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POLYKETIDE QUINONES

University of Melbourne (Australia) PH.D. 1984

POLYKETIDE QUINONES

A Thesis

Presented for the Degree of

DOCTOR OF PHILOSOPHY

by

PETER JAMES CHALMERS

Department of Organic Chemistry

University of Melbourne

October 1983

To my wife, Kym.

TABLE OF CONTENTS

ACKNOWLEDGEMENTS

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I would also like to thank my family for their support, without whom it would not have been possible to complete the work described here. My appreciation is also expressed to Dr. P. G. McKay for a sample of 2,5-dichlorobenzoquinone and to Dr. B. Franck for an authentic sample of endocrocin.

The financial support of a Commonwealth Postgraduate Research Award is gratefully acknowledged.

SUMMARY

The Thesis initially considers the directing effect of a quinonoid halo-substituent towards nucleophiles, which has been determined using specific ^{13}C labelling. The orientation of addition of nucleophiles from the first row of the periodic table has thereby been elucidated for the first time.

Information so derived was used subsequently in an investigation of the synthesis of polyketide-derived quinones. Successive Diels-Alder cycloadditions served to annelate a chloro quinonoid nucleus with highly functionalized butadienes. In this way the natural anthraquinones, endocrocin, emodin and 2-acetylemodin have been synthesized. The related naphthoquinone orientalone, whose structure is revised, was also prepared for the first time by this approach.

PART I

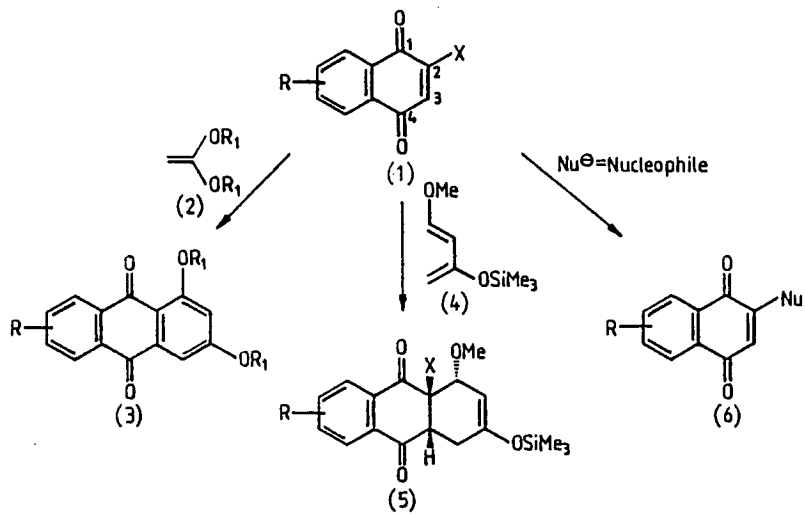
REACTIONS OF LABELLED QUINONES

WITH NUCLEOPHILES

CHAPTER 1

INTRODUCTION

Quinones, in particular halo-substituted quinones, have found considerable use as intermediates in the synthesis of natural products.[1,2] The halogen on the quinonoid double bond activates the quinone towards a number of processes and controls their regiochemistry. For example, annelation of halo naphthoquinones (1) with 1,1-dialkoxyethenes (2) in a 1:2 process gives the anthraquinones (3), the new 1,3-dioxygenated ring being attached in a regiospecific manner[3] (Scheme 1). Regardless of the electronic effect of



Scheme 1

substituents (R) on the benzenoid ring, the orientation of addition in every case results from reaction of the more nucleophilic terminus of the polar alkene at the carbon vicinal to that bearing halogen.[3-6]

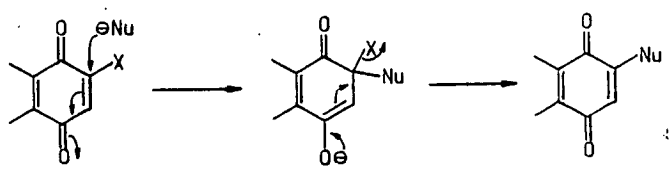
In a structurally similar reaction, highly polarized butadienes such as (*E*)-1-methoxy-3-trimethylsilyloxy-1,3-butadiene (4)[7] undergo [4π+2π] cycloaddition to halo quinones to give adducts (5).[8] Whilst it is likely that this process is mechanistically unrelated to the addition of 1,1-dialkoxyethenes (2), the orientation of addition is also controlled by the halogen (Scheme 1). Such Diels-Alder cycloadditions are discussed in greater detail in Chapters 3, 4 and 5 of this Thesis. In addition to these examples, which involve annelation, the halo group in (1) is also susceptible to direct displacement by nucleophiles producing substituted quinones (6). In some cases involving appropriate nitrogen or oxygen nucleophiles this has given access to a number of natural products.[6,9,10] The regiochemistry of such displacement processes is considered in detail in Chapter 2.

