good, but the *p*-toluidine reaction is slow and gives only 40% of the theoretical yield.



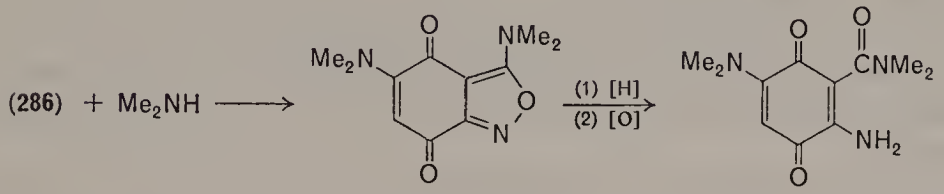
R^1 = Et, *n*-C_6H_{13}, 4-MeC_6H_4
R^2 = H, Et
R^1, R^2 = $(CH_2)_5$ (603)

An interesting azide substitution and subsequent cyclization has been reported (equation 604)[623]. A variety of substituted quinones can be prepared from **286** (e.g. equation 605).



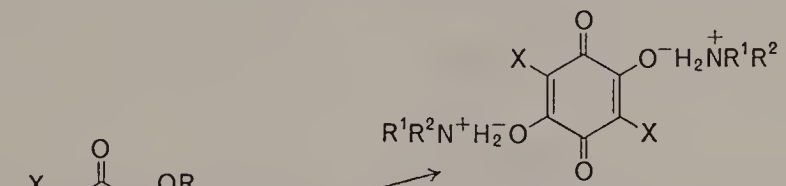
(604)

(286)



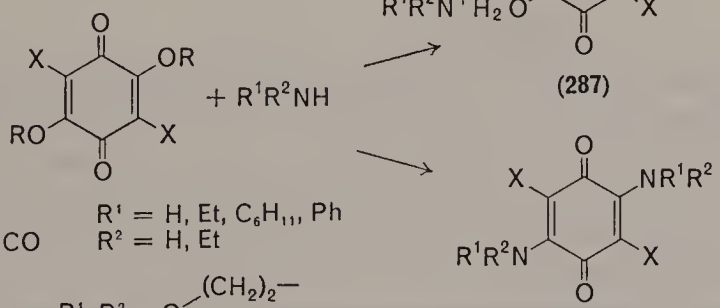
(605)

The esters of certain halogen hydroxy-substituted 1,4-benzoquinones can be regarded as mixed anhydrides since, for example, chloranilic acid is more acidic than the carboxylic acids. Thus, the competition between aminolysis and substitution (equations 606 and 607 respectively) is of



(606)

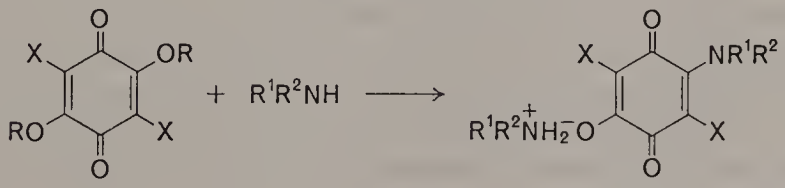
(287)



(607)

(288)

interest[624]. Mixed products (**289**) were also found under appropriate conditions (equation 608). It is especially interesting to note that the two



(608)

(289)

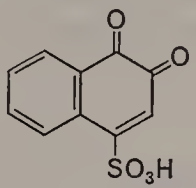
reactions proceed independently; when the salts (**287** or **289**), or the corresponding free acids, were treated with amines under different conditions no conversion to the substitution products (**288**) could be observed.

Both the basicity of the amine and the nature of the ester influence the product distribution. The amines studied showed the following decrease in substitution reaction:

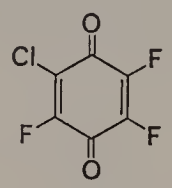
aniline > cyclohexylamine > morpholine > diethylamine

The mixed product **289** was important except with diethylamine where aminolysis was essentially the only reaction with either ester. Except for aniline, higher temperatures tend to favour aminolysis; with aniline only substitution was found. The diacetate of fluoroanilic acid was allowed to react with ammonia and cyclohexylamine in hopes of learning about the ease of substitution of the fluorine atoms. However, only aminolysis was observed.

Two new reagents for the identification of amino acids and protein residues have been introduced (**290** and **291**)[625,626]. It has been found possible to make a classification scheme practical using the substitution chemistry of these quinones.



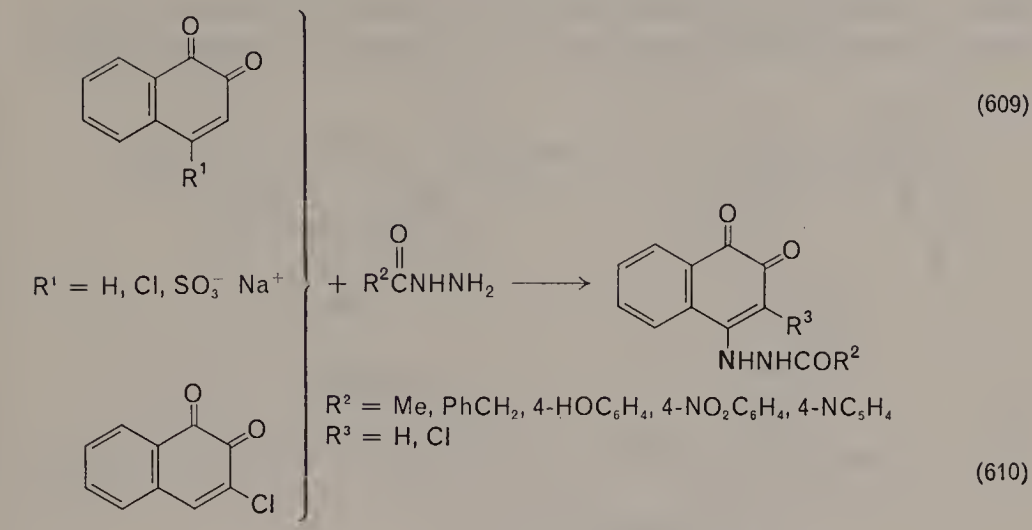
(290)



(291)

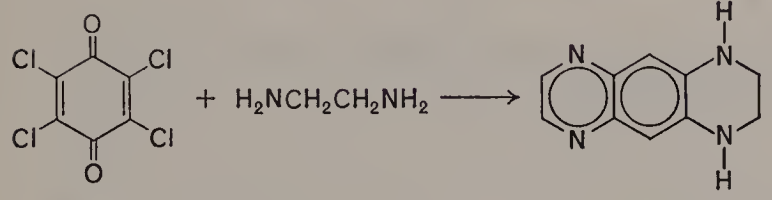
The reactions of a series of acid hydrazides with various naphthoquinones have been reported and the substitution chemistry is informative[627]. With 1,2-naphthoquinones having 4-substituents, substitution takes place; with a 3-substituent, addition takes place (equations 609 and 610). Addition, rather than substitution, is also observed with 2-chloro-1,4-naphthoquinone.

In a study of substitution reactions between molecules containing more than one site for addition and/or substitution, the following interesting observation was made. The reaction of ethylenediamine with chloranil gives a heterocycle that must be the result of a rather complex reaction sequence (**292** in equation 611)[628]. On the other hand, reaction between ethylenediamine and 2,5-dimethoxy-1,4-benzoquinone produces only simple substitution (equation 612). Clearly, there is a great deal to be learned about this 'simple' system. Several other bifunctional amines were studied and the expected reactions (i.e. analogous to equation 612) were found.



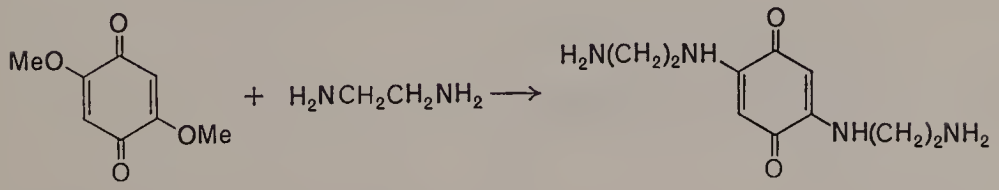
(609)

(610)



(611)

(292)

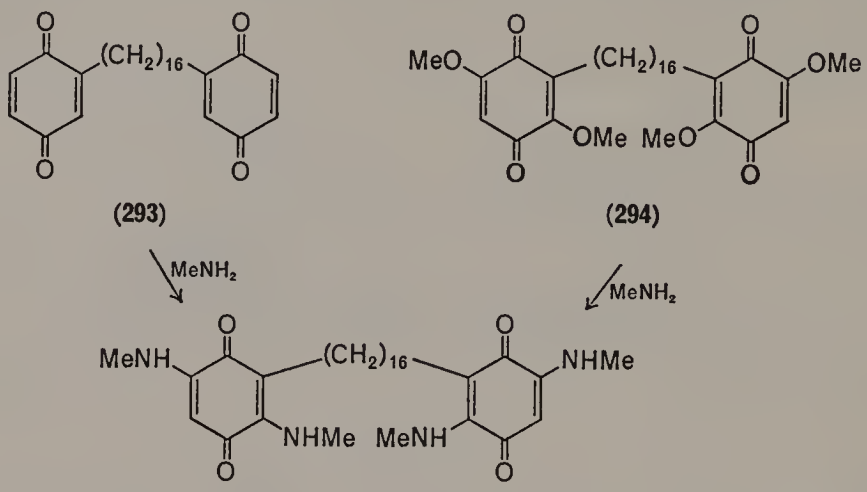


(612)

The substitution of various quinonoid groups by nitrogen continues to be of considerable practical importance. One report of the synthesis of a large number of substituted 1,4-naphthoquinones for growth inhibitory testing includes a fine, brief survey of many of the most useful methods[235]. In addition to the synthesis of potentially useful drugs[629–631] an interesting characterization of a natural product has been reported (equation 613)[632]. The synthetic quinone **293** was obtained by Friedel–Crafts and oxidative reactions. The natural quinone **294** was derived from the isolated natural product by reduction of an alkene and methylation of two hydroxy groups.

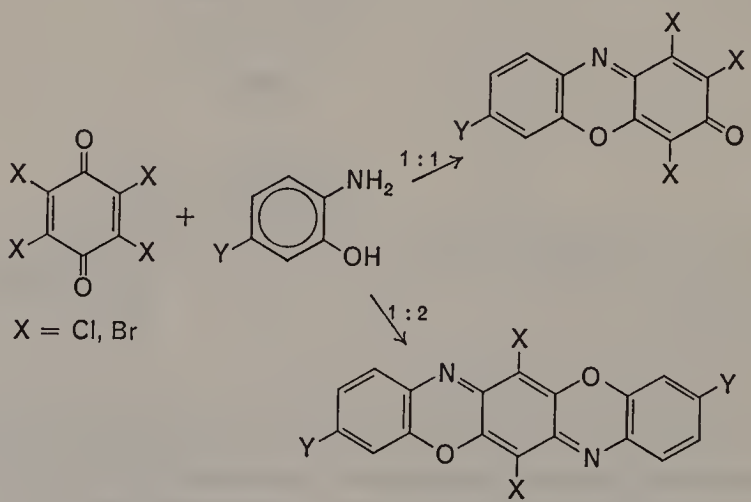
The work of Reynolds and Van Allan with bifunctional aromatics in heterocyclic synthesis[618] has been expanded to the benzoquinone series[633].

When chloranil or bromanil reacts with various 4-substituted *o*-aminophenols, either mono- or diadducts can be obtained by changing reactant



(613)

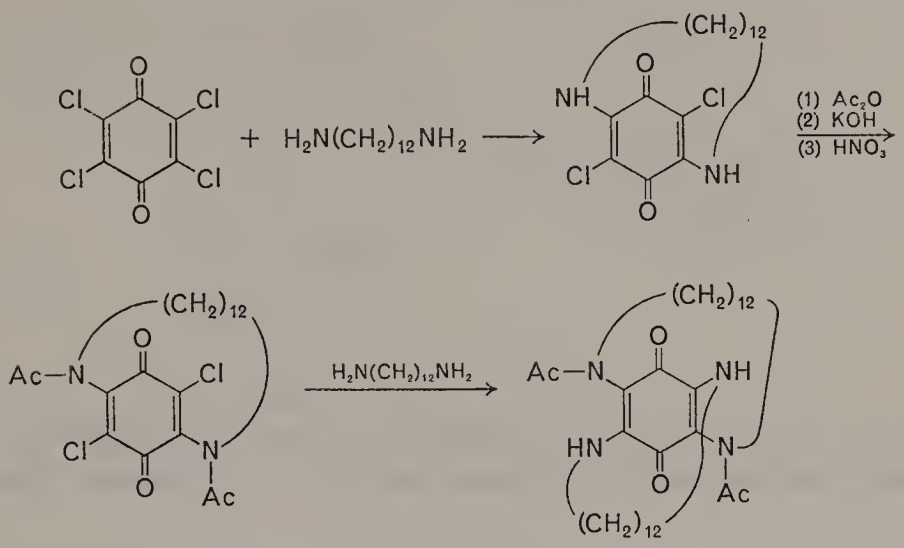
ratios (equations 614 and 615). Similar results were obtained with *o*-aminothiophenol or its zinc salt.



(614)

(615)

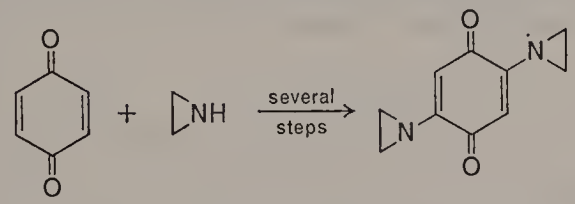
The synthetic problems associated with interlocking rings and related topological considerations have fascinated organic chemists for a long time and very recently quinone substitution chemistry provided an interesting fresh approach[634]. When a single 1,4-benzoquinone has both the 2,5-substituents and the 3,6-substituents locked in rings, the total system is, in fact, a Möbius-strip with one twist. Such a molecule has been prepared (equation 616).



(616)

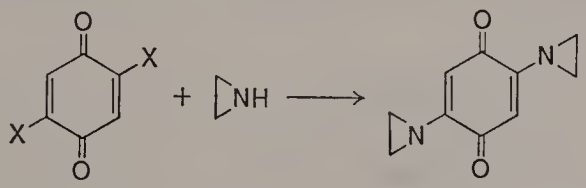
C. Substitution by Ethylenimine

The observation that quinones and hydroquinones bearing ethylenimino substituents are effective cytostatic agents has caused a great deal of synthetic effect in this particular nitrogen substitution area[635–637]. As with other imines, normal Michael addition of ethylenimine followed by oxidation is a useful route to some quinone derivatives (equation 617).



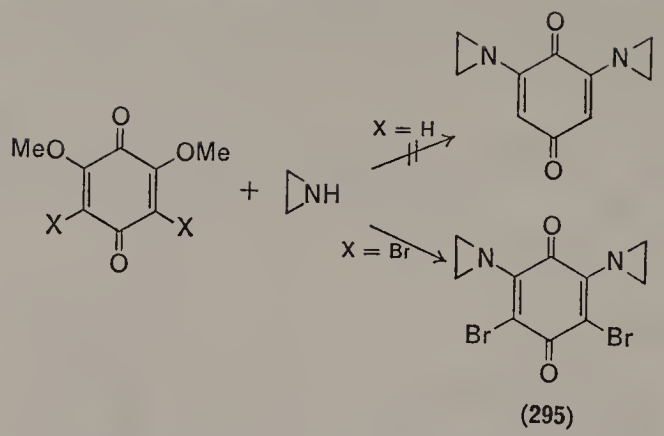
(617)

More often, substitution chemistry, of the type discussed in this section, is the preferred route (equation 618).



(618)

The examples of 2,5-dichloro- and 2,5-dimethoxy-1,4-benzoquinone are interesting in view of a study of 2,6-dimethoxy-1,4-benzoquinone[638]. This *meta* isomer shows no substitution reactivity toward ethylenimine, but its 3,5-dibromo derivative reacts smoothly under the same conditions (equations 619 and 620). The two bromine atoms in **295** can be replaced

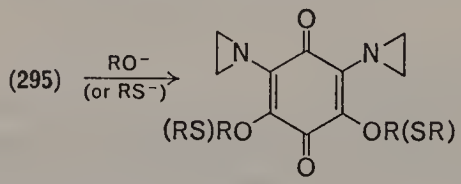


(619)

(620)

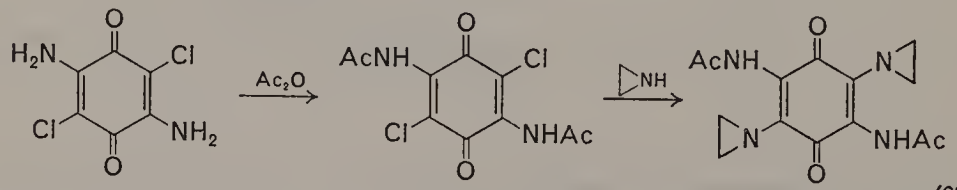
(295)

by alkoxy or thioalkoxy groups (equation 621). A rationalization of this observation on the basis of resonance contributors is presented. It is



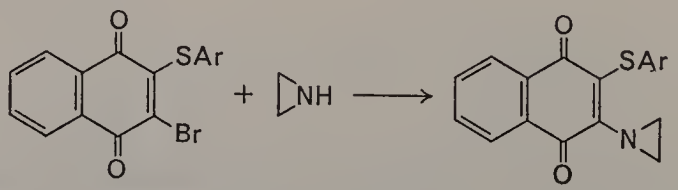
(621)

important to note another experimental observation. In the closely related structure, 2,5-diamino-3,6-dichloro-1,4-benzoquinone, the halogen atoms are unreactive toward nitrogen substitution. This limitation, which we have seen several times before, can be overcome by acetylation (equation 622). The synthesis of quinones with adjacent arylmercapto and



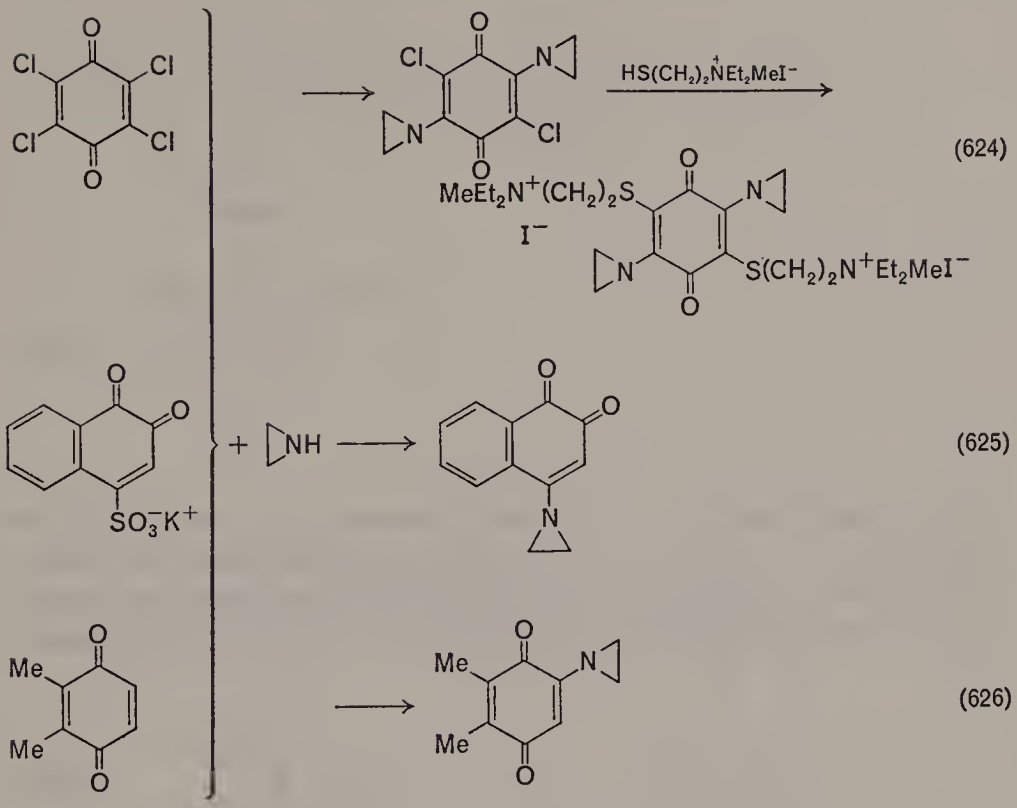
(622)

ethylenimino groups has also been carried out in the 1,4-naphthoquinone series (equation 623)[639].



(623)

Gauss and Petersen have continued to make synthetic contributions in the ethylenimino-substituted quinones[640–642]. A hydrophilic quinone type, derivatives of 1,2-quinones and monoethylenimino 1,4-quinonoid compounds have been prepared (equations 624–626). Satisfactory conditions

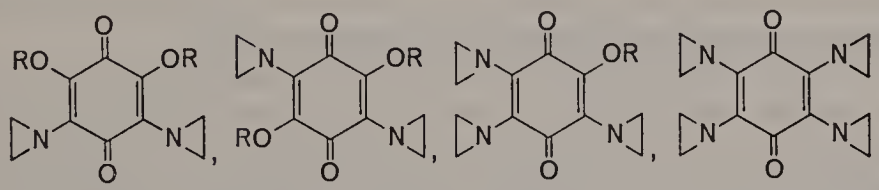


(624)

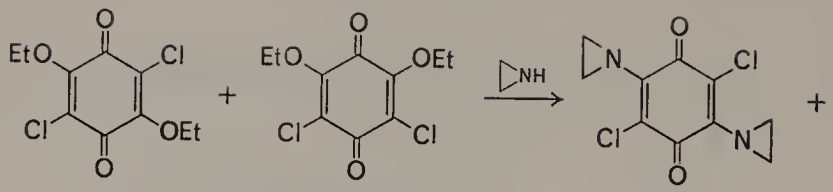
(625)

(626)

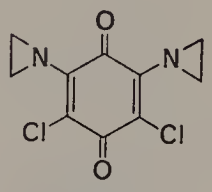
have been found for the selective introduction of ethylenimino groups on alkoxy-substituted 1,4-benzoquinones; for example, the following have been prepared:



Berlin and Makarova, in detailed studies of the preparation and properties of the ethylenimino-substituted 1,4-benzoquinones, have shown that the chemistry possesses a great deal of interesting detail[643]. Both 2,5-diethoxy-3,6-dichloro- and 2,6-diethoxy-3,5-dichloro-1,4-benzoquinones react smoothly with a cold alcohol solution of ethylenimine to yield the corresponding diethylenimino dichloro products. Furthermore, it was found that both products can be prepared conveniently from a mixture of starting materials because of the difference in their solubilities (equation 627). The slightly soluble **296** precipitates first and further cooling provides the somewhat more soluble isomer **297**.