Given that methods exist for the introduction of a halogen substituent into either position on the quinonoid double bond,[11-13] the processes in Scheme 1 offer considerable versatility. However, their synthetic value is dependent upon being able to identify the orientation of attack with respect to the 2- and 3- positions and hence to predict the structure of the product. This is often complicated by the ambiguity of structural assignment in isomeric quinones where unsymmetrically isomeric substitution on one side of the quinonoid nucleus is frequently not reflected in a routinely predictable spectroscopic change on the other. For example, it is often difficult to differentiate a 2-substituted-1,4-naphthoquinone from its 3-substituted isomer, as is necessary in consideration of products such as (6). It is similarly difficult to discriminate between 5,7-disubstituted-9,10-anthraquinones and their 6,8-disubstituted regiomers, as is necessary in the case of products

such as (3). While such distinctions can ultimately be made by relatively laborious chemical procedures,[11,14-16] they often do not lend themselves to resolution by routine examination of ^{1}H and ^{13}C nuclear magnetic resonance (n.m.r.) spectra, especially if only one of the two possible regiomers happens to be available.[17]

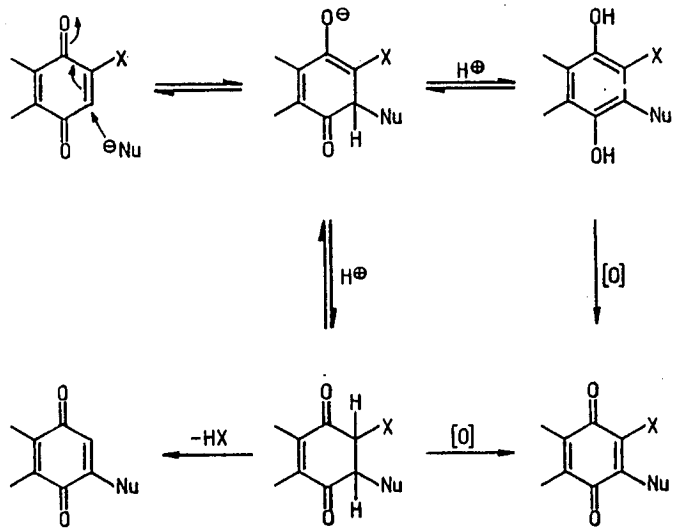
In principle, addition of a diene such as (4) suffers from the same regiochemical difficulty. However, the fact that it is often possible to isolate true cycloadducts (5) retaining the halogen has made is possible to establish both the regiochemistry and stereochemistry of addition by X-ray crystallographic and ^{1}H n.m.r. data.[8] Nevertheless, in cases where the intermediates such as cycloadducts (5) which retain the halogen, in particular nucleophilic displacement reaction, (see Schemes 2 and 3), are not isolable owing to ready elimination, assignment of structure once again becomes much less straightforward.

Hitherto, there has been no rigorous examination of the regiochemistry of nucleophilic displacement of a quinonoid halogen as in conversion (1) to (6). It is mechanistically feasible for displacement of halogen to occur by nucleophilic attack at either of the quinonoid carbons 2 or 3. Nucleophilic addition at the carbon bearing the halogen, designated as *ipso* attack, is shown in Scheme 2.[18] Expulsion of halide from the resulting enolate produces a substituted quinone. Alternatively, the nucleophile can attack the unsubstituted



Scheme 2

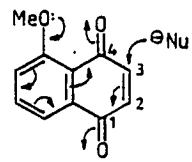
carbon, designated as vicinal attack, as seen in Scheme 3.[18] Protonation of the intermediate enolate followed by elimination of hydrogen halide again produces a substituted quinone. Oxidation of the dihydro intermediate could lead to the disubstituted quinone retaining the halogen.



Scheme 3

The bond forming processes in Schemes 2 and 3 are shown as involving nucleophilic attack of the quinonoid system and they are treated in these purely conventional terms in the subsequent discussion. Such treatment is not meant to exclude mechanistic variants, for example reversible kinetic 1,2-addition across the quinonoid carbonyl moiety[19] or prior single electron transfer[20] to the quinone followed by radical coupling. The critical difference exemplified by the two Schemes is the site of initial attack, *ipso* or vicinal to the halo-substituted carbon.

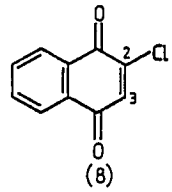
To differentiate between these two regioisomeric modes of addition requires choice of a substrate that allows differentiation of the quinonoid positions 2 and 3. Earlier work on naphthoquinones,[21] chiefly by Thomson,[11,18,22,23] has shown that the course of nucleophilic addition is controllable by the electronic influence of substituents in the benzenoid ring. For example, electron donation of the 5-methoxy group in quinone (7) as shown ensures that nucleophilic addition is controlled by the 1-carbonyl and hence occurs preferentially at position 3. In the absence of mechanistic complication, the site of attack is evident from the structure of the product since both positions 2 and 3 are distinguishable by reference to the methoxy group, though as noted earlier the determination of isomeric structures is not always straightforward.



(7)

In the same way displacement of halide from 2(3)-halo-5-methoxy-1,4-naphthoquinone would allow identification at the site of attack as *ipso* or vicinal to the halo substituted carbon. However, the object in considering Schemes 2 and 3 was to obtain fundamental information about the directive influence of the halo substituent electronically unperturbed by other substituents in the benzenoid ring. Accordingly, 2-chloro-1,4-naphthoquinone (8) was chosen for study.

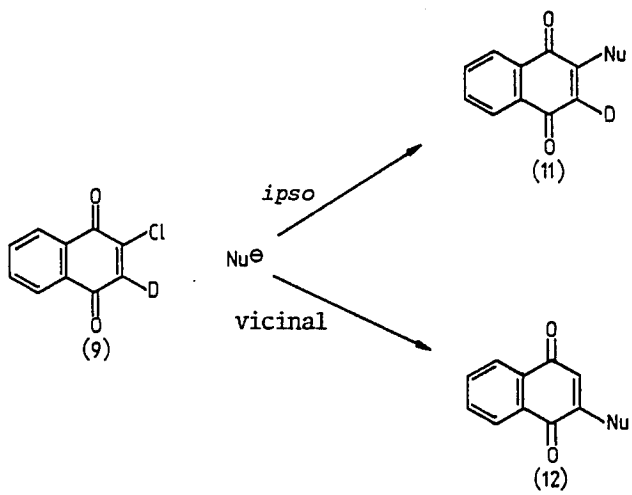
A choice of a halo naphthoquinone rather than a halo benzoquinone precludes competitive reactivity on the non-halogenated side of the quinonoid nucleus. In blocking that side of the molecule by a



(8)

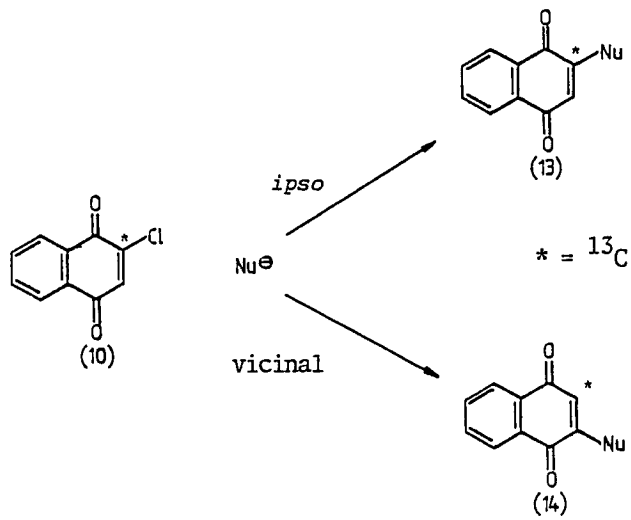
sterically or electronically significant substituent, for example a *t*-butyl group,[24] as noted earlier can exert its own directive influence on the course of the reaction.