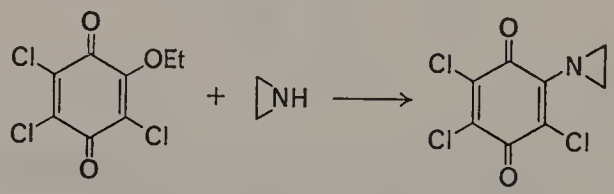


(296)



(297) (627)

In a closely related study these same chemists found a method for the preparation of 2-ethoxy-3,5,6-trichloro-1,4-benzoquinone (see section VIII.D) and through this intermediate one of the limited number of examples of monoethylenimino quinones (equation 628)[644]. Further amine

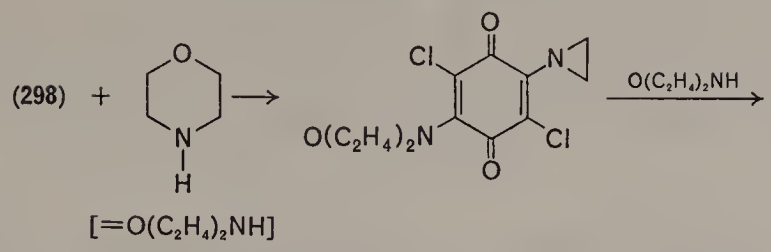


(298) (628)

substitution chemistry is possible with this product (**298**) and a number of unusual quinones can be prepared (e.g. equation 629).

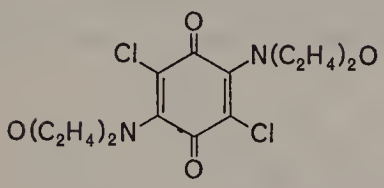
The study of competitive substitution and aminolysis of chloranilic salt esters discussed earlier (see section VIII.B.2) was actually preceded by a related exploration of the reactions of ethylenimine[645]. In the presence of triethylamine, a benzene solution of ethylenimine reacts with either the acetate or benzoate of chloranilic acid to give the bistriethylammonium salt of chloranilic acid; i.e. aminolysis results (equation 630). When triethylamine alone was the reagent, monoaminolysis took place. Mixed product resulted with ethylenimine alone; i.e. both monosubstitution and monoaminolysis were found (equation 631). In all cases the halogen atoms were unaffected and the benzoate was significantly less reactive than the acetate.

Fluoranil is a particularly important synthetic intermediate because the fluorine atoms are quite easily and selectively replaced (see also section VIII.D)[646, 647].

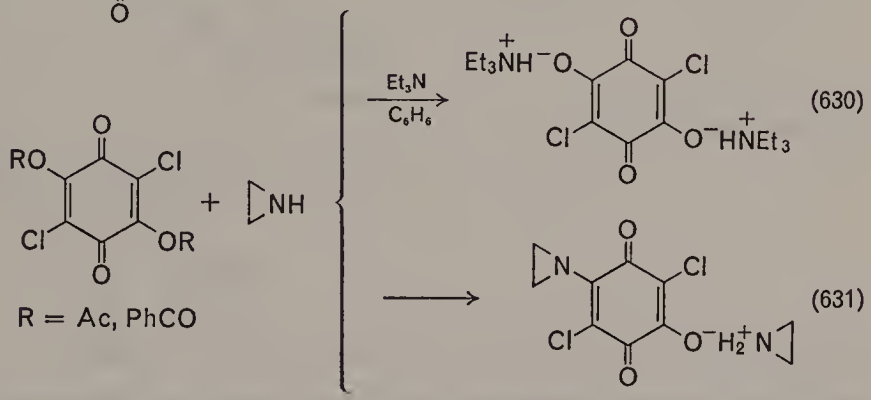


(298)

[=O(C2H4)2NH]



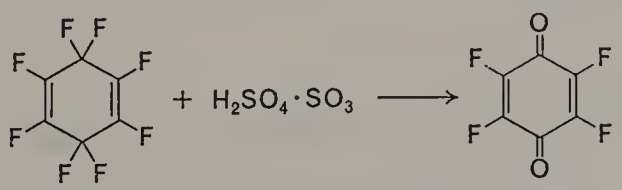
(629)



(630)

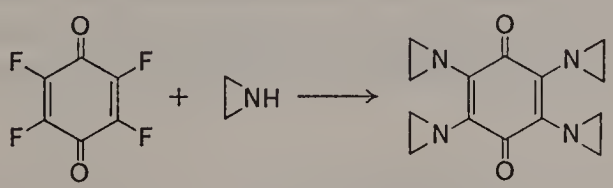
(631)

An interesting preparation of fluoranil has been reported (equation 632)[648]. The problem of obtaining perfluoro-1,4-cyclohexadiene, except



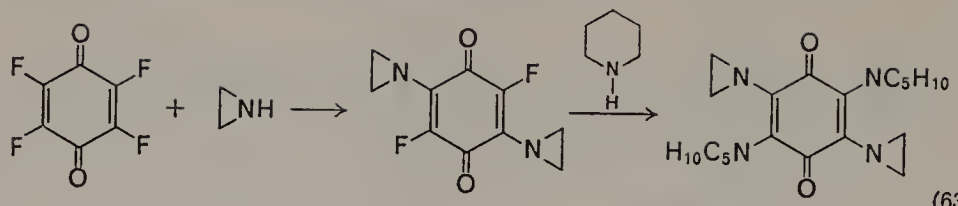
(632)

from fluoranil, may seriously limit the application of this reaction[291]. Unlike most amine substitution reactions, the tetraamino derivatives can be prepared directly from fluoranil (equation 633)[649]. At lower temperatures



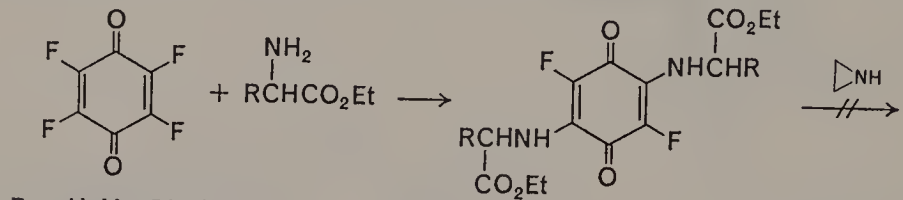
(633)

disubstitution takes place; this reaction can be followed by substitution of another amine (equation 634). In an attempt to obtain analogous compounds containing the esters of α-amino acids, only disubstitution was



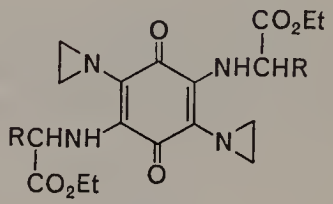
(634)

found and subsequent reaction with ethylenimine does not take place (equation 635). The desired product **299** was obtained, in low yield, by



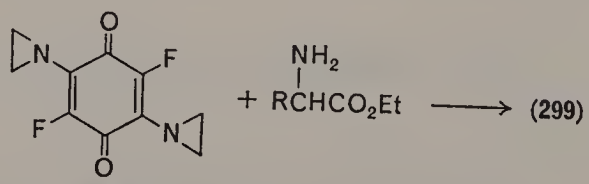
R = H, Me, $PhCH_2$

(635)



(299)

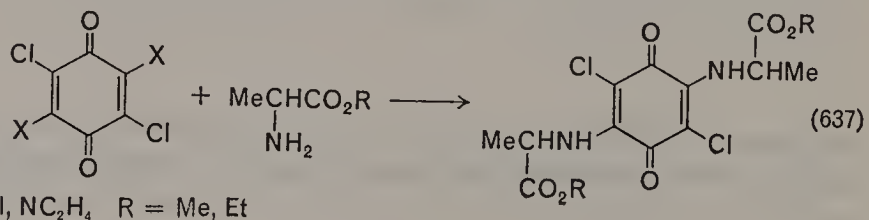
the reverse reaction sequence. The failure of the ethylenimino groups to be opened or displaced is unique and **300** represents the sole direct route to a large class of tetranitrogen-substituted 1,4-benzoquinones (equation 636).



(300)

(636)

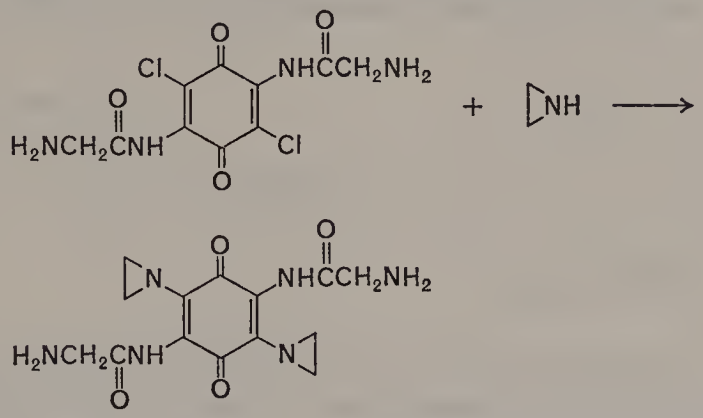
Some earlier studies are related to this discussion. It has been reported that when chlorine atoms or ethylenimino groups are present, they can be displaced by esters of α-amino acids (equation 637)[650]. A supplementary technique for preparing tetranitrogen-substituted 1,4-benzoquinones in



X = Cl, NC_2H_4 R = Me, Et

(637)

which two ethylenimino substituents are included, involves amide formation (equation 638)[651]. The peptide-like character of these compounds

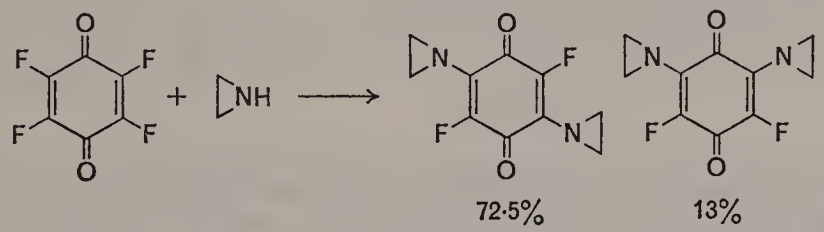


(638)

is apparent (see section II.C.3). A survey of the literature shows the ease of displacement of quinonoid substituents by amines:

$$F > N\langle > OR > OAr > SR > OAc \text{ or } OCPh > Br,Cl$$

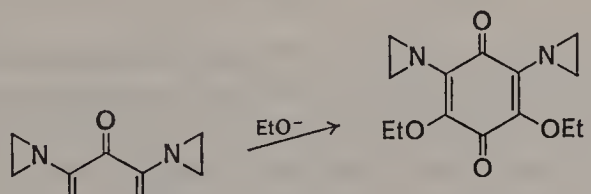
A further useful aspect of the reaction of fluoranil with ethylenimine is the discovery that a small amount of the 2,6-isomer is formed and can be conveniently obtained because of its greater solubility (equation 639)[652].



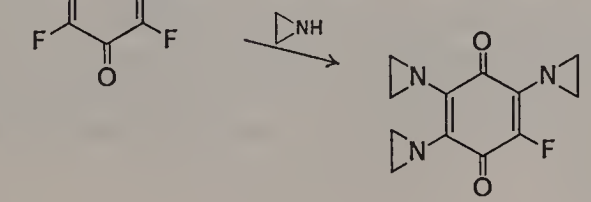
72·5% 13%

(639)

It was also learned that its subsequent reactions proceed much more easily than those of 2,5-diethylenimino-3,6-difluoro-1,4-benzoquinone (equations 640 and 641).

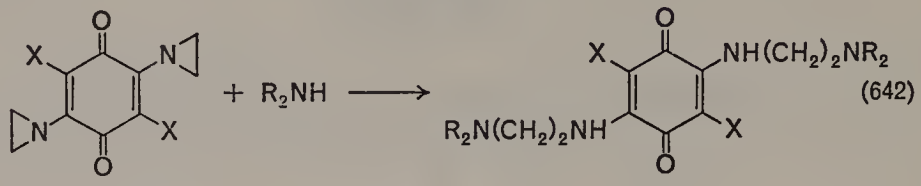


(640)



(641)

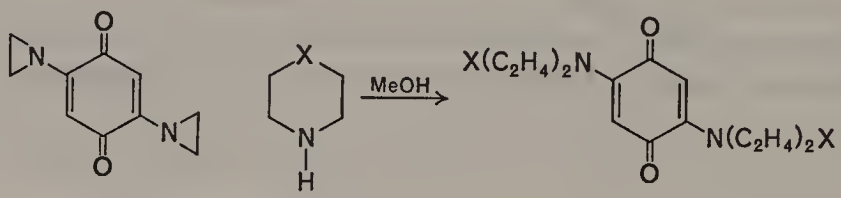
The ethylenimino-substituted quinones themselves have shown some interesting chemistry. In a study of the reactions of such compounds with secondary amines, ring opening was often observed (equation 642)[653].



(642)

X = H, Cl, OEt
R_2 = Me-Ph, Et_2, C_5H_{10}, $(C_2H_4)_2O$

The other substituents attached to the quinonoid ring have an effect on the ease of the reaction. Longer reaction times and poorer yields were found where X = OEt than when X = Cl. This effect can be understood on the basis of the resonance contributors involved. With 2,5-diethylenimino-1,4-benzoquinone, and either piperidine or morpholine in methanol, the alternate path of ethylenimino displacement was found (equation 643).



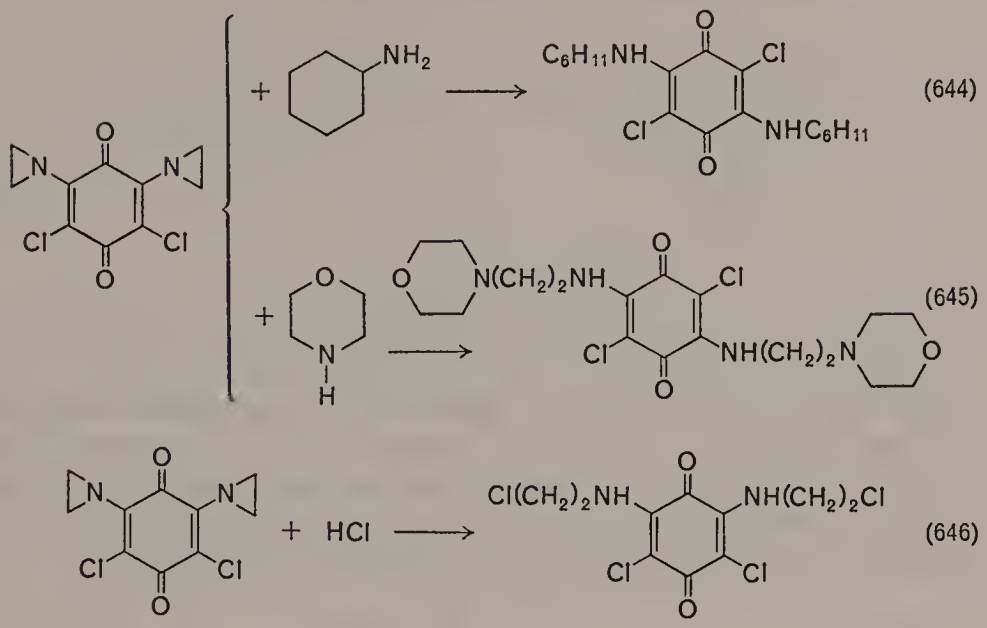
(643)

X = CH_2, O

A similar study was conducted with primary amines and only substitution was observed (often in excellent yield)[654]. Once again, the presence of an ethoxy group on the quinonoid ring led to a less favourable reaction, while chlorine enhanced the reactivity. As would be expected, the basicity of the amine plays an important role in determining the rate of reaction.

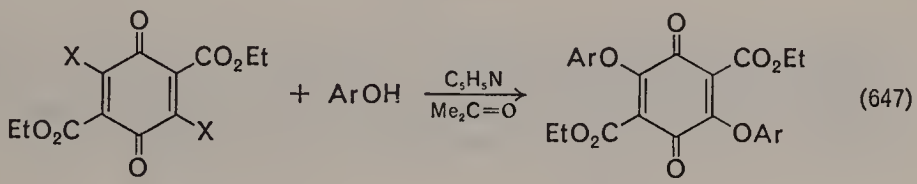
The potential synthetic usefulness of these substitution reactions is clear and an effort to make use of them revealed an interesting rearrangement (equation 644)[643]. The rearrangement even takes place along with ring opening (equation 645). The yields of rearranged products are much lower than in direct preparation from the 2,5-isomer. A complex series of addition–elimination reactions is offered as a possible mechanism.

Finally, it has been shown that hydrochloric acid causes simple ring opening (without rearrangement) to the 2-chloroethylamino derivative (equation 646)[650].



D. Oxygen and Sulphur Substitution of Quinones

The large amount of work that has been expended on the substitution chemistry of quinones by nitrogen should not completely obscure the valuable studies of oxygen and sulphur nucleophiles. An early synthetic effort, the aryloxy displacement of halogen, provided valuable synthetic intermediates (equation 647)[655].

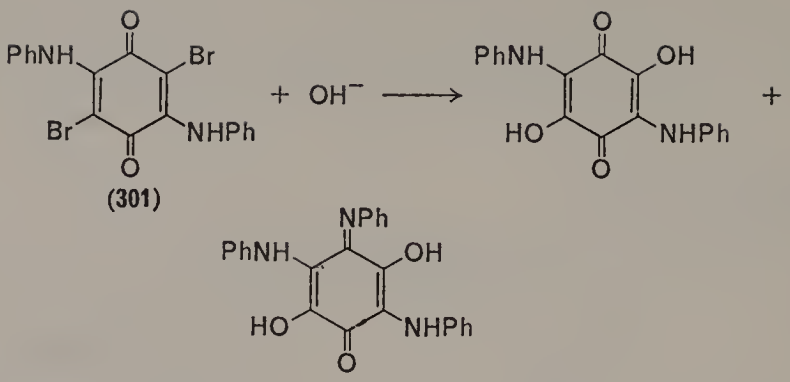


X = Cl, Br

Ar = Ph, 2-, 3- and 4-MeC_6H_4, 2- and 4-$MeOC_6H_4$, 4-ClC_6H_4

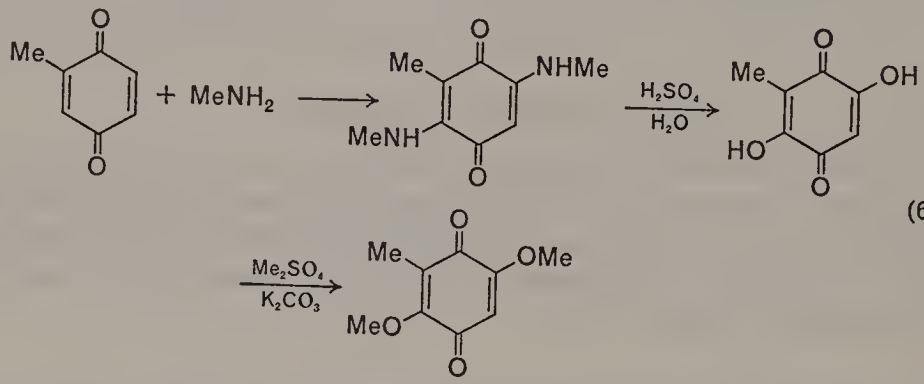
In the process of establishing the structure of a dibromodianilino quinone, its reaction with hydroxide ion led to a somewhat surprising result (equation 648)[656]. None of the expected bromanilic acid was obtained. Furthermore, bromanilic acid was unaffected by either aniline or hydroxide ion. The structure of **301** had been demonstrated earlier by its synthesis from 2,5-diphenoxy-3,6-dibromo-1,4-benzoquinone and aniline[530]. The ease with which quinonoid groups are displaced by hydroxide ion was suggested as:

PhO > Br > NHPh > OH



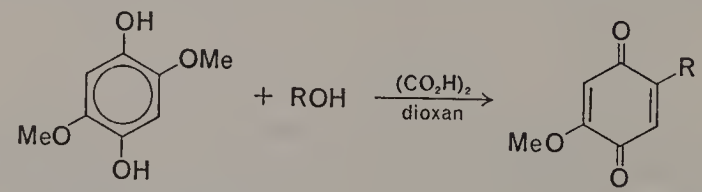
(301) (648)

The preparation of the three dimethoxy-2-methyl-1,4-benzoquinones has been referred to earlier (see sections II.C.1 and II.D.3)[85]. The 3,6-dimethoxy isomer was made using an acid-catalysed hydrolysis (equation 649). Actually this compound had been made by the same method much earlier, but its correct structure was not known[84].



(649)

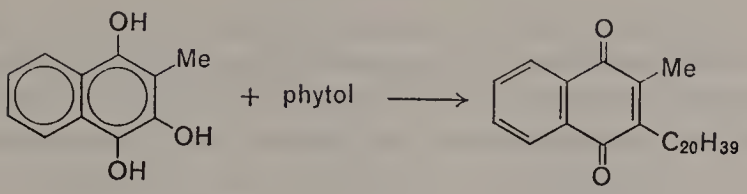
Fieser and Gates discovered an interesting and useful alkylation reaction that involves the displacement of a hydroquinone methoxy substituent and concurrent oxidation (equation 650)[657]. These allylic



(650)

R = phytyl ($C_{20}H_{39}$)
farnesyl ($C_{15}H_{25}$)
geranyl ($C_{10}H_{17}$)
$PhCH{=}CHCH_2$

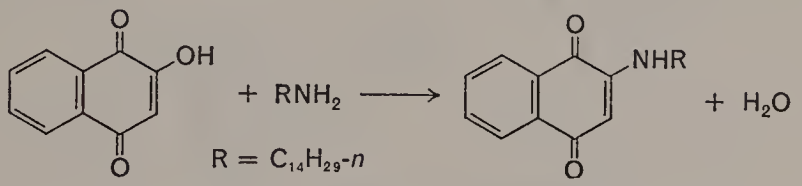
alcohols are capable of replacing a hydroxy group and 1,4-naphthalenediols are also suitable substrates. For example, the reaction of phytol and 2-methyl-1,3,4-naphthalenetriol (phthiocol hydroquinone) constitutes an interesting synthesis of vitamin K_1, (**302** in equation 651).



(651)

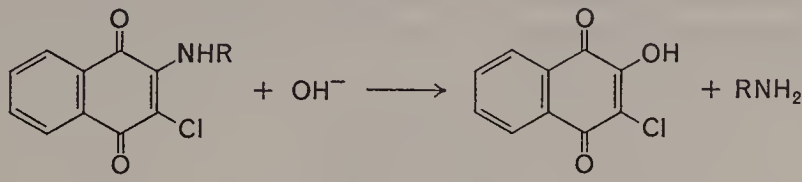
(302)

An interesting bit of oxygen–nitrogen substitution information came out of efforts to prepare naphthoquinone antimalarials of the lawsone type. Attempts to add amines resulted in displacement of hydroxide (equation 652)[335]. An alternate route also failed showing the marked



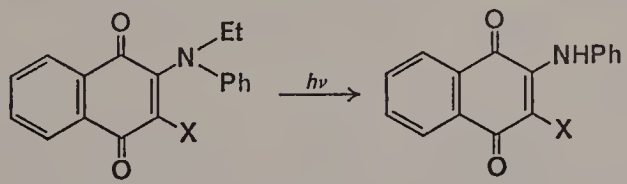
(652)

difference often found between benzo- and naphthoquinones (equation 653).



(653)

The interaction of 2,3-substituents on the 1,4-naphthoquinone ring and its effect on basic hydrolysis has been studied in more detail as the result of an interesting photochemical dealkylation (equation 654)[658]. Treatment



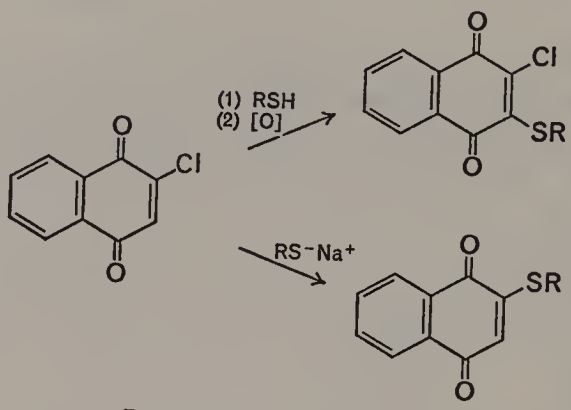
(654)

(303) (304)

X = Cl, Br

of either chloro or bromo **303** with hydroxide results in the smooth displacement of halogen. The simple anilino compounds (**304**) are hydrolysed to 3-halolawsone as reported above for the amine analogues[335]. The *N*-acetyl compounds related to **304** were prepared and showed properties similar to those of the *N*-ethyl derivatives.

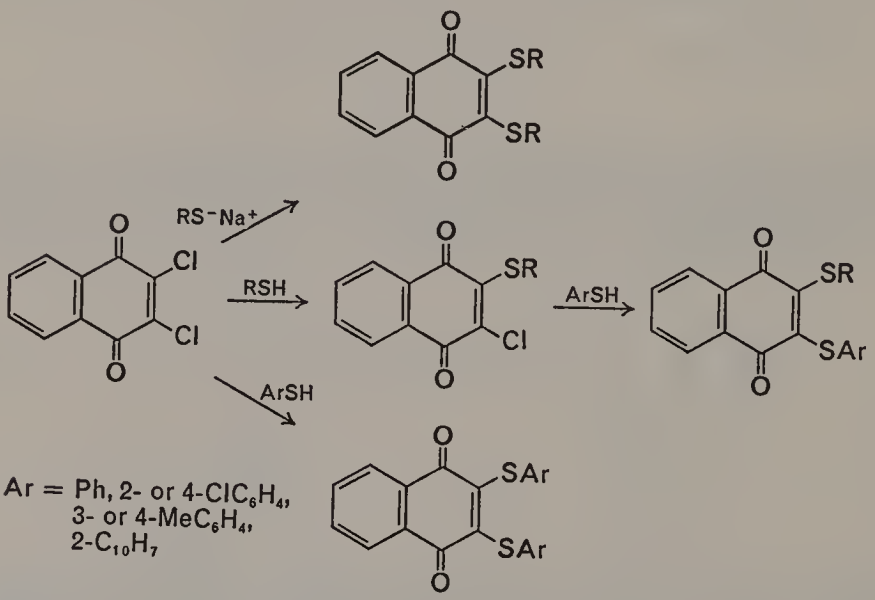
A great many alkyl and aryl mercapto-substituted quinones have been made by addition reaction (see section II.B), but substitution routes are also important. The inhibition of enzymes has played a vital role in motivating this chemistry from the earliest days. Fieser and Brown showed that either addition or substitution can be achieved under the



(655)

(656)

proper conditions (equations 655 and 656)[30]. They also developed useful modifications with 2,3-dichloro-1,4-naphthoquinone (equations 657–659).



(657)

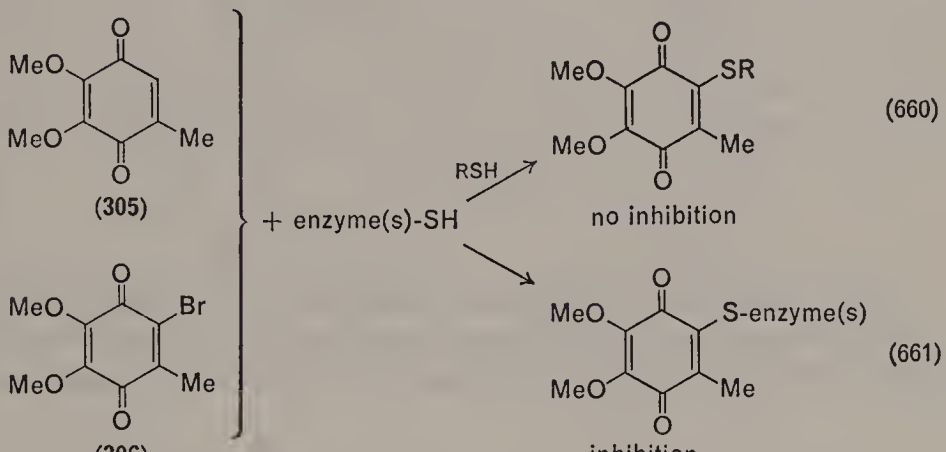
(658)

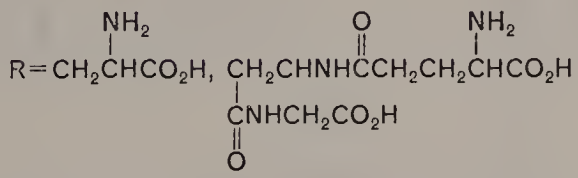
(659)

While these are valuable synthetic methods and appear to be quite general, the yields of symmetrical 2,3-dialkylmercapto-1,4-naphthoquinones are quite low in the examples given. A change of solvent (methanol to benzene–methanol), a reduction of reaction temperature

(refluxing methanol to 15°C) and the potassium salt instead of the sodium salt brought about a marked improvement[659]. Only *n*-propylmercaptide gave a really poor yield (15%), probably because of its low solubility.

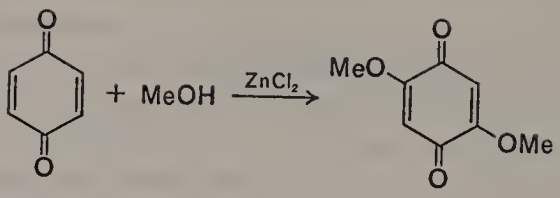
It has been found that two simple 1,4-benzoquinones (**305** and **306**) cause marked inhibition of oxidation and phosphorylation in beef-heart mitochondria[660]. When compounds containing mercapto groups (e.g. cysteine or glutathione) are added to the system, the inhibition can be prevented and at least partly reversed. The suggested cause of both inhibition and protective action is reaction between the quinones and mercapto groups of the enzymes and cysteine or glutathione (equations 660 and 661). The observed spectral changes are also consistent with the reactions shown.





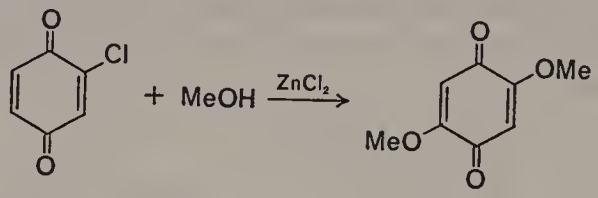
A second and more detailed study dealt with addition reactions of the type associated with quinone **305**[661]. It was shown that heart-muscle enzymes are inhibited by a series of alkyl- and or methoxy-substituted 1,4-benzoquinones. The quinone must have at least one unsubstituted position, not adjacent to a methoxy group, for inhibition to take place. No evidence for methoxy group substitution was reported.

The direct introduction of methoxy groups into a quinone has been accomplished (equations 172 and 662)[180, 214, 215, 662], but both early and later investigators were only partially successful; i.e. 2,5-dimethoxy-1,4-benzoquinone and 2-methyl-5-methoxy-1,4-benzoquinone. In a recent



(662)

attempt to prepare chloromethoxy-1,4-benzoquinones, the following substitution reaction was found (equation 663)[662]. Such compounds have been prepared by base-catalysed displacement of chlorine by methanol (equation 664)[171].



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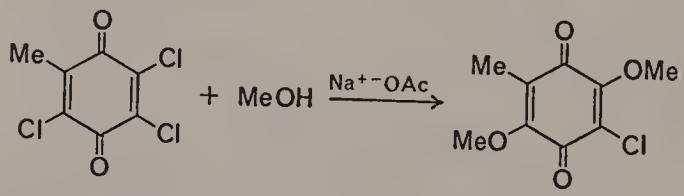
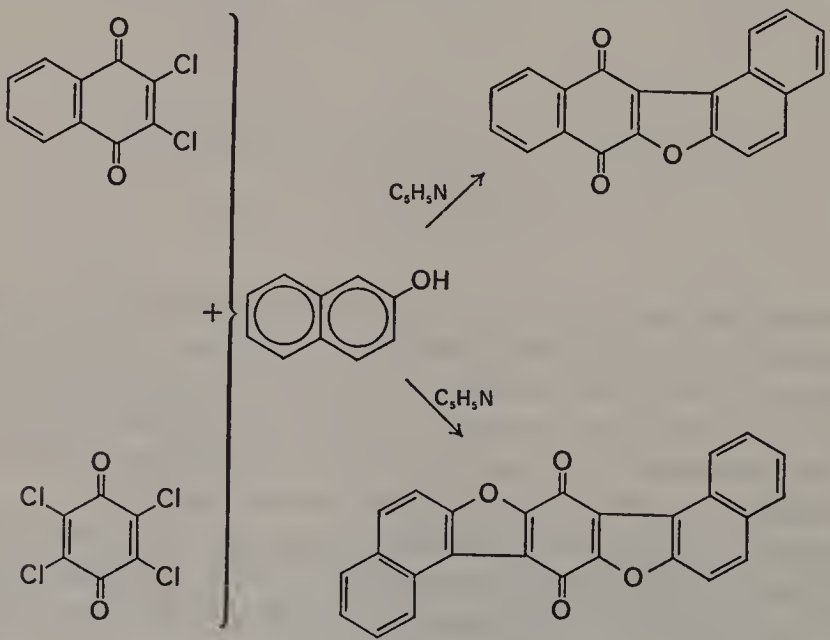


(664)

Certain examples of phenolic condensation with quinones constitute useful routes to polycyclic furans (equations 665 and 666)[663–665]. The evidence for these structures is adequate, as is that for the initial product

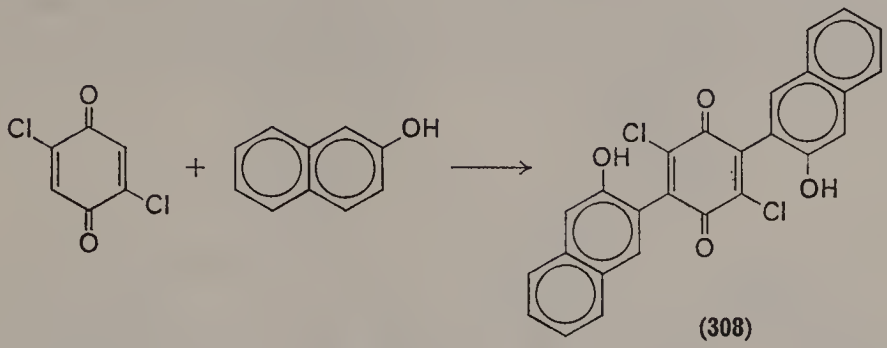


(665)

(666)

(307)

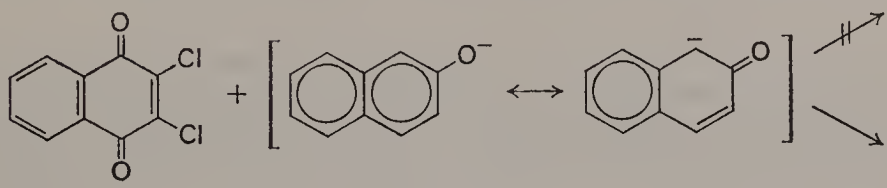
of the condensation of 2-naphthol and 2,5-dichloro-1,4-benzoquinone (**308** in equation 667). The structure of **308** raises some interesting questions



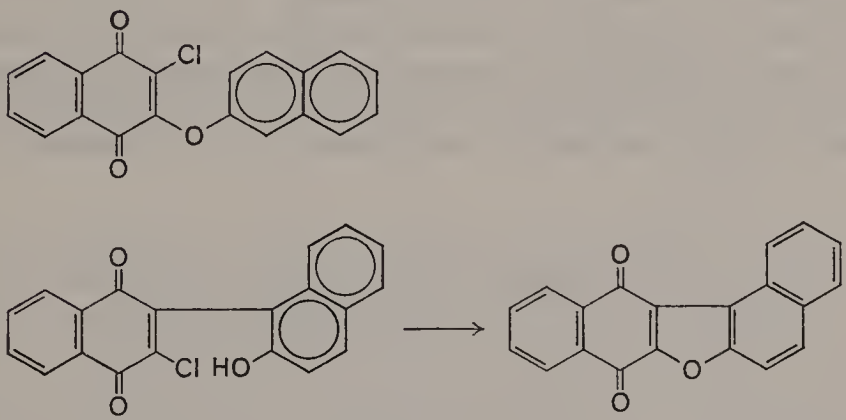
(667)

(308)

about the mechanism of the reaction; a short period of refluxing in pyridine converts **308** to **307**. One proposed intermediate is the ether formed by *O*-alkylation of the naphthol anion (equation 668)[666]; however, the most recent study has shown the presence of an intermediate analogous to **308** (equation 669)[667]. Not only is this pathway consistent with the



(668)

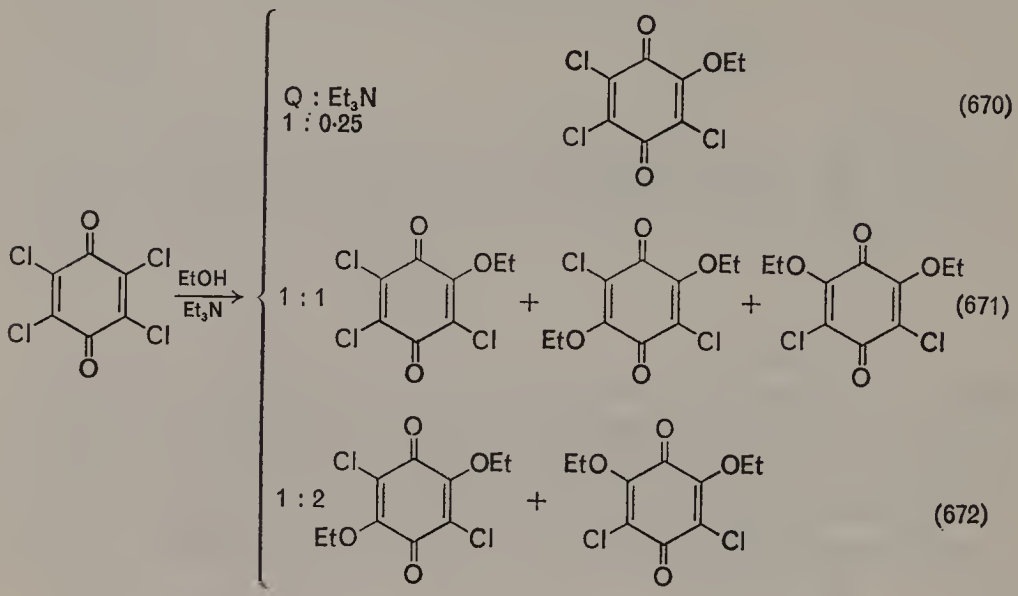


(669)

intermediates found here and in the earlier study[665], but it provides a much more satisfactory explanation of the final cyclization step.

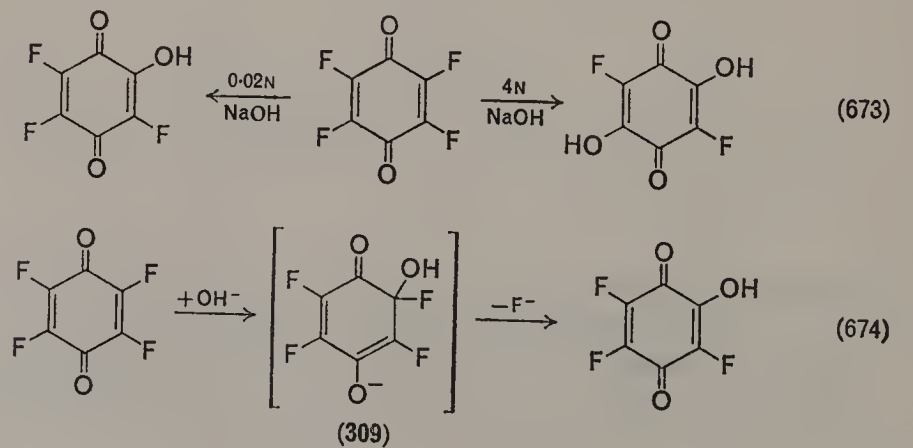
The general interest in the combination of halo and alkoxy substituents on quinonoid rings has produced the following interesting data (equations 670–672)[643]. The two isomeric diethoxy products can be separated quite

efficiently by fractional crystallization and the optimum condition for the preparation of the monoethoxy compound is described[644].



(670) (671) (672)

The utility of fluoranil as a substrate for nitrogen substitution has already been presented (see section VIII.C). The reactions of fluoranil with oxygen nucleophiles are also impressive[668]. A comparison of the four haloanils shows that, with a wide range of nucleophiles, all four fluorine atoms can be replaced; two is the maximum for most combinations of nucleophiles and chlor-, brom- or iodanil. An exception to this generalization is the reaction of fluoranil with hydroxide ion, where either one or two fluorine atoms can be displaced under appropriate conditions (equation 673). The kinetics of the hydrolysis of fluoranil was studied and a simple addition–elimination mechanism proposed (equation 674).

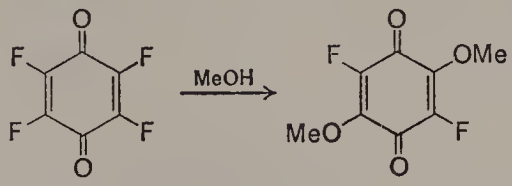


(673) (674)

(309)

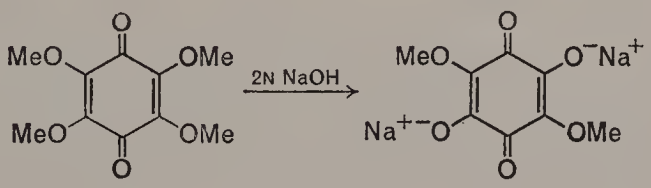
Catalysis by the acetate ion was also observed and explained by a similar pathway.

The nucleophilic substitution of fluorine by methoxide also takes place under mild conditions and in good yield. Simply dissolving fluoranil in methanol results in disubstitution (equation 675). With methoxide ion,



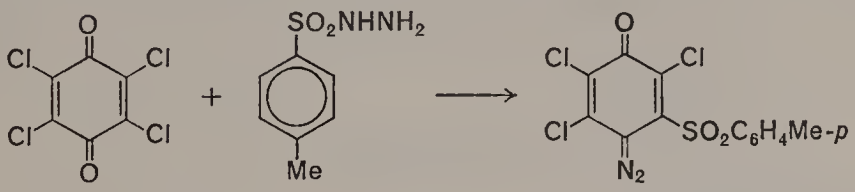
(675)

an excellent yield of tetramethoxy-1,4-benzoquinone is obtained. This last compound reacts very smoothly with hydroxide (equation 676). The reaction of fluoranil with phenoxide ion is very rapid even at low temperatures and produces tetraphenoxy-1,4-benzoquinone[669].



(676)

An interesting, and apparently quite complex, reaction has been reported between halogenated 1,4-benzoquinones and tosylhydrazine (equation 677)[670]. The mechanism of the reaction is not at all clear, but

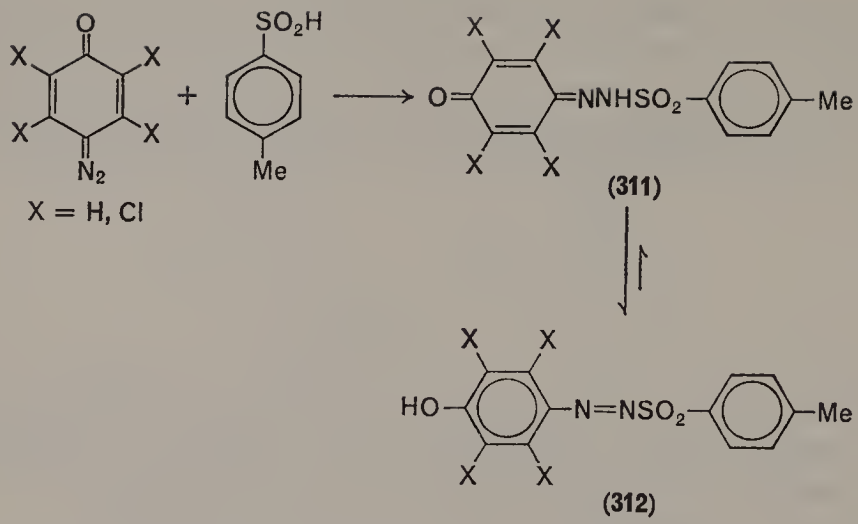


(677)

(310)

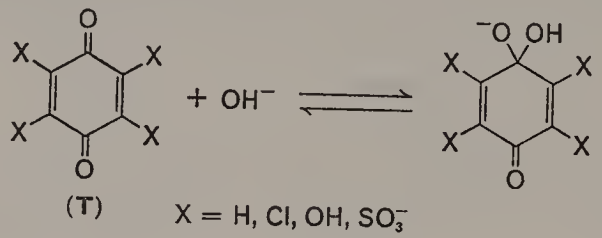
seems to be closely associated with the diazide formation. An attempt to prepare **310** by reaction between the diazide and sulphinic acid produced the hydrazone **311** by addition (equation 678). Several hydrazones were shown to exist chiefly as the sulphonylazophenol tautomer **312**.

The intermediate usually suggested for the nucleophilic substitution of quinones (**309**) appeared to receive some experimental support from a study of the u.v. spectra of chloranil in basic solution[671]. The spectrum of chloranil in ice-cold 2N sodium hydroxide is quite different from that of 2-hydroxy-3,5,6-trichloro-1,4-benzoquinone. This last compound is obtained in a nearly quantitative yield upon cold acidification of the basic solution. This interpretation has been seriously questioned by Bishop



(678)

and Tong[672]. They studied the u.v. spectra of several quinones at very short reaction times as a function of pH. At a given pH, no change in the spectrum could be observed between 12 and 300 ms and acidification completely regenerated the starting material. The reaction was thus described as the reversible 1,2-addition of hydroxide to the carbonyl group (equation 679). The data at various pHs allowed formation constants to be calculated by



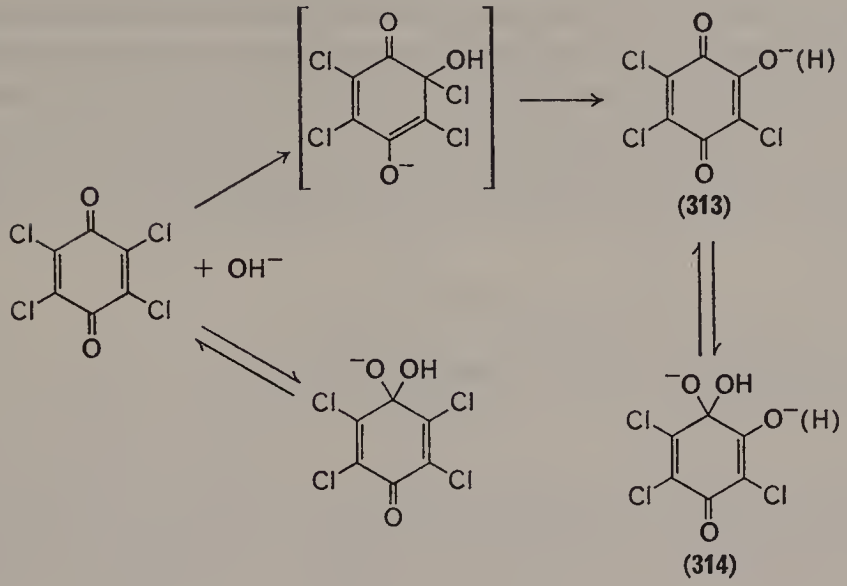
(679)

following formula:

$$K_c = \frac{(\mathbf{T}\cdot OH)}{(\mathbf{T})(OH^-)}$$

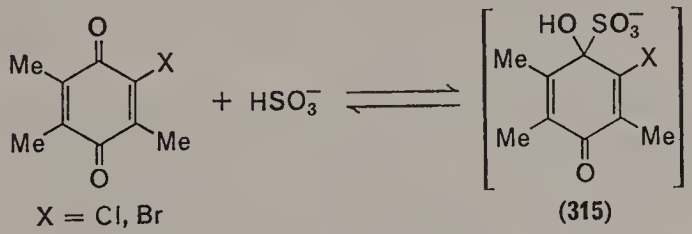
The consistency of the calculated values is an excellent argument for the proposed equilibrium, as is the observed reversibility.

In the case of 2-hydroxy-3,5,6-trichloro-1,4-benzoquinone, Bishop and Tong argued that the product must be formed very rapidly from chloranil and that the observed spectrum is really that of 1,2-carbonyl addition (**314** in equation 680). If this were not the case, their observation, that putting the final product (**313** after acidification) into basic solution produces the same spectrum, would not be possible.



(680)

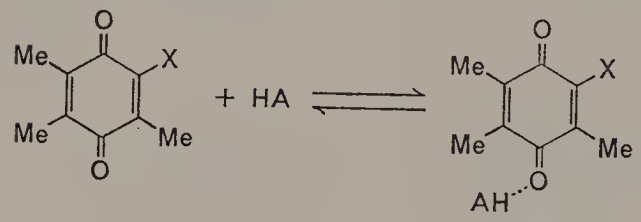
In large measure the above analysis grew from an earlier and more detailed study of the substitution of quinone halides by the sulphite anion[673]. The substrate, 2-halo-3,5,6-trimethyl-1,4-benzoquinone, was chosen so that competing 1,4-addition might be avoided. It happily turned out that the selection also avoided the complication of a redox reaction between quinone and bisulphite. An unexpected complication analogous to that described above with hydroxide was found; i.e. 1,2-carbonyl addition (equation 681). The α-hydroxysulphonate (**315**) was not isolated



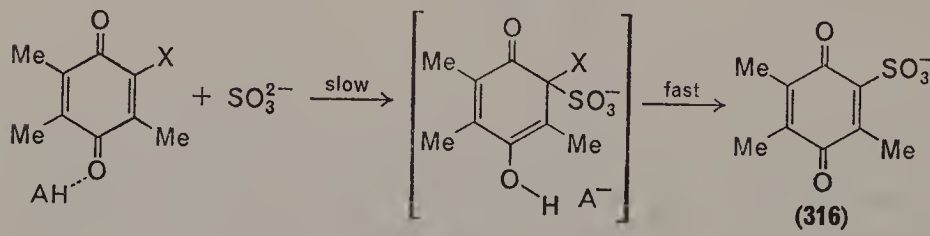
(681)

in a form pure enough for rigorous structure determination, but the u.v. spectrum is quite suggestive. For example, similar spectra were obtained with duroquinone and 3,5,6-trimethyl-1,4-benzoquinone where substitution does not take place. The complete reversibility of the reactions and the favourable comparison with formation constants for aldehydes and ketones argue for structure **315**. These equilibria must be taken into account in kinetic studies of the substitution reactions, except in the case of 2-iodo-3,5,6-trimethyl-1,4-benzoquinone. In this instance the rate of disappearance of quinone is equal to the rate of release of iodide. The observation requires

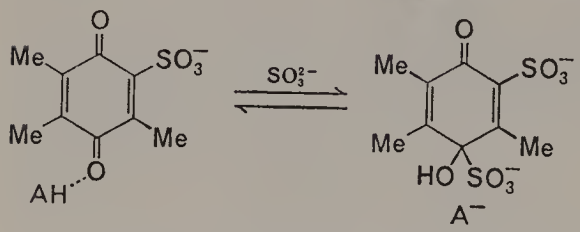
either that the rate of substitution is much faster than the rate of adduct formation or that the equilibrium lies far to the quinone carbonyl side. The interpretation of the kinetic data shows that both adduct formation and substitution are general-acid-catalysed. The proposed mechanism is the addition–elimination typical of many carbonyl reactions (equations 682–684). The product **316** also forms a bisulphite adduct by 1,2-addition



(682)



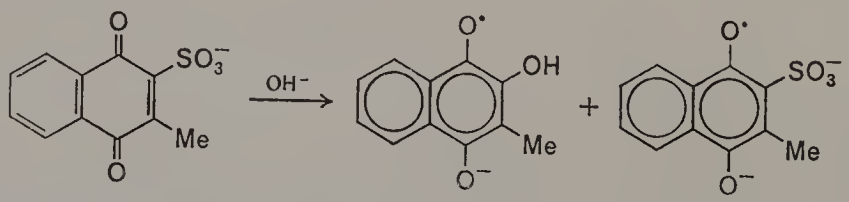
(683)



(684)

to the carbonyl group. All three quinones (2-iodo, 2-bromo and 2-chloro) gave the same product and a crude sample showed $-SO_3^-Na^+$ in the i.r. Thus, it was assumed to be **316**.

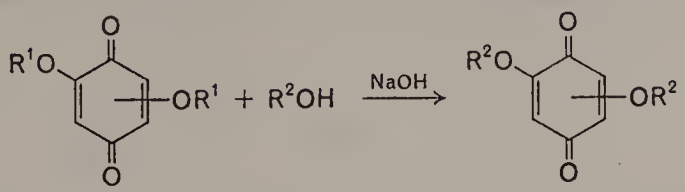
The rate of semiquinone ion radical formation with the haloanils and iodide ion has been studied[674]. The reaction is first-order in quinone and second-order in iodide. The reaction rate varies in the following order: F > Cl > Br > I. In another nucleophilic substitution reaction, evidence has been presented that the displacement takes place on the ion radical (equation 685)[675].



(685)

Yet another study reported a series of e.s.r. spectra of quinones in alcohol or dimethyl sulphoxide solutions[676]. There was no doubt from the

spectra that rapid exchange of alkoxy groups occurs in alcoholic solution (equation 686) and this conclusion was supported by product isolation.

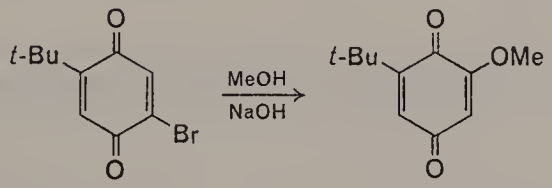


(686)

R^1, R^2 = Me, Et, *n*-Pr, *i*-Pr

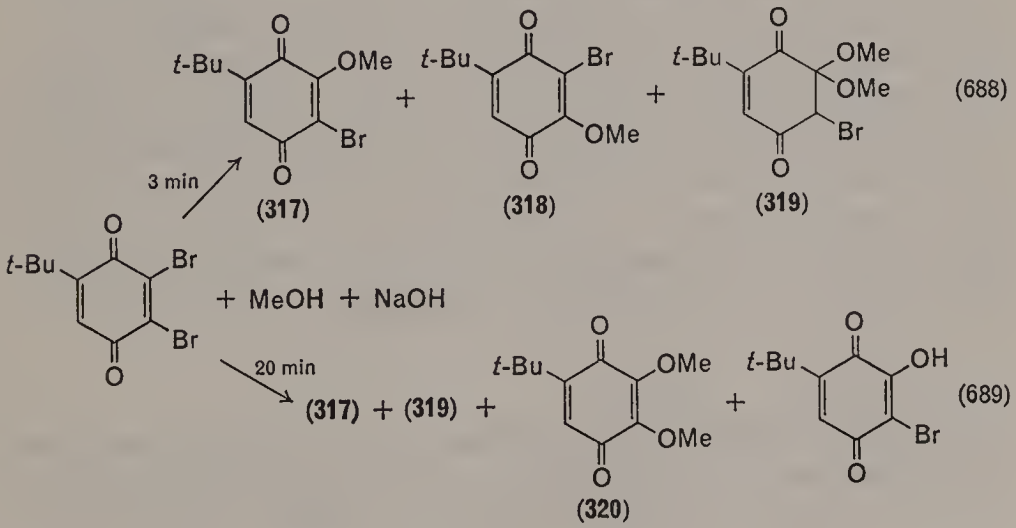
The e.s.r. signal arises from the subsequent reduction of the quinone to the semiquinone. Evidence is presented for a two-equivalent reduction involving hydride transfer.

The extension of this study to halogen displacement demonstrated an interesting rearrangement reaction (equation 687). With 3-bromo-5-*t*-butyl-1,4-benzoquinone a mixture of rearranged and normal substitution



(687)

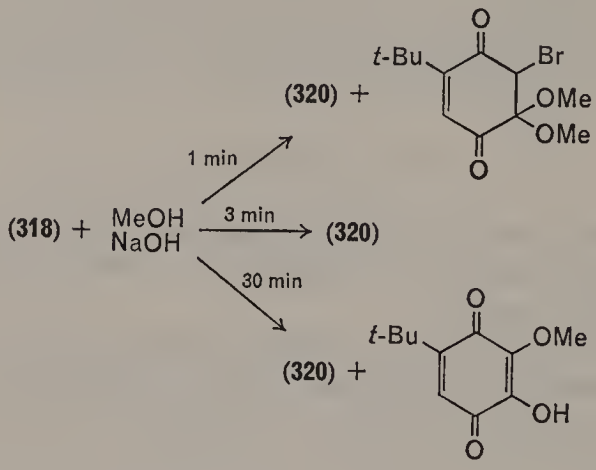
product (2:1) was obtained. The mechanism of the rearrangement was investigated in the quinone 2,3-dibromo-5-*t*-butyl-1,4-benzoquinone. Strong evidence was obtained for a variety of products and intermediates at different reaction times (equations 688 and 689). It was also shown that



(688)

(689)

318 is converted to **320**. These experiments also produced useful intermediates for mechanistic speculation (equations 690–692). These observations seem best explained by the establishment of equilibria (equation

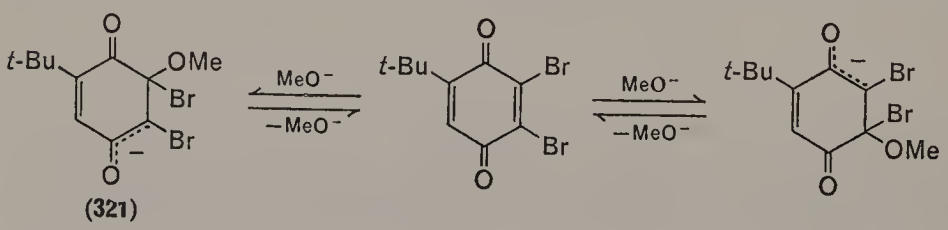


(690)

(691)

(692)

693) and preferential solvation of **321**. The structures of these intermediates and products were satisfactorily established. The importance of solvation

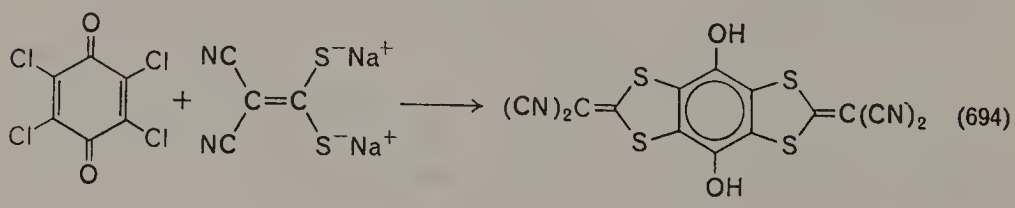


(693)

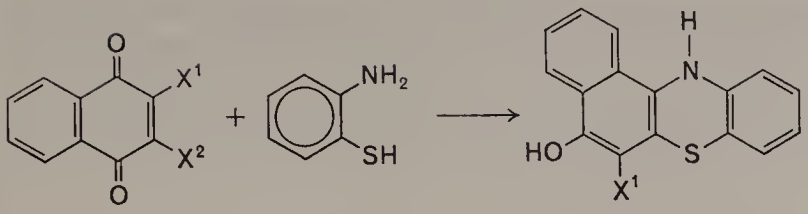
was demonstrated by adding dimethyl sulphoxide and observing the shift from mostly C-3 attack (methanol) to C-2 attack (DMSO).

Two recent reports of heterocyclic syntheses by quinonoid addition also contain useful substitution chemistry (equations 694 and 695)[48,49].

The lignin found in hardwood is known to be paramagnetic and 2,6-dimethoxy-1,4-benzoquinone appears to be the structural precursor of the paramagnetic species[677]. A combination of e.s.r. and u.v. spectra of basic solutions of this quinone showed that the semiquinone radical is formed in quite high concentration. Preceding the observation of the e.s.r.



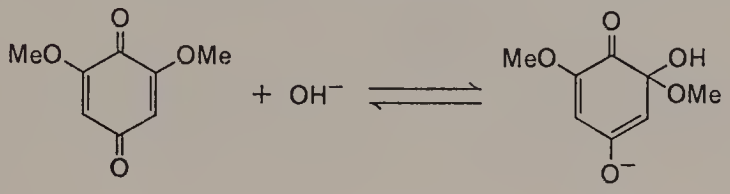
(694)



(695)

X^1 = Cl, MeO, Me, NHAc
X^2 = H, Cl

signal, an equilibrium between the quinone and base is rapidly established (equation 696). The proposed mechanistic path for subsequent conversion



(696)

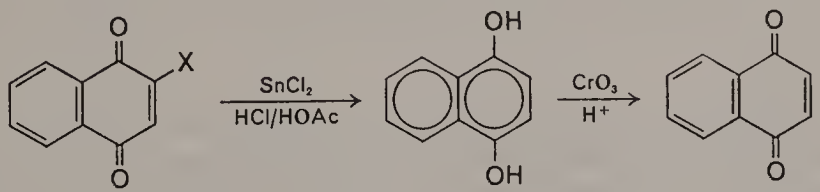
(322)

to semiquinone and substitution product is essentially that of Eigen and Matthies (see section II.F.1)[221], except that the conversion of **322** to product is the rate-determining step. This situation is not unexpected since **322** cannot enolize rapidly as could the unsubstituted 1,4-benzoquinone studied earlier.

E. Other Substitution Reactions

A few reports of significant experiments are found that do not fit any of the major areas of interest within quinone substitution chemistry.

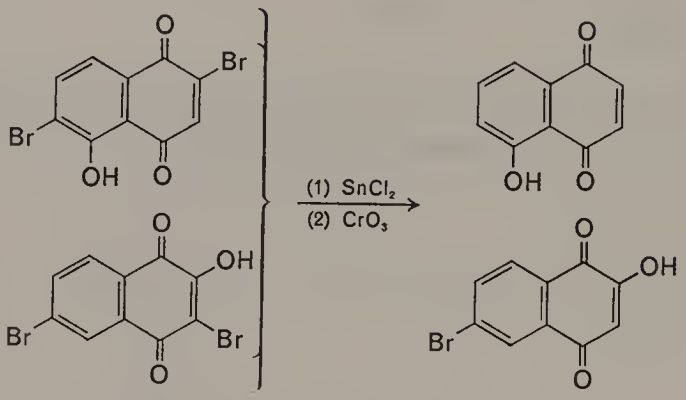
For example, Bruce and Thomson have evaluated the range of substituents that can be removed directly from 1,4-naphthoquinones[678]. The general method involves reductive elimination of the substituent with acidic stannous chloride followed by chromic acid reoxidation (equation 697). The intermediate, 1,4-naphthalenediol, was usually not isolated.



(697)

The following groups were removed in fair to excellent yield: Cl, Br, NHPh, SR, SAr, SO_2Ar, SO_3H. Hydroxy groups were removed in some cases, although in poor yield. Hydriodic acid was also used for the direct

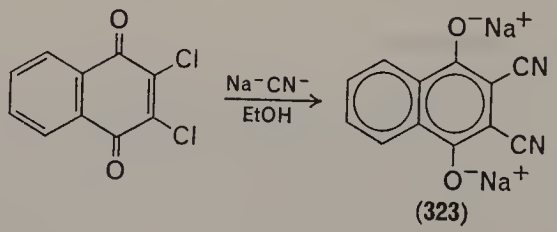
elimination of halogen. This reagent appears satisfactory for 2-alkyl-3-halo-1,4-naphthoquinones, but in the other cases the two-step process gave superior yields. One interesting observation is that halogen in the benzenoid ring is also removed if that ring is phenolic (equations 698 and 699).



(698)

(699)

In view of the very extensive studies of 2,3-dichloro-1,4-naphthoquinone substitution chemistry that have been reported, Reynolds and Van Allan were surprised to find in 1964 that cyanide had been neglected[679]. What would appear to be a very simple substitution reaction, in fact turns out to be quite complicated (equation 700). It seemed most reasonable that



(700)

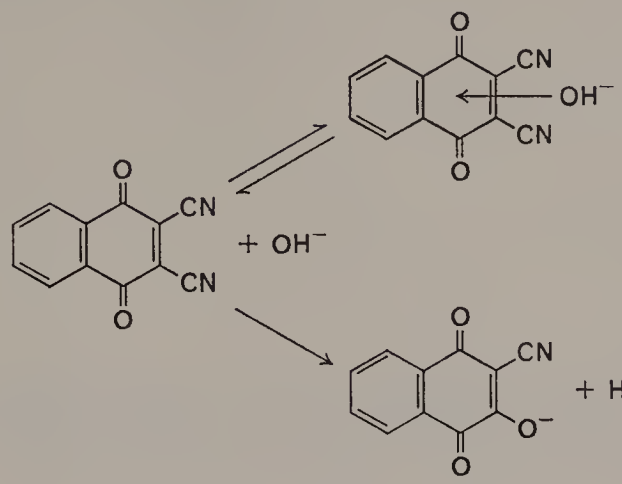
(323)

the direct substitution product was reduced by cyanide, and when 2,3-dicyano-1,4-naphthoquinone was treated with aqueous sodium cyanide it went into solution immediately as **323**. The quinone acts as a strong π-acid and also undergoes substitution by hydroxide (equations 701 and 702).

The reactions of 2,3-dipiperidino-1,4-naphthoquinone with dry hydrogen halides have been reported[680]. In one case the hydrogen bromide salt was isolated and is assumed to be an intermediate in the other reactions (equation 703).

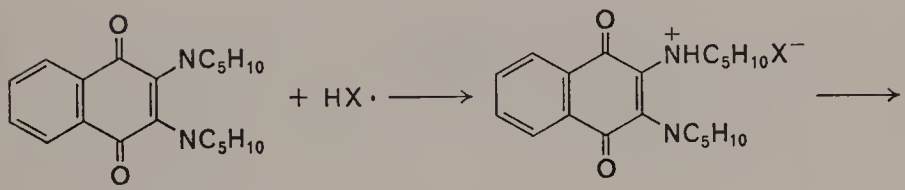
A synthetically useful dealkylation reaction has been found in the combination of halodi-*t*-butyl-1,4-benzoquinones and anhydrous

hydrohalogen acids (equation 704)[681]. An analogous reaction occurs with 3-chloro-2,6-di-*t*-butyl-1,4-benzoquinone.



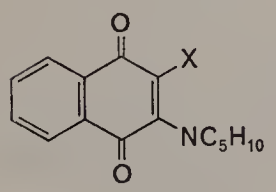
(701)

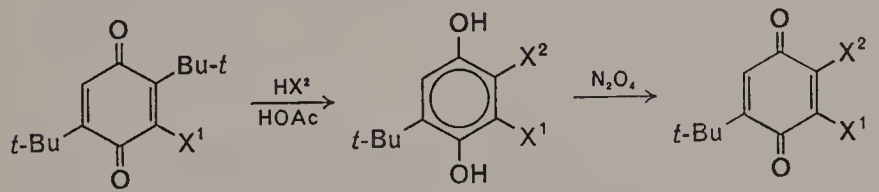
(702)



X = F, Cl, Br

(703)

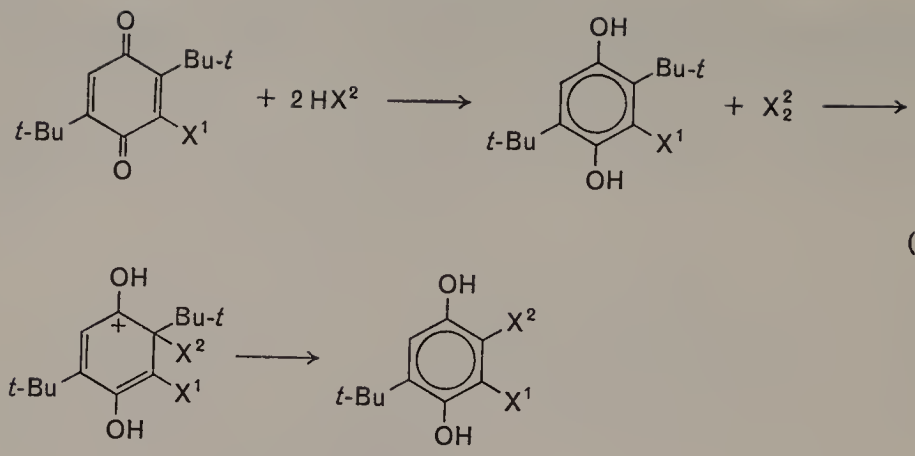




(704)

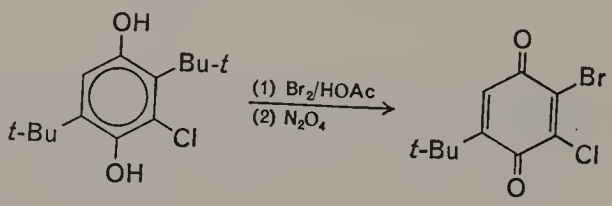
X¹, X² = Cl, Br

The mechanism suggested as accounting for the dealkylation consists of an initial redox reaction followed by electrophilic substitution (equation 705). In support of this proposal it was found that with excess cyclohexene present an excellent yield of 1,2-dibromocyclohexane is obtained; thus supporting the first step. The second step was tested by allowing



(705)

3-chloro-2,5-di-*t*-butylhydroquinone to react with bromine in acetic acid. After treatment with nitrogen oxide, 2-bromo-3-chloro-5-*t*-butyl-1,4-benzoquinone was obtained in high yield (equation 706).



(706)

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CHAPTER 18

Quinone methides

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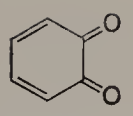
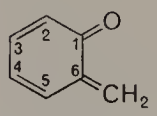
I. INTRODUCTION

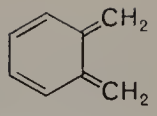
The name quinone methide is derived from a structural analogy between this class of compound and the quinones. If one oxygen atom of a quinone is replaced by a methylene group, a quinone methide results; such compounds have also been called quinomethanes[1], methylenequinones and quinomethines. If both oxygen atoms of a quinone are replaced by methylene groups, the so-called quinodimethanes result[2,3]; in this case the name quinone dimethide, analogous to quinone methine, has not become popular[2]. Quinone methides are listed as cyclohexadiene derivatives in the Subject Index of *Chemical Abstracts*.



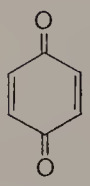
o-Benzoquinone



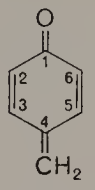
o-Benzoquinone methide (6-methylene-2,4-cyclohexadien-1-one)



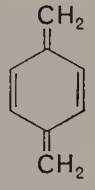
o-Benzoquinodimethane



p-Benzoquinone

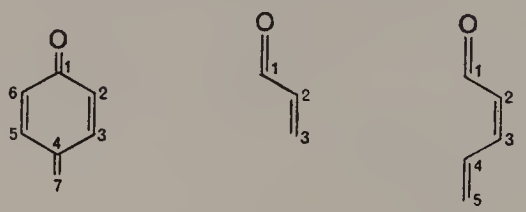


p-Benzoquinone methide (4-methylene-2,5-cyclohexadien-1-one)

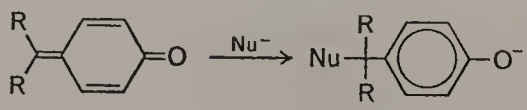


p-Benzoquinodimethane

Being vinylogous carbonyl systems, quinone methides should be compared with α,β-unsaturated ketones and with ketones having longer conjugated groups.



Such compounds behave as ambifunctional electrophilic reagents: in addition to the usual electrophilic reactivity of the carbonyl group, the conjugated centre 3, 5 or 7 can enter into reaction as in the Michael reaction. A special situation arises with the quinone methides from the transition of the quinonoid to a benzenoid system on addition of a nucleophile at C-7. This carries with it a large gain in energy owing to the



aromatic structure of the product; examples of this favoured mode of reaction are given in the section on reactions of quinone methides. All other modes of addition are disfavoured in comparison with this type.

Quinone methides assume a position between quinones and quinodimethanes. The similarities and differences arising from the analogous topologies can be seen in the HMO description. Figure 1 shows the

FIGURE 1. Energy levels and occupation of the Hückel molecular orbitals for three *p*-quinonoid π-systems (heteroparameters $\alpha_O = \alpha_C + 1{\cdot}0\beta_{CC}$, $\beta_{CO} = \beta_{CC}$). The numerals are the eigen values x_i in the expression $\varepsilon_i = \alpha + x_i\beta$ of the corresponding MO with index i.

π-molecular orbitals for *p*-quinonoid systems. The lowest unoccupied molecular orbital (LUMO) of *p*-benzoquinone lies at a particularly low level and indicates well-developed reactivity of this molecule as an electrophile, and the LUMO is also relatively low for the quinone methide. According to Fukui[4] the electron distribution in the extreme orbitals is determinant for a comparison of kinetic reactivity. Figure 2 shows, on

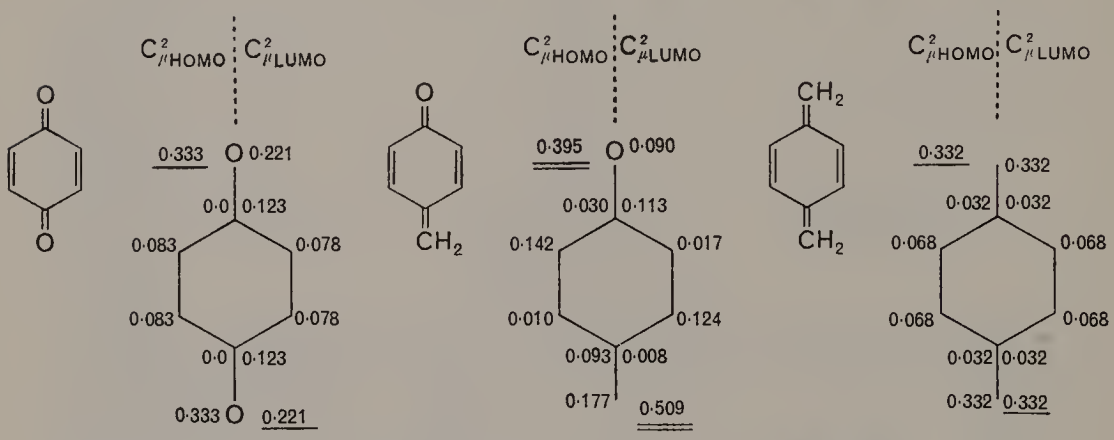


FIGURE 2. Squared coefficients C^2 at the centre μ in the highest occupied molecular orbital (HOMO), figures to the left of the atomic centre) and in the lowest unoccupied molecular orbital (LUMO, figures to the right of the atomic centre). Particularly large values are underlined.

the right of the atoms, the squared coefficients of the LUMOs of the three quinonoid systems. Quinone methide, placed in the middle, shows an exceptionally high value at the *exo*-carbon atom of the methylene group, so this centre is characterized by particularly high electrophilicity and, as the reactions described in section XI will show, quinone methides are susceptible to attack by nucleophilic reagents.

The electron distribution in the highest occupied molecular orbital (HOMO) is determinant for the nucleophilic reactivity of the quinonoid systems. Figure 2 shows the squared coefficients of the HOMOs to the left of the atoms; here too the quinone methide system shows a particularly high value, so that the oxygen atom of quinone methides should be readily attacked by electrophiles.

The π-charge distribution shown in Figure 3, according to HMO, indicates that in the quinone methide system the attack of an electrophile is supported by the negative charge on the oxygen atom, and the same is true for the attraction of a nucleophile by the positively charged *exo*-carbon atom of the quinone methide. In the quinone the attack of an

electrophile is favoured only by coulombic attraction, and in the non-polarized quinodimethane there is no control of the attacking reagents by charge interaction.

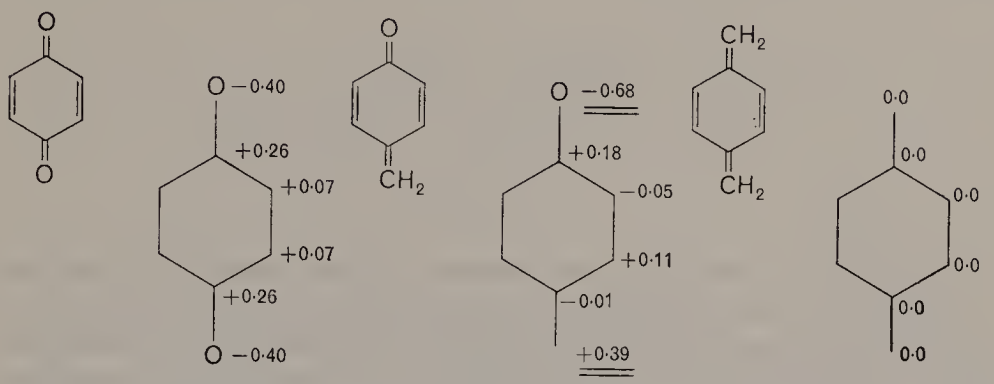
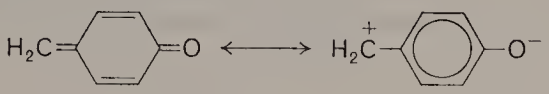
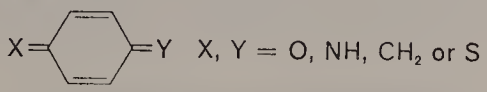


FIGURE 3. Distribution of the effective charge in the π-systems of three *p*-quinonoid systems according to the HMO model (cf. Figure 1).

The quinone methides thus assume a special position. There, high reactivity towards electrophiles as well as towards nucleophiles is displayed in high electron densities in the limiting orbitals and also in suitable polarization corresponding to the formulation of the two most important valence-bond resonance structures[5,6].



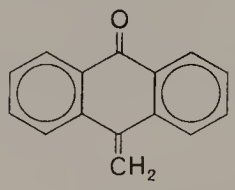
The reactivity of quinonoid systems is further influenced by the interchange between the initial quinonoid structure and the possible benzenoid structure of transition states or end products. In Coppinger and Bauer's calculations[7] the relative stabilities of *p*-quinonoid systems (**1**) are defined as the difference between the quinonoid ground state and a benzenoid transition state; they find that the stability increases with increasing electronegativity of X and Y.



(**1**)

The reactivity of unsubstituted quinone methides is generally so high that they cannot be isolated under normal conditions: in the absence of a compound with which they can react the molecules react with one another, forming dimers, trimers and polymers. These reactions will be described in section 12.

The quinone methide can, however, be isolated if the benzenoid character of the ring in the quinonoid system is weak, as, for example, in the methyleneanthrone (2)[8].

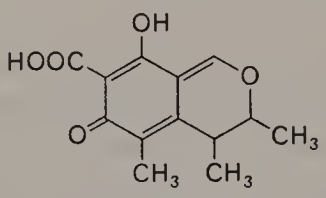


(2)

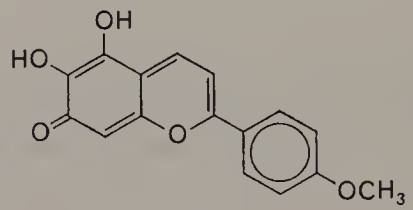
In spite of its arbitrariness, the quinone methides treated in this section are limited to those showing the quinone methide reactivity discussed above. The molecular diagrams displayed in Figure 4 for fuchsone (3), diphenoquinone (4) and stilbenequinone (5) show that only slight relationship exists between these molecules or their derivatives and quinone methides: the fuchsone derivatives lead into the class of triphenylmethane dyes and the diphenoquinones are better regarded as phenylogous quinones.

The importance of quinone methides in the chemistry of phenolic resins has been treated in several reviews[9–11].

The natural occurrence of quinone methide structures is mainly in the vegetable kingdom. They play a large part in the chemistry of lignin[12] and they are found also among wood pigments and other vegetable dyes.



Citrinin



Carajurone

Citrinin and carajurone are two typical examples. Naturally occurring quinone methides have been described previously in several reviews[12–16] and will therefore not be discussed further in this chapter.

II. PREPARATIVE METHODS

Syntheses of quinone methides are usually started from the corresponding phenols. The different synthetic routes described here will explain their division among the later sections. The routes displayed in Scheme 1 for *p*-benzoquinone methide are representative for all quinone methides and are valid for both *para*- and *ortho*-quinonoid systems in general.

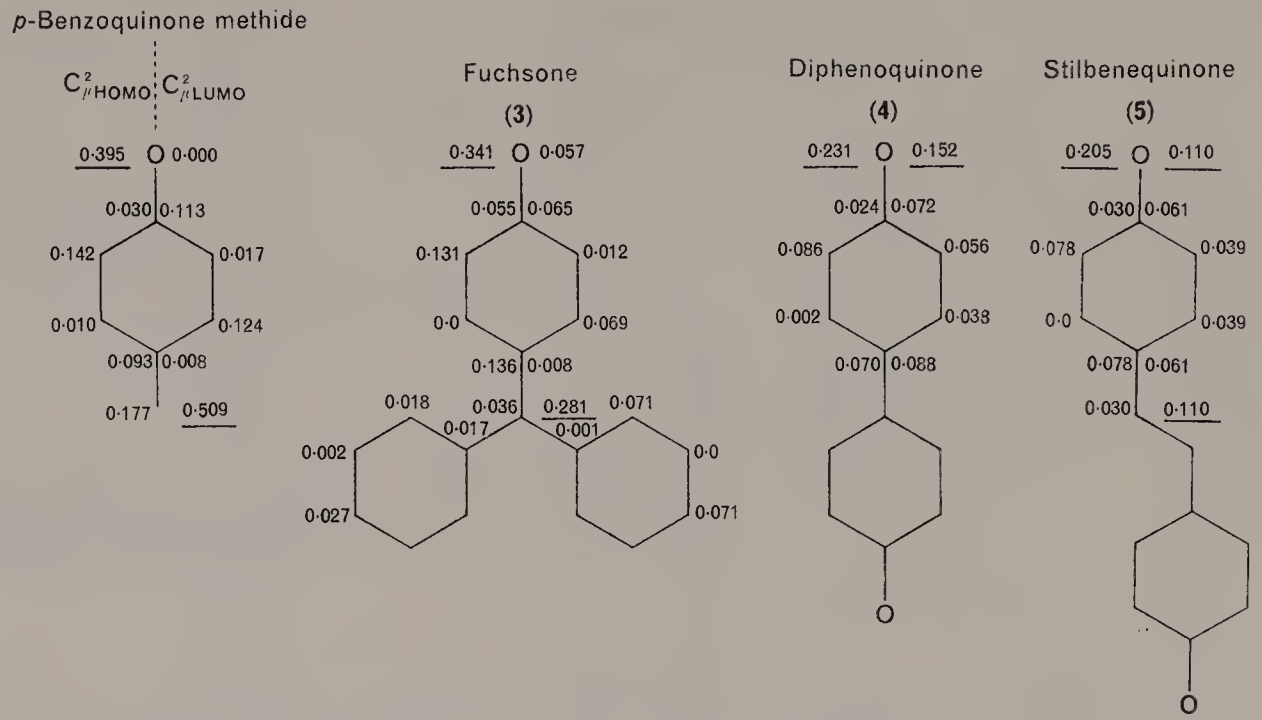
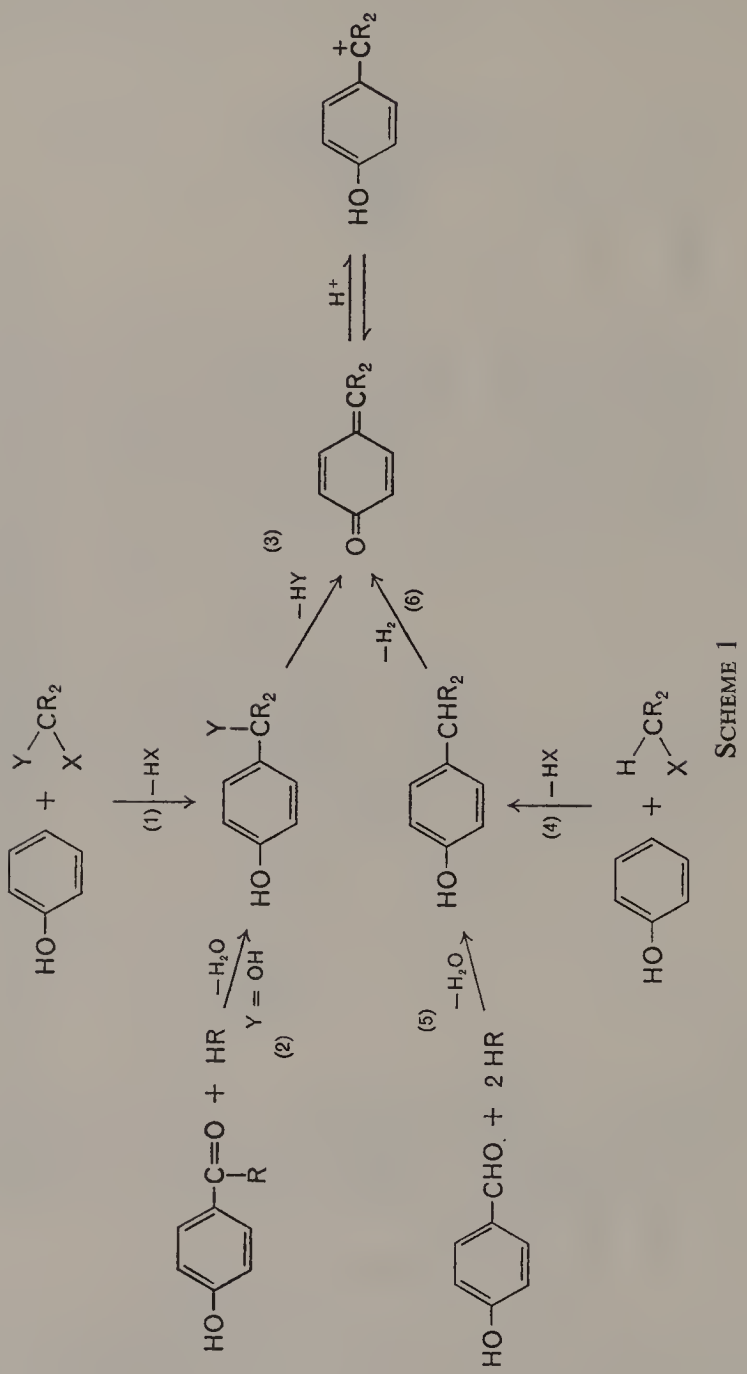


FIGURE 4. Squared coefficients in HOMO and LUMO of *p*-quinonoid systems. For symbolism see Figure 2.



SCHEME 1

Reactions of type (1) are electrophilic aromatic substitutions of a phenol. When the group Y is suitable the subsequent elimination (3) leads spontaneously to formation of the quinone methide, but when Y = OH more forcing conditions are necessary.

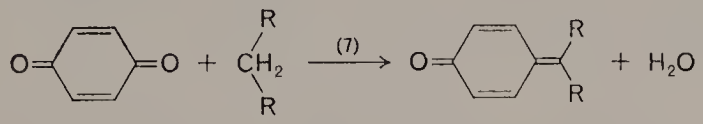
In reactions of type (2), addition of HR to the carbonyl group of an aromatic hydroxy-ketone leads to the same intermediate as in type (1). In this case, RH is often replaced by the metallated derivative, e.g. the Grignard compound RMgBr.

As in route (1), reactions of type (4) employ electrophilic aromatic substitution for synthesis of the intermediate, but this is dehydrogenated to the quinone methide in a subsequent oxidation step (6).

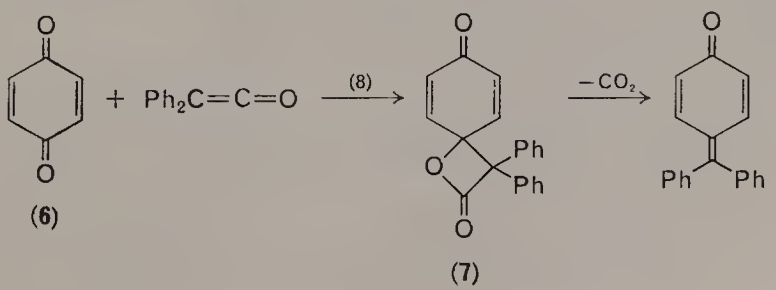
In reactions of type (5), aromatic hydroxy-aldehydes are converted into derivatives which are subsequently oxidized in step (6).

The quinone methides are not often isolated themselves but are obtained as salts indicated on the extreme right of Scheme 1. These salts are usually readily deprotonated and this step can be regarded as part of the elimination process (3).

The possibilities for synthesis of quinone methides from quinones are greatly limited by the low electrophilicity of the carbon atom of the quinone carbonyl group (cf. the squared coefficient of these atoms in the LUMO of *p*-benzoquinone displayed in Figure 2). It is only rarely that quinones can be condensed with CH-acidic components in a reaction shown in general form as type (7).

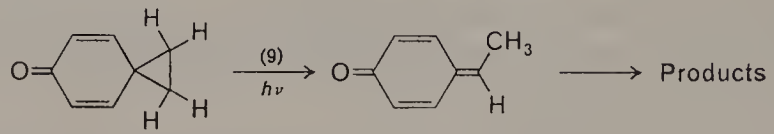


The most favoured electrophilic attack on the oxygen atom of a quinone is utilized in reactions of type (8) which involve treatment with diphenylketene. The quinone methides are formed by elimination of CO_2 from the spirans such as **7** formed from **6**.



(6) (7)

This type of reaction (8) proceeds by ring opening of a spirocyclohexadienone. In reactions of type (9) it is a photochemical ring cleavage that leads similarly to quinone methides, although these are formed only as intermediates (**9**).

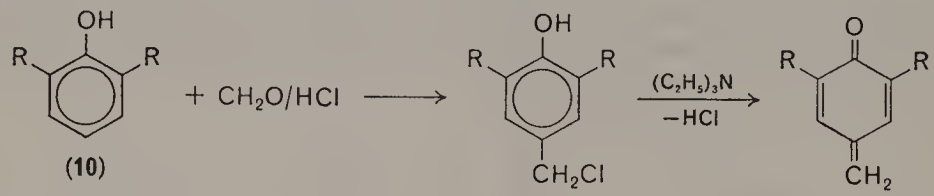


(**8**) (**9**)

In the following sections the reactions of types 1–9 of Scheme 1 are discussed individually. The formation of one quinone methide by alteration of another is treated in the section on reactions.

III. SYNTHESIS BY ELECTROPHILIC AROMATIC SUBSTITUTION OF PHENOLS AND SUBSEQUENT ELIMINATION

Chloromethylation of the phenol (**10**, R = *t*-butyl) and subsequent elimination of hydrogen chloride by triethylamine at −15° lead to orange-red solutions of the quinone methide (**11**, R = *t*-butyl)[17–19]. Although **11** cannot be isolated since dimerization and other reactions

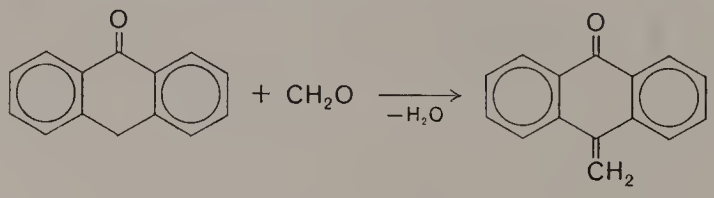


(**10**)
R = CH_3 or *t*-butyl

(**11**)

occur on concentration of the solutions[18], the dilute solutions can be preserved for several days in the dark[19]. The dimethyl derivative (**11**, R = CH_3) can be prepared analogously in solution[17].

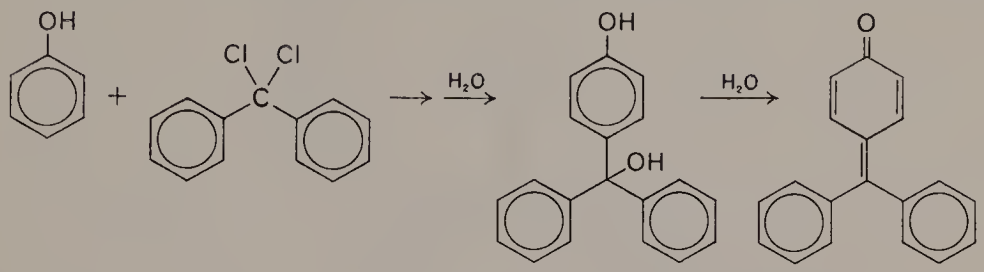
A further quinone methide without substituents on the methylene group can be obtained by condensing anthrone with formaldehyde under catalysis by base[8,19–21]. In this case elimination of water follows spontaneously. The resulting quinone methide, **12**, named methyleneanthrone, is stable and can be isolated as colourless crystals.



(**12**)

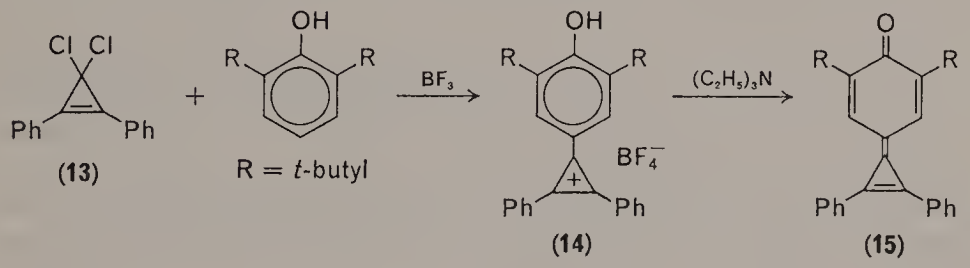
Condensation of anthrone with aldehydes is very generally applicable[22], but the resulting methyleneanthrones retain few properties of quinone methides, as will be discussed in the section of reactions.

Ketones are as a rule too feebly electrophilic to be able to attack phenols. However, numerous quinone methides, in particular fuchsone derivatives, have been prepared by condensing ketone dichlorides with phenols and then eliminating water from the resulting alcohols[22–30]. The synthesis of fuchsone itself from benzophenone dichloride and phenol may be formulated as an example[31]. However, electrophilic aromatic



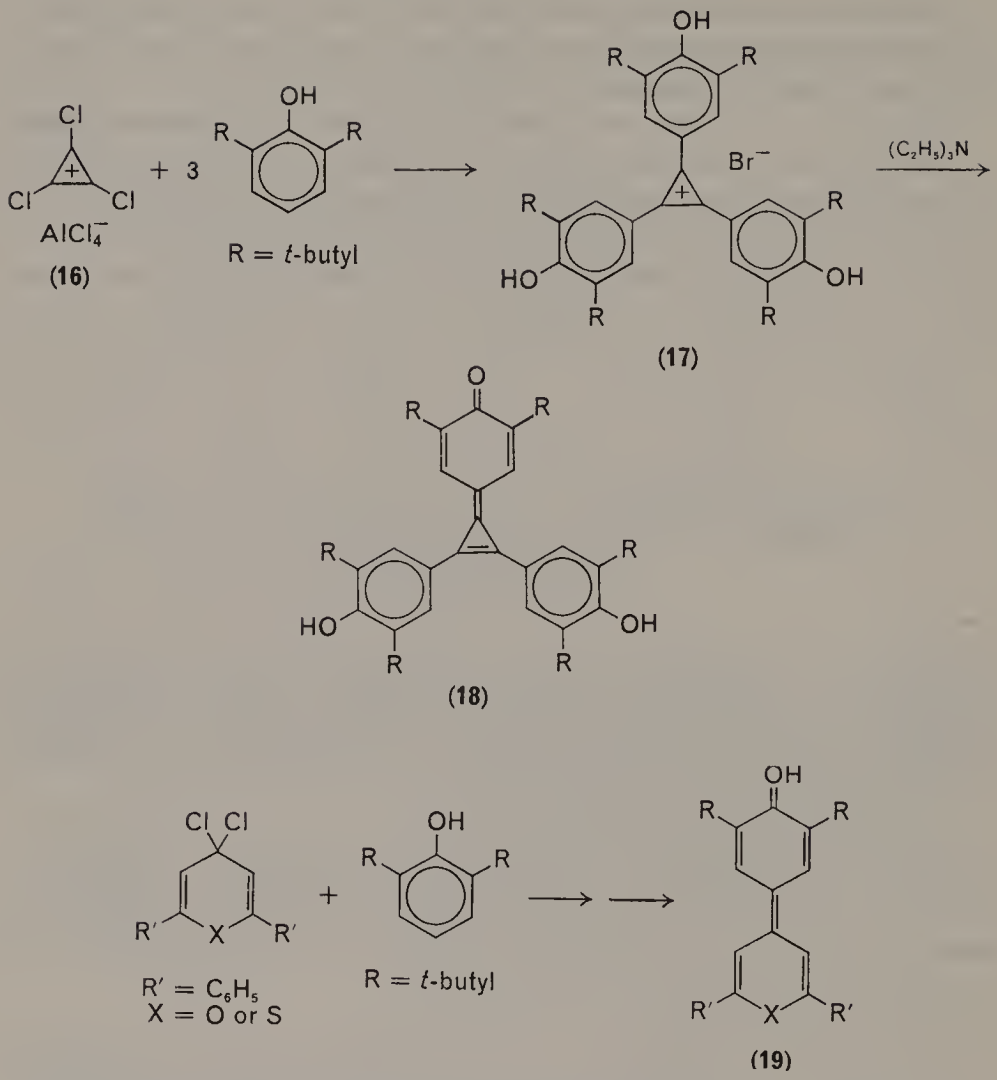
substitution of phenols by ketone dichlorides must generally be catalysed by addition of a Lewis acid; in such syntheses of fuchsone derivatives the whole range of Friedel–Crafts catalysts has been utilized for activation of the ketone dichlorides[32, 33].

The dichloride **13**, which can be easily prepared from diphenylcyclopropenone and phosgene, reacts rapidly with phenols if catalysed by boron trifluoride[33]; being cyclopropenylium derivatives, the resulting salts, **14**, are particularly stable, but they can be deprotonated by triethylamine to the red quinone methides **15**[34].



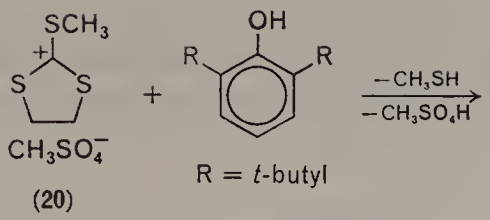
In the following reaction, three phenol nuclei are substituted by the trifunctional cyclopropenylium salt **16**; the product can be isolated as the bromide **17**, which on dehydrobromination leads to the red quinone methide **18**[35].

The quinone methides **19** can be obtained by analogous treatment of phenols with the dichlorides from pyrone and thiapyrone[36].

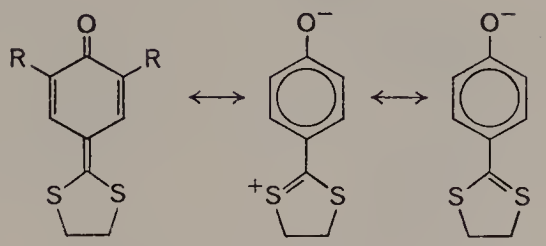


Ring substitution of phenols by resonance-stabilized carbenium ions is very generally applicable. For example, reaction of the dithiolanium salt **20** with 2,6-di-*t*-butylphenol affords, after spontaneous loss of methanethiol, a good yield of the very stable quinone methide **21**[37]. The structure of this resonance-stabilized product is reflected in the dipolar limiting formulae, e.g., **21b** and **21c**; this weakens the electrophilicity of the *exo*-carbon atom of the quinone methide, decreasing its reactivity, so that this quinone methide is stable and can be isolated. The same holds for examples **15**, **18** and **19**.

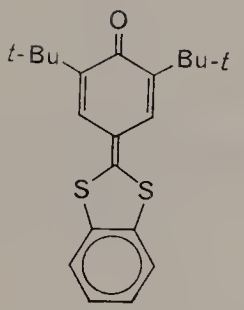
To the same group of compounds belong the quinone methides **22**, **23** and **24** prepared, respectively, from 1,3-benzodithiolium salts[37], 1,2-dithiolium salts[38–40] and benzothiazolium salts[41].



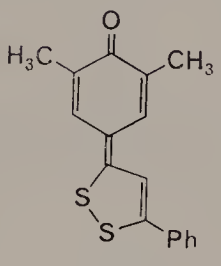
(20)



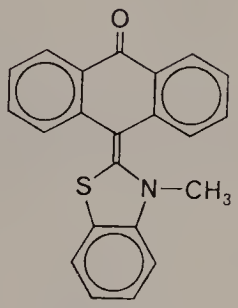
(21a) (21b) (21c)



(22)

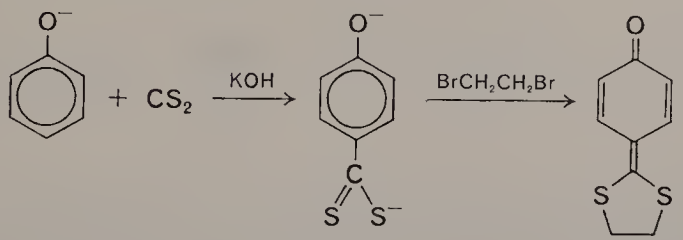


(23)



(24)

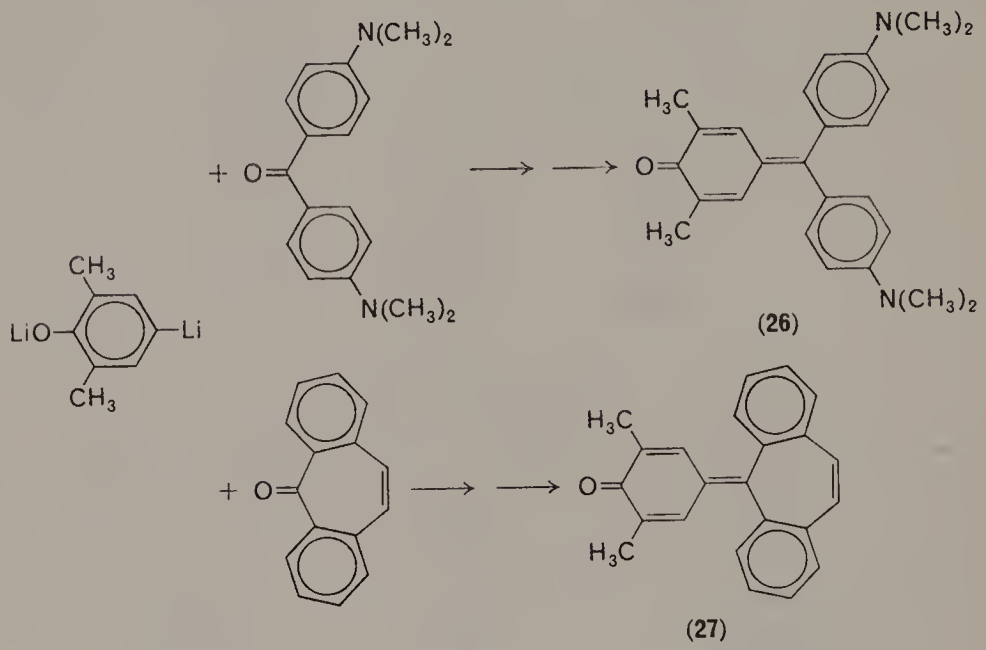
Reaction of phenoxides with carbon disulphide as electrophile also leads to ring substitution[42]. This results in the anions of *p*-hydroxydithiobenzoic acids, which can be alkylated by, e.g., 1,2-dibromoethane. The quinone dimethides **25** obtained in this way have the same type of structure as was formulated above in **21**.



(25)

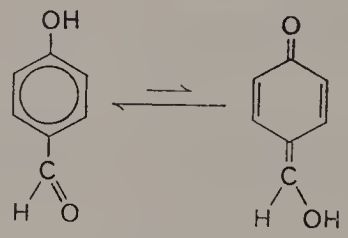
In their synthetic principle the following reactions of metallated aromatic compounds with carbonyl compounds also belong to this

section. The phenolic component is so strongly activated by replacement of a hydrogen atom by lithium that it reacts even with relatively unreactive ketones. The result is alcohols that are converted by loss of water into quinone methides such as **26**[43] and **27**[44].



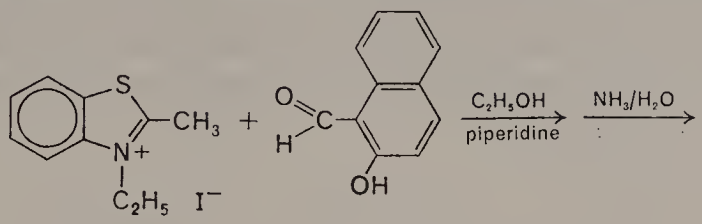
IV. SYNTHESIS FROM AROMATIC HYDROXY-ALDEHYDES AND -KETONES

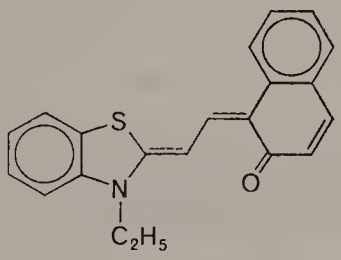
Hydroxybenzaldehyde can be formulated in a tautomeric form as hydroxy-quinone methide, thus:



Condensation of such aldehydes with CH-acidic components leads to blocking of the tautomerism and thus to fixation of the quinonoid structure. Of the numerous quinonoid dyes prepared in this way[45–53] only one, the annexed violet benzothiazole derivative, can be formulated here as example[54].

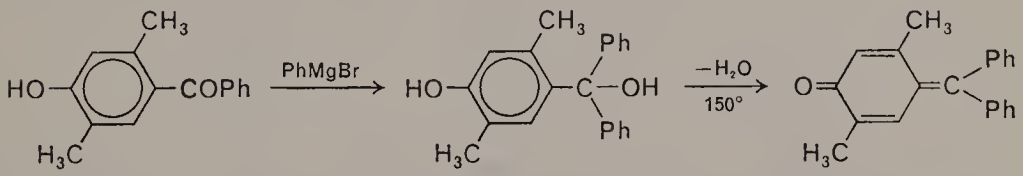
Interaction of aromatic hydroxy-ketones with organometallic compounds occurs by a similar type of condensation[22,29,55]. Loss of water



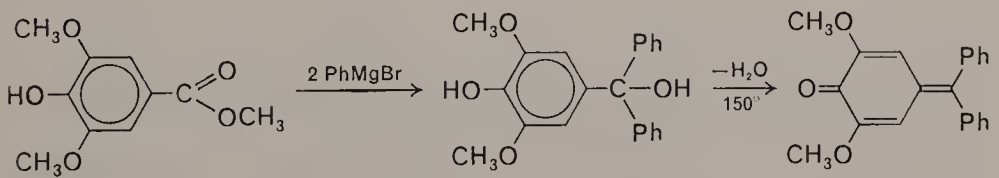


Violet

from the resulting alcohol leads to quinone methides, e.g. the annexed fuchsone derivative[56].



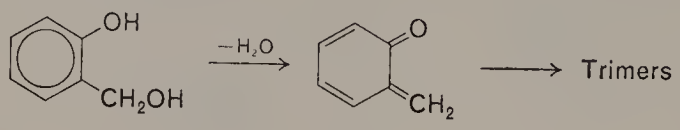
In the next synthesis the alcoholic intermediate is obtained from a hydroxybenzoic ester by successive Grignard reactions and its dehydration leads to another fuchsone derivative[57].



Elimination of water at a high temperature, as formulated for the last two reactions, is often used in the synthesis of quinone methides, and particularly of fuchsones[58–60]. This elimination of water is also an important step in other methods of quinone methide synthesis and is stressed in the next section, even though this separation is somewhat arbitrary.

V. SYNTHESIS BY ELIMINATION AND DEPROTONATION

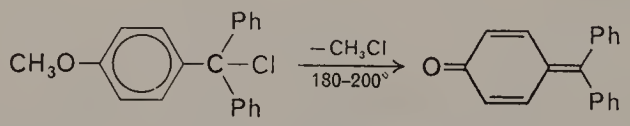
When *o*-hydroxybenzyl alcohol was pyrolysed and the products trapped at −196°, the presence of *o*-benzoquinone methide **28** could be proved spectroscopically[61]. When warmed, it was converted into trimers which had been known for some time[62,63]; their formation will be discussed in the section on reactions.



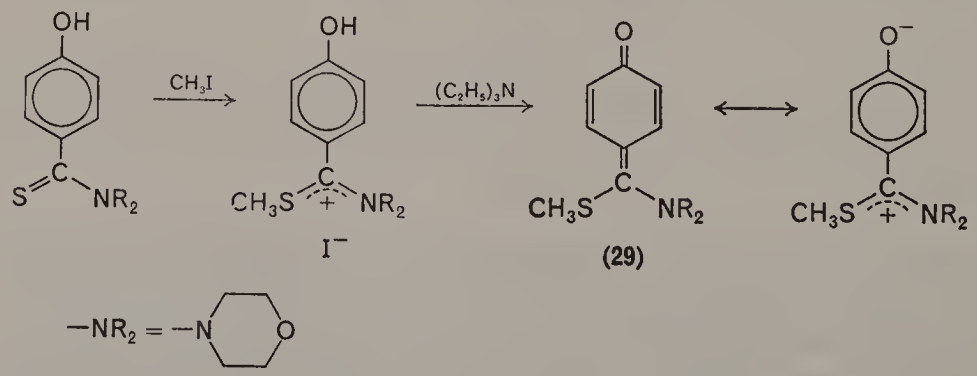
(28)

Elimination of hydrogen chloride was described in section I. Removal of hydrogen bromide from appropriate hydroxybenzyl bromides should also lead to quinone methides, but often only products of further reaction could be isolated[64–67].

In the fuchsone series alkyl halide can also be removed at elevated temperature, an example being afforded by the synthesis of fuchsone itself from *p*-methoxy-α,α-diphenylbenzyl chloride[1].



In the synthesis of donor-stabilized quinone methides of type **29**, deprotonation of the intermediate cations is the last step; the intermediate salts can be isolated[68]. Here both the salts and the quinone methides owe their stabilization to conjugation of the carbenium centre with electron-

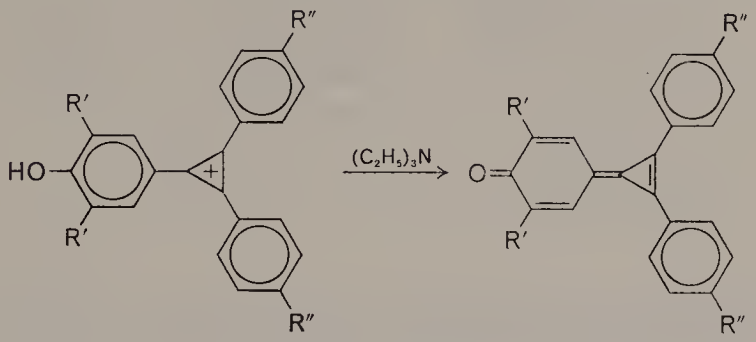


(29)

shifting substituents; there is a 'push–pull' stabilization of the quinone methide system due to the attractive effect of the oxygen atom and the

shift by the donor substituents. Further development of this idea leads to push–pull stabilization of the corresponding quinodimethanes[69].

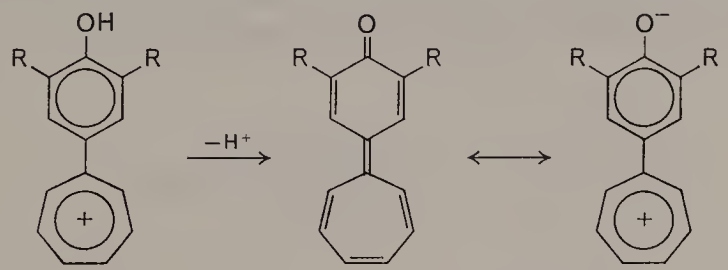
Similar stabilization occurs with the quinone methides **30**, obtained from (hydroxyaryl)cyclopropenylium salts[70,71] as mentioned above.



R′ = H or Br
R″ = H or OH

(30)

Synthesis of **32** from the (hydroxyaryl)tropenylium salts **31** belongs to the next section since dehydrogenation is involved, but it may be mentioned here that the easy deprotonation of the salts again affords resonance-stabilized, deeply coloured quinone methides[44,72–76].

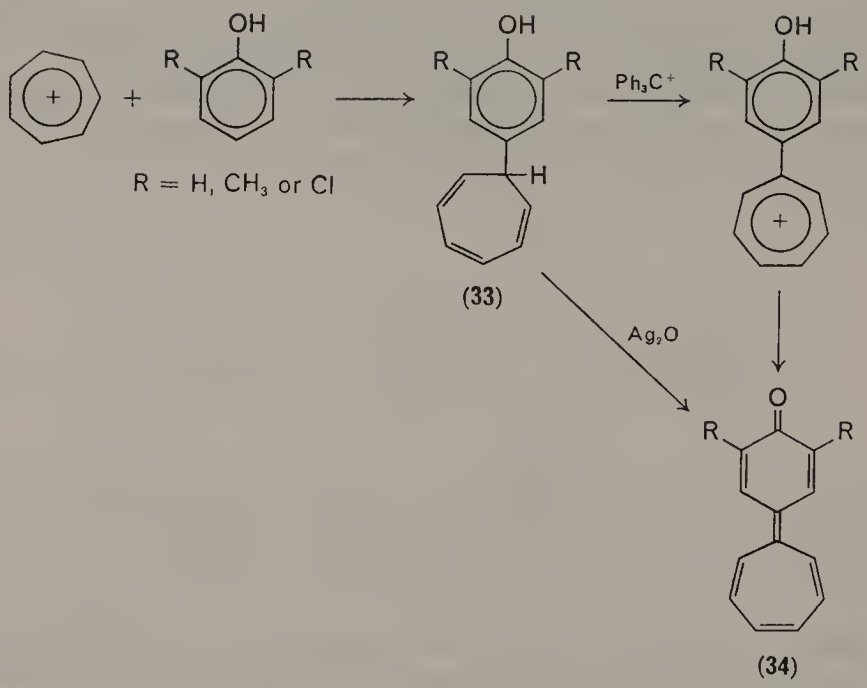


(31) **(32)**

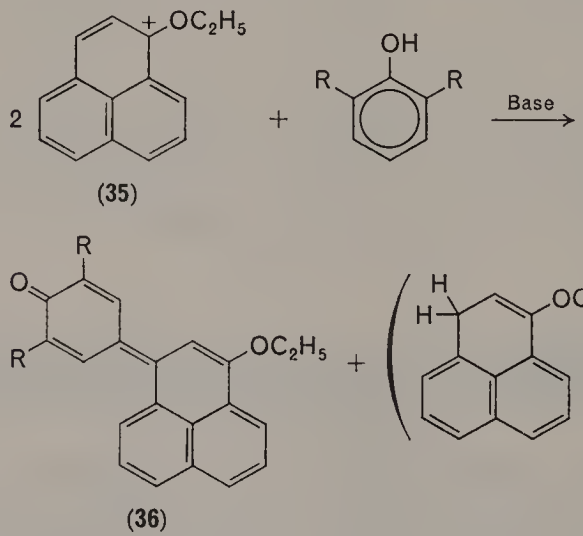
R = H, CH_3 or *t*-butyl

VI. SYNTHESIS BY ELECTROPHILIC AROMATIC SUBSTITUTION OF PHENOLS AND SUBSEQUENT OXIDATION

Numerous synthetic routes to tropylidenephenols (**33**) provide a connexion to the last example in the preceding section. Reaction of most 2,6-di-substituted phenols with tropylium salts stops at the intermediate hydrogenated stage **33**, and the subsequent dehydrogenation to quinone methides **34** is then effected either by using an excess of the tropylium salt or by isolating the phenolic **33** and treating it with a triphenylcarbenium salt or other oxidizing agent such as silver oxide[44,72–76].

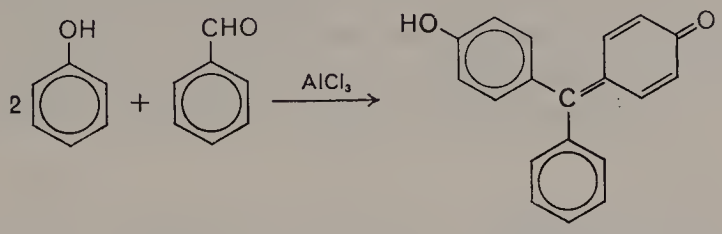


The ethoxyphenalenium salt **35** is also able to substitute phenols, and in this case the product is oxidized spontaneously to the blue quinone methide **36** by a second molecule of the carbenium salt **35**[77].



Phenols can also be substituted by using aldehydes as the electrophile, particularly if the reaction is catalysed by a Lewis acid. The following synthesis of benzaurin **37** is effected in this way; the intermediate product is not isolated but is at once dehydrogenated[78]. As this example shows,

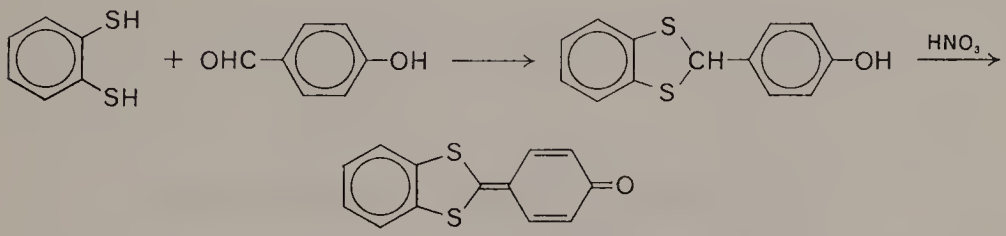
this type of synthesis leads into the fuchsone series and the triphenylmethane dyes, and very many further reactions of this type are described in the literature[79–81].



Benzaurin (37)

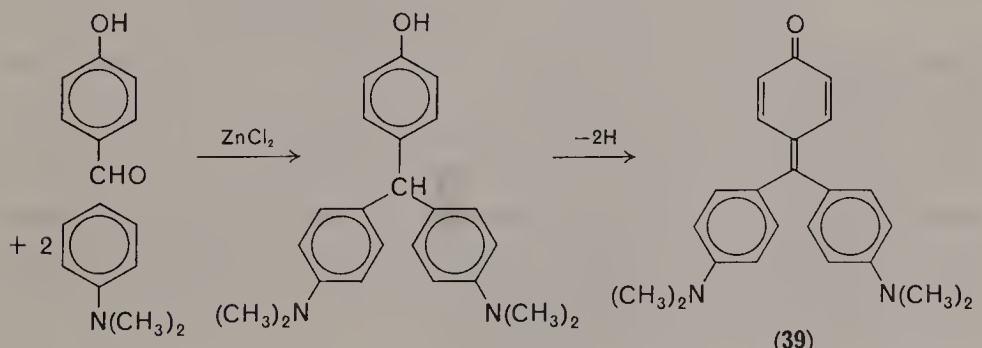
VII. SYNTHESIS FROM AROMATIC HYDROXYALDEHYDES BY OXIDATION OF THEIR DERIVATIVES

The synthetic principle underlying this section can be seen most clearly in the formulae below showing preparation of the push–pull stabilized quinone methide **38**[82]. Oxidation of the mercaptal of the aromatic aldehyde by nitric acid occurs by way of a nitrate.



(38)

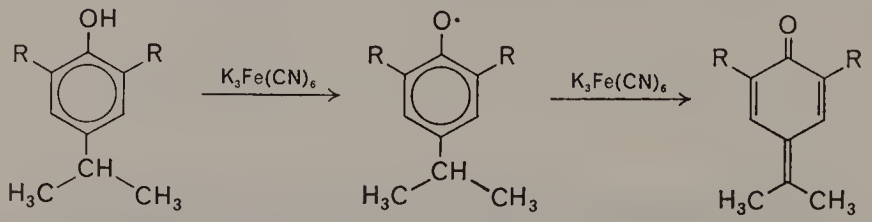
Further, preparation of the fuchsone derivative **39** and analogous triphenylmethane dyes proceeds through derivatives of aromatic hydroxyaldehydes that are very easily oxidized[83].



(39)

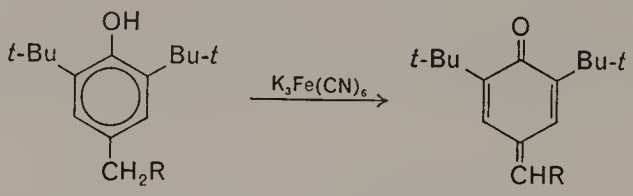
VIII. SYNTHESIS BY OXIDATION OF (HYDROXYARYL)METHYL COMPOUNDS

Potassium hexacyanoferrate(III) has been found particularly valuable as an oxidizing agent for preparation of a variety of quinone methides from (hydroxyaryl)methyl derivatives, as illustrated[84]. This oxidation should be formulated as occurring through aryloxyl radicals[85], and these can themselves act as dehydrogenating agents[86]. The general applicability of



R = *t*-butyl

oxidation by potassium hexacyanoferrate(III) is illustrated by the variety of substituents R listed under the following formulae for the 2,6-di-*t*-butyl case[87–89]. The reaction can, however, be effected by very many other oxidizing agents, and silver oxide[17,90], lead oxide[91–94] and choranil[95]

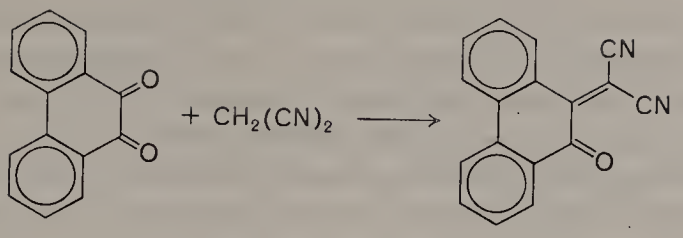


R = CH_3, C_2H_5, iso-C_3H_7, *n*-C_4H_9, C_6H_5, CH_2OH, COOH, CN, or piperidine

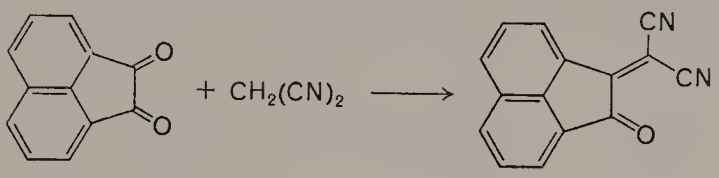
inter alia, have each been used with success. Very often, however, formation of stilbenequinones or related dimerization products occurs as a side-reaction, and this applies also to oxidation by potassium nitrosodisulphonate[96].

IX. SYNTHESIS FROM QUINONES

Condensation of the carbonyl group of quinones with CH-acidic compounds, which is often used for synthesis of methylene derivatives in other series, rarely succeeds, owing to the low electrophilicity of the quinone carbonyl atom (see section I). However, in special cases, such as phenanthraquinone and 1,2-acenaphthenequinone, reaction with malonodinitrile affords quinone methides **40** and **41** carrying the two cyano-groups[97]; in these two cases the quinonoid character is weakened, the relationship to 1,2-quinones being obvious.

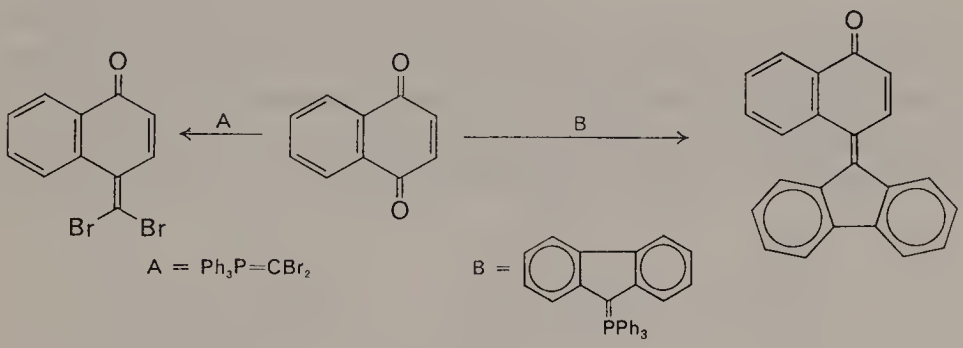


(40)

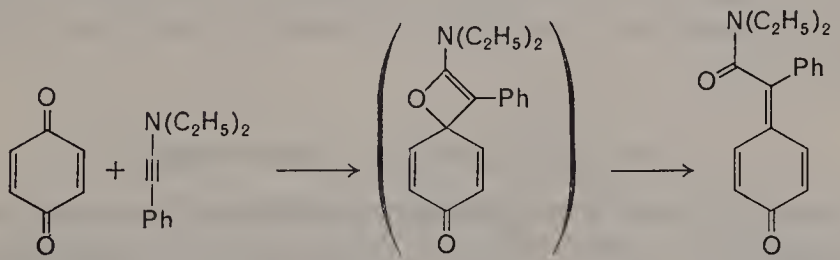


(41)

Synthesis of methylene derivatives from carbonyl compounds by the Wittig reaction can be carried out in the quinone series, as illustrated here for the formation of two quinone methides from 1,4-naphthoquinone[98].

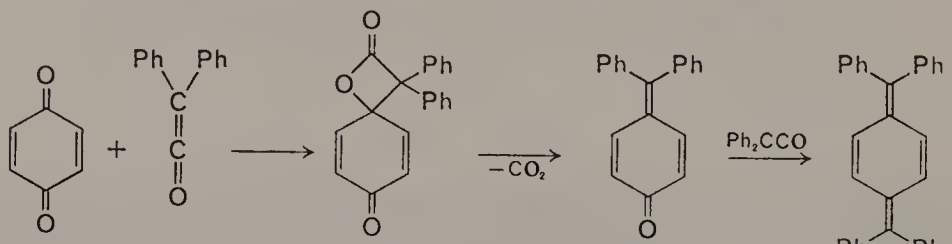


It is also possible to cause reaction between the carbonyl group of quinones and very reactive ynamines. For instance, *p*-benzoquinone and *N*,*N*-diethyl-2-phenylethynylamine afford the quinone methide **43**, whose formation is most simply formulated as occurring through the intermediate **42** with subsequent ring-opening[99].

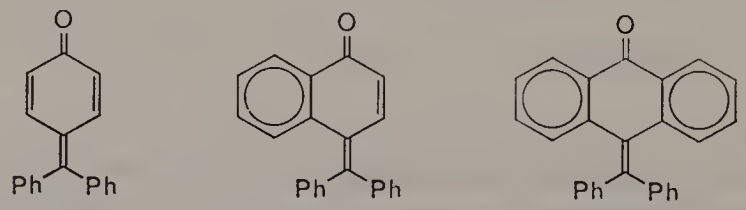


(42) (43)

In these reactions, electrophilic attack on the oxygen atom of the quinone system plays a considerable part in the further course of the reactions, but in the earlier syntheses of quinone methides and quinodimethanes from quinones and diphenylketene attack by the electrophilic ketene on the oxygen atom of the quinone is the cause of the first reaction step[100]. The lactone **44**, for instance, can be isolated and gives the quinone methide **45** by loss of CO_2. When two equivalents of diphenylketene are used both carbon groups of the quinone react, yielding quinodimethanes such as **46**[100].



The fuchsone derivatives prepared in this way show a striking hypsochromic shift of the longest wavelength band in the series benzo-, naptho- and anthra-quinone methide, i.e. the colour becomes paler as the size of the conjugated systems increases. The hypsochromic shift is still more marked with the corresponding quinodimethanes, so much so that this



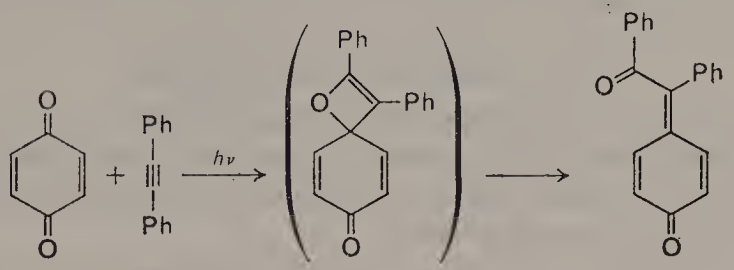
unusual effect led Staudinger to doubt the quinonoid structure of tetraphenylanthraquinone dimethane[101]. The shifts can, however, be explained by MO calculations[102,103], in which the decrease in quinonoid character through the series benzo-, naphtho- and anthra-quinone is seen to play a significant role.

X. PHOTOCHEMICAL SYNTHESES

As a monocyclic four-electron process the addition of the triple bond of an ynamine to the carbonyl double bond of a quinone described in the preceding section should be thermally unfavourable[103,104]; it will be made

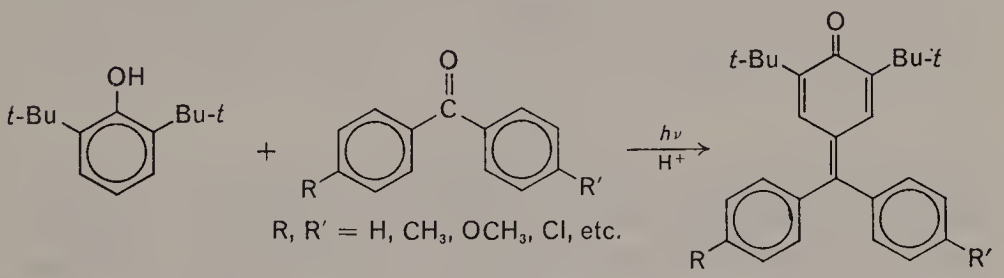
much easier by polarization of the two components and can proceed through polar intermediates.

The Woodward–Hoffmann rules for cyclic transition states[103,104] stipulate that a photochemical process is favourable when the thermal process is unfavourable, and a suitable example of this is provided by photochemical addition of tolane to *p*-benzoquinone, as illustrated[105,106].

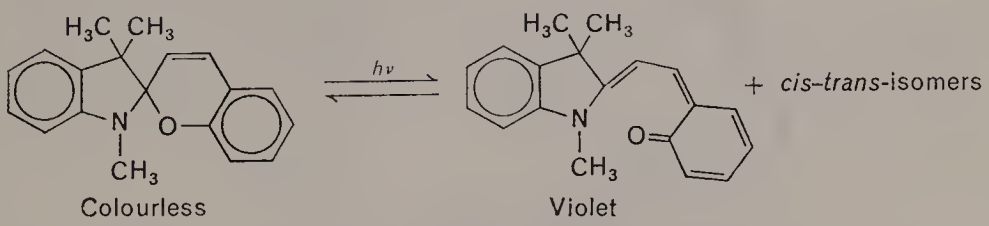


As in the thermal reaction of the ynamine this reaction also is most simply formulated as involving a spirocyclic intermediate.

Photochemical activation is also utilized in synthesis of the series of fuchsone derivatives shown below[107].

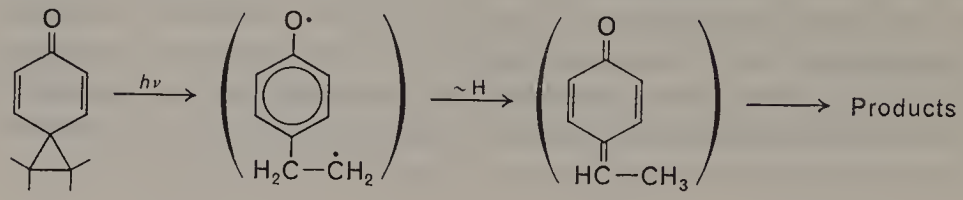


In the chemistry of photochromic dyes light energy can be used to open a spiran system, and quinone methides are often formed as chromophores; a violet indole derivative and its isomers exemplify the principle[108,109].



Of particular interest is the photochemical cleavage of a cyclopropane ring involved in a spiro-junction. Quinone methides are obtained from the

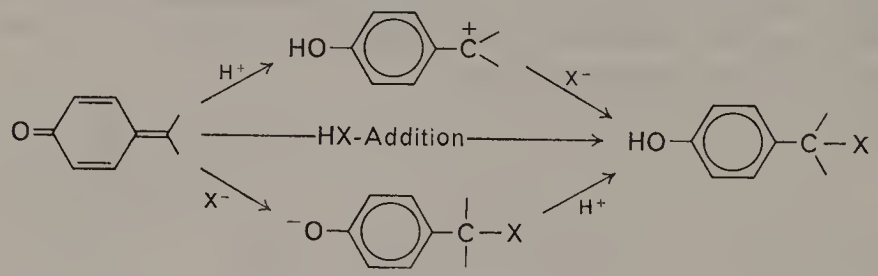
diradicals formed as intermediates, but under the reaction conditions further reactions set in to give the products isolated[110,111].



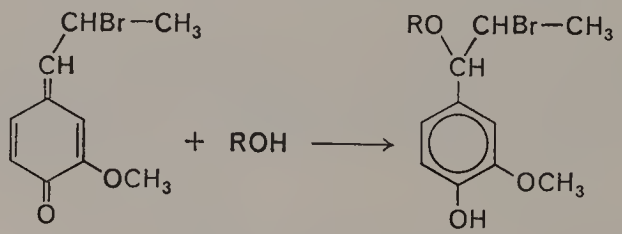
XI. GENERAL REACTIONS

As mentioned in the Introduction, quinone methides constitute a rather unstable and thus reactive class of compound. This great reactivity results from the higher energy potential of the quinonoid than of the corresponding aromatic structure.

Being vinylogous carbonyl compounds, the quinone methides are especially amenable to addition reactions of Michael type (cf. the scheme below). The addition occurs stepwise in both cases, i.e. addition of the



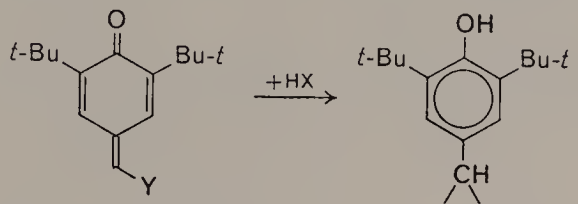
electrophile precedes that of the nucleophile or *vice versa*, but in both cases the ring becomes aromatic in the first step. The rate of addition of alcohols to quinone methides depends to a substantial extent on the acid strength of the alcoholic component[112]: the more easily the proton is removed, the faster is the addition. This, however, implies that in such cases addition of the proton to the nucleophilic centre of the methide (i.e. to its oxygen atom) is the important step. Higher alcohols add extremely



ROH: PhOH > Sugar > H_2O > CH_3OH > C_2H_5OH

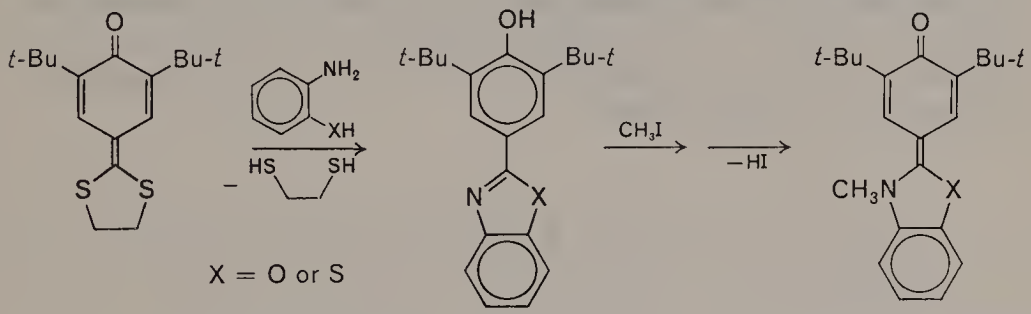
slowly but, as shown in the scheme, their reaction is greatly accelerated by traces of acid[113,114].

The same dependence on the acid strength of a component HX is found with the quinone methides **47a** and **47b**[115]: the nucleophilicity of the oxygen atom of the methide is further increased by the donor substituents Y. On the other hand, when the substituent is an electron acceptor, as in **47c** and **47d**, the quinone methide reacts only with very strong nucleophiles[115] and it is then the electrophilicity of the carbon atom at the other end of the conjugated system that determines the reaction since the nucleophilicity of the oxygen atom is too greatly weakened to be effective.



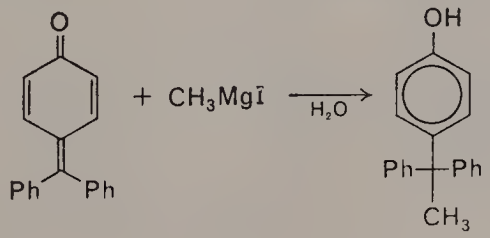
(**47a**) Y = $N(CH_3)_2$
(**47b**) Y = OCH_3
(**47c**) Y = CN
(**47d**) Y = COOH

Nucleophilic substitution is also the basis for conversion of a 2,6-di-*t*-butylbenzoquinone methide containing a 1,3-dithianylidene group into other methides by *o*-amino-phenol or -thiophenol[116]. The sulphur substituents are removed as 1,2-ethanedithiol owing to the more strongly nucleophilic amino-group[116] and the resulting phenolic compound can be

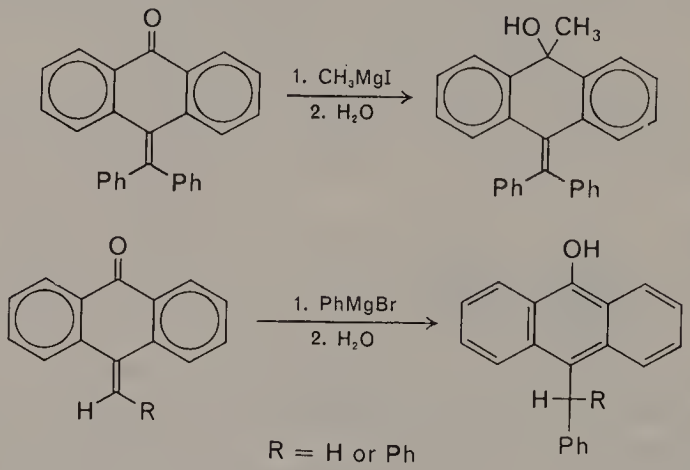


converted by alkylation into its ammonium salt, whereafter deprotonation restores the quinone methide system.

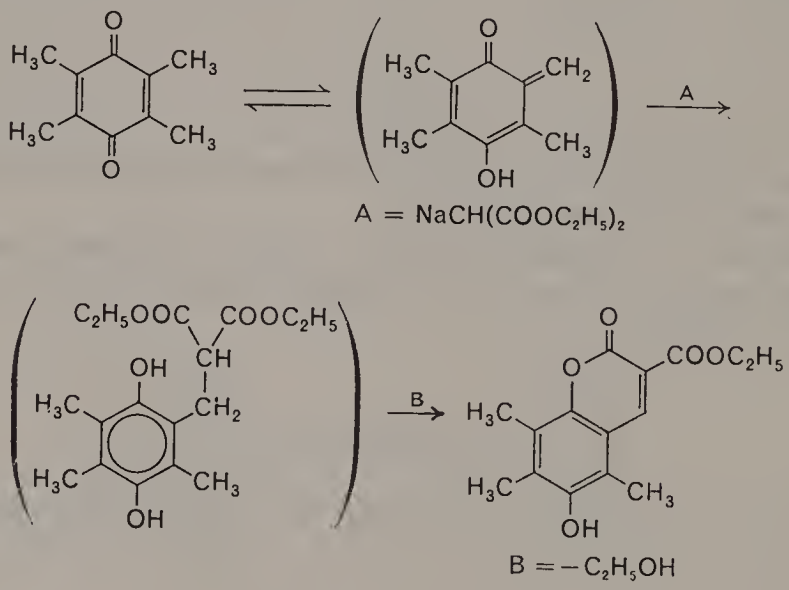
1,6-Addition of Grignard reagents to quinone methides occurs, as expected, with formation of the phenolic system, as illustrated for diphenyl methide[117].



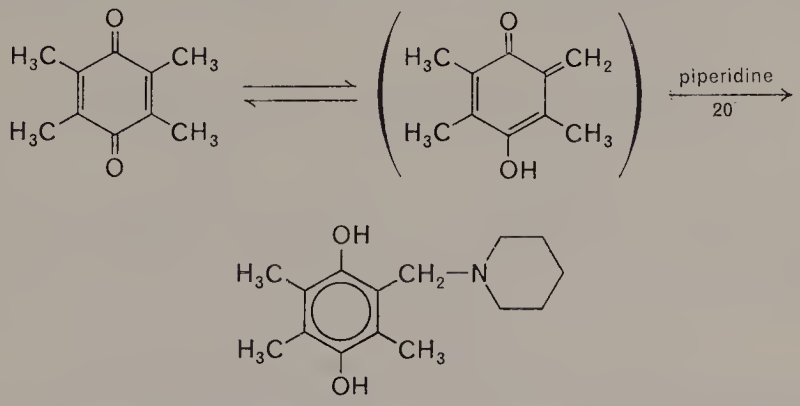
The corresponding 1,4-naphthoquinone methide reacts analogously, but methylmagnesium bromide reacts with 9,10-anthraquinone methide by 1,2-addition to the carbonyl group[117]; here the less pronounced quinonoid (or benzenoid) character of the central ring of the anthracene system makes itself felt, but in other cases 1,6-addition of phenylmagnesium bromide can still occur[118]. The two modes of addition are shown in the formulae.



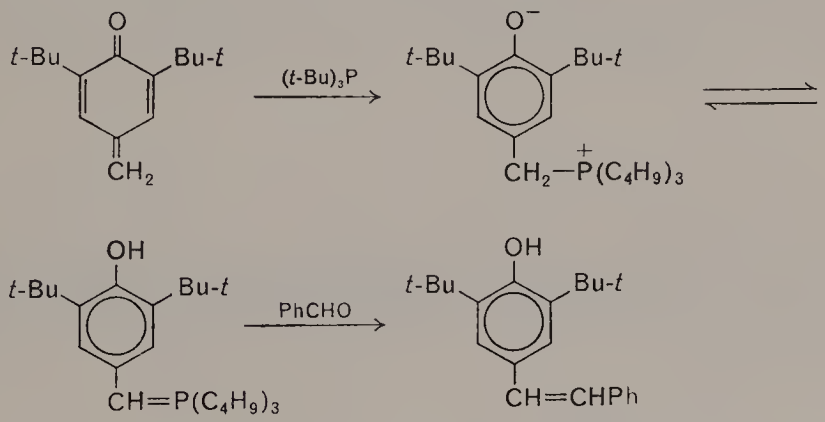
Addition of CH-acidic compounds to quinone methides follows the HX scheme[119]. It plays a large part in the chemistry of duroquinone; *o*-quinone methides, which can be formulated as the enolic form of the quinone, are assumed as intermediates[120,121], with the results illustrated in the following reaction sequence.



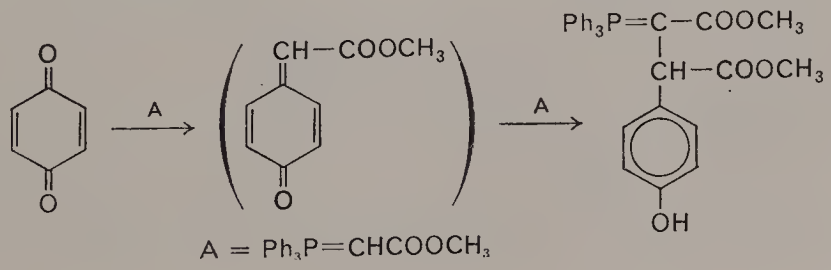
Duroquinone can be readily aminated in the side-chain at room temperature and this great reactivity is again attributed to the *o*-quinone methide. After oxidation of the resulting diphenolic product to its quinone analogue, further amino groups can be introduced[122].



Interaction of tributylphosphane and a quinone methide affords a good yield of the phosphonium betaine; this cannot be isolated but it can be trapped by the Wittig reaction with benzaldehyde[123]. The ready addition of phosphanes or phosphites to quinone methides is also involved in transformations and dimerizations of the latter[124].

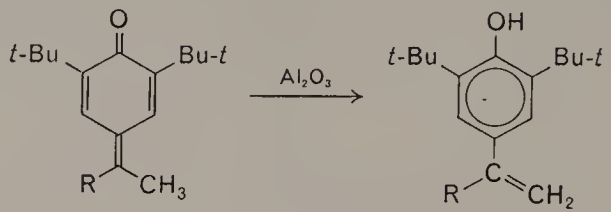


In section IX, on the syntheses of quinone methides from quinones, the Wittig reaction with quinones was cited. That synthesis fails with methyl trimethylphosphoranylideneacetate and *p*-benzoquinone because



the intermediate quinone methide reacts with a second molecule of Wittig reagent and that adduct is stabilized by prototropy[125].

An analogous prototropy is shown by 2,6-di-*t*-butylbenzoquinone methide and its 7-methyl and 7-phenyl derivatives, the reaction being catalysed by alumina[126].

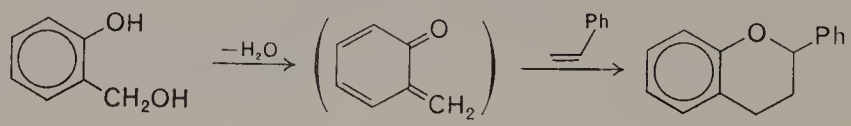


R = H, CH_3 or Ph

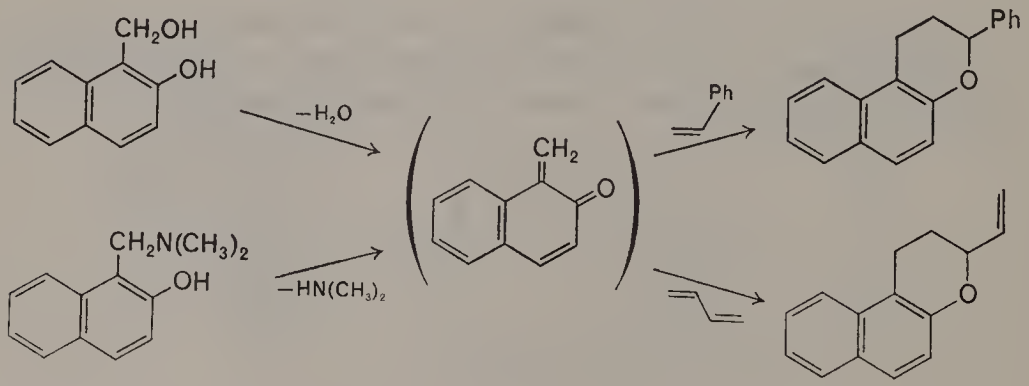
XII. CYCLOADDITION REACTIONS

Transition from the quinonoid to the corresponding benzenoid structure can be achieved particularly easily with *o*-quinonoid systems by a bond shift during the course of a Diels–Alder reaction, and this is the driving force for the great tendency of *o*-quinone methides to dimerize.

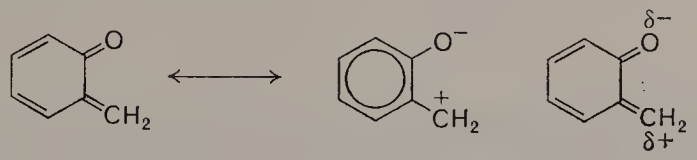
On formation of *o*-quinone methide by dehydration of *o*-hydroxybenzyl alcohol in the presence of an olefin, addition of the latter occurs[127,128], yielding flavan if the olefin is styrene. The same reaction



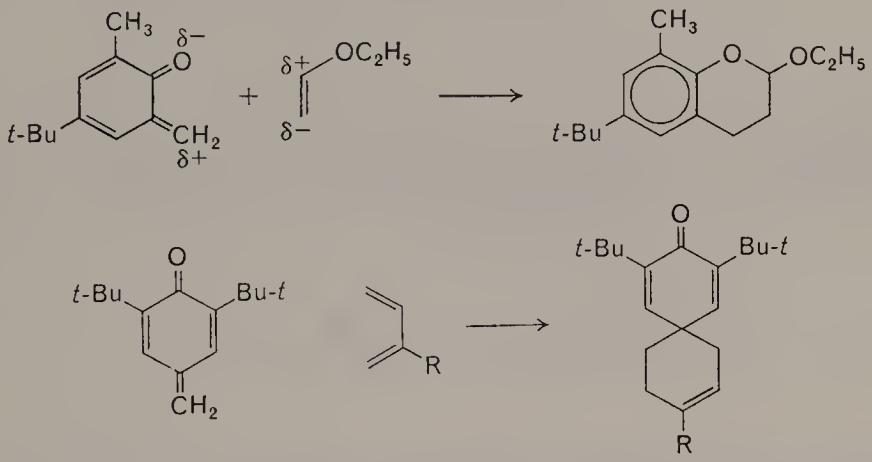
occurs with *o*-naphthoquinone methide obtained by either of the two methods illustrated[129]; the products formed on use of styrene and butadiene are both shown.



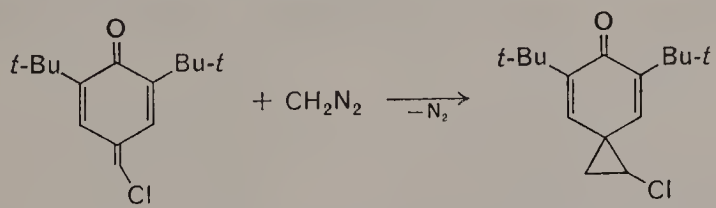
In all cases the *o*-quinone methide acts as a heterodiene component, and the high regiospecificity corresponds to polarization of the methide in the manner shown. This is particularly clear in the reaction with ethyl vinyl ether, which is quantitative[130].



p-Quinone methides can not react as the diene components, for with these compounds the *exo*-methylene group behaves as the dienophile; this can be exemplified by the behaviour of 2,6-di-*t*-butyl-*p*-benzoquinone methide with substituted butadienes[131].

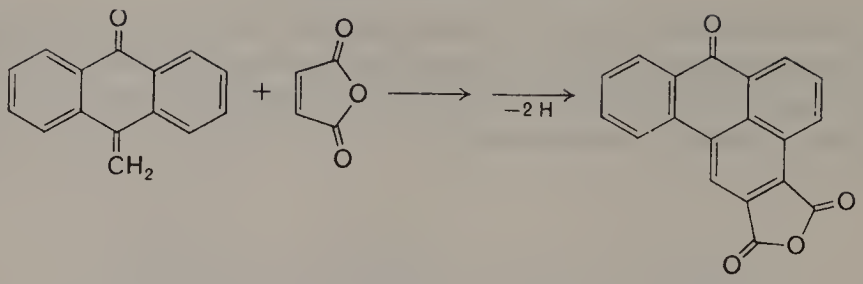


The methylene group also acts as dienophile in reactions with diazomethane, for spirocyclopropyl derivatives are formed in very good yield, as shown here for a 7-chloromethide[132].

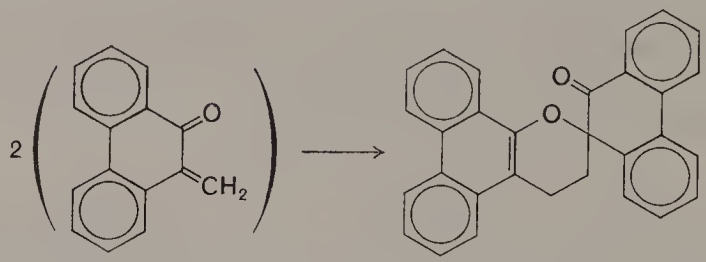


However, in the case of methyleneanthrone the double bond next to the methylene group can enter into the reaction; thus, after addition of maleic anhydride and dehydrogenation the product is found to be a benzanthrone derivative[132, 134].

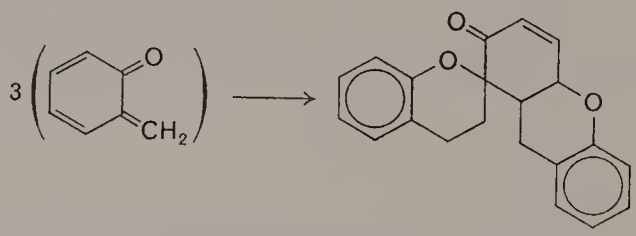
In the absence of a suitable addendum, the considerable tendency of an *o*-quinone methide to add to a heterodiene system leads to dimerization,



one molecule acting as heterodiene and another as dienophile. Phenanthraquinone methide provides such an example[135,136]. Very often,

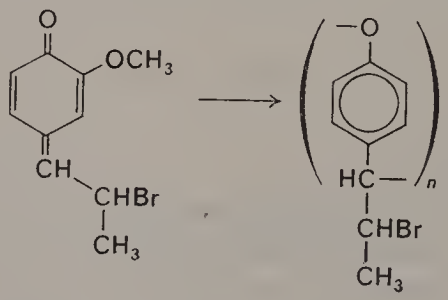


however, trimeric products are formed in attempts to prepare quinone methides, such as that shown from *o*-benzoquinone methide[63,137]. Indeed a large number of compounds described in the early literature as quinone



methides are really dimers or, more often, trimers[138]; colour alone allows a decision between the yellow quinone methides and their colourless oligomers.

Self-addition of *p*-quinone methides leads to polymeric 1,6-adducts[112].



XIII. ACKNOWLEDGMENT

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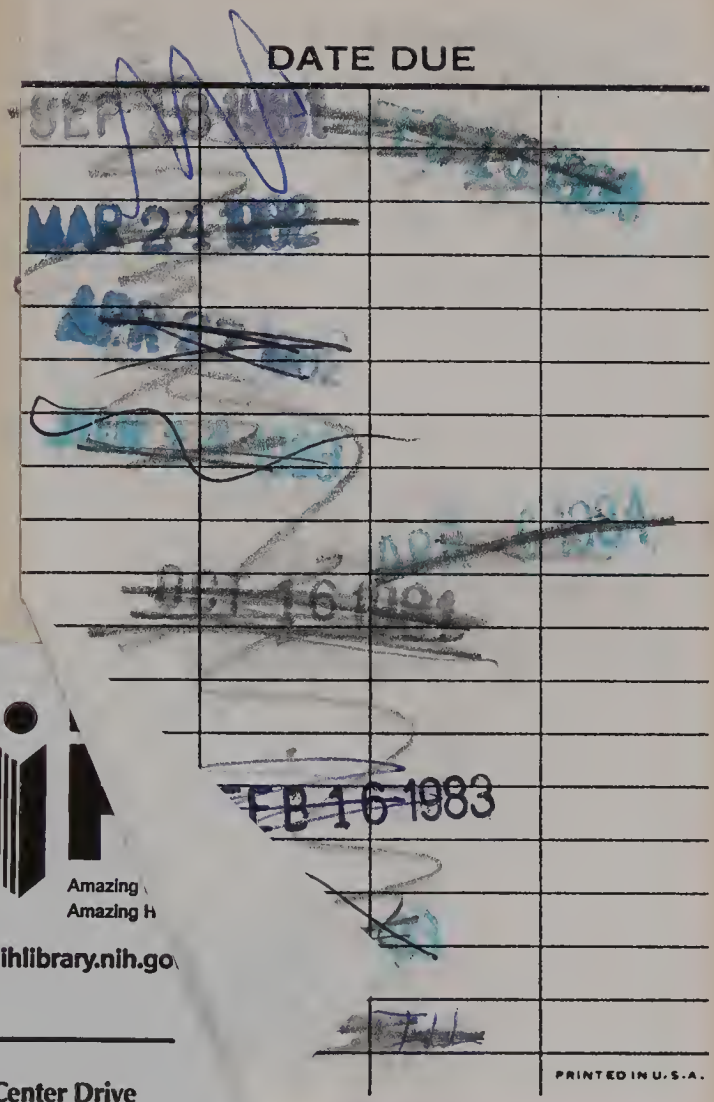
Subject Index

For *o*- and *p*-quinones *see* 1,2- and 1,4-compounds, respectively



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