Differentiation of the two modes of addition to 2-chloronaphthoquinone was planned by using the isotopically labelled quinones (9) and (10). In principle *ipso* attack of (9) should result in retention of the label and the product from vicinal attack ought to be unlabelled (Scheme 4). It was anticipated that naphthoquinones (11) and (12) could be readily distinguished by spectroscopic means.



Scheme 4

The carbon-labelled quinone (10) was also considered. This offered the advantage that possible loss of label by a mechanism(s) other than that in Schemes 2 and 3, or complications due to isotope effects were obviated. The two positional possibilities for the products (13) and (14) would in this case be recognizable by ^{13}C n.m.r. spectroscopy (Scheme 5). However, quinone (10) specifically labelled at position 2 was unknown at the commencement of this work.



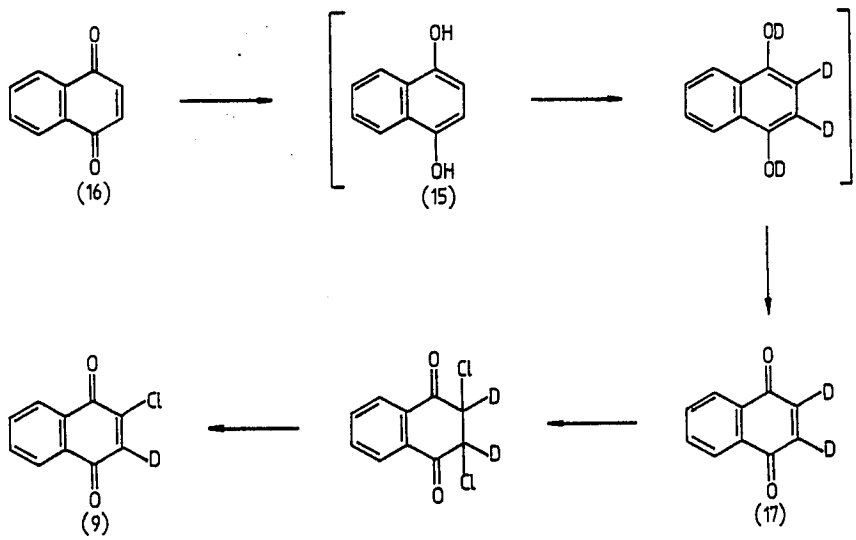
Scheme 5

CHAPTER 2

RESULTS AND DISCUSSION

2.1 Reactions of 2-Halo[3-^{2}H]-1,4-naphthoquinone

There are a limited number of examples of isotopically labelled quinones[25,26] in the literature. The deutero chloro naphthoquinone (9) was first prepared by Twaddle[27] according to Scheme 6. In this earlier work preliminary experiments were carried out reacting deuterated quinone (9) with selected nucleophiles. A number of these reactions have been repeated and refined in the present study and for overall completeness the results are presented in this Section, though most of their implications are deferred until they can be compared in conjunction with carbon-labelled material (Section 2.2).



Scheme 6

Deuterium was incorporated by base-catalysed exchange at C2 and C3 of naphthoquinol (15), prepared *in situ* by catalytic hydrogenation

of naphthoquinone (16). Oxidation furnished the dideuterated quinone (17) containing 89% incorporation of isotope determined by analysis of the mass spectrum.[28] Reaction with chlorine by a known procedure[11] yielded the labelled 2-chloronaphthoquinone (9). The isotope content of (9) (93%) was enriched in comparison to that of (17), presumably due to the deuterium isotope effect operating during elimination of hydrogen chloride from the dichloro intermediate.

The deuterium incorporation in (9), and in products derived from it, was estimated most usefully from integration of the residual signal for the quinonoid proton in the ^{1}H n.m.r. spectrum. The mass spectra of the substituted quinones discussed in this Section contain significant M-1 peaks and this complicates analysis.[28]

The deuterated quinone (9) was treated with selected nucleophiles from the first row of the periodic table. Fluoride and methoxide were chosen as examples of charged nucleophiles, along with the amines; aziridine, morpholine and pyrrolidine. The amines represent a wide range of basicities and nucleophilicities; aziridine (pK_a 8.0) and morpholine (pK_a 8.7) are significantly less basic than pyrrolidine (pK_a 11.3).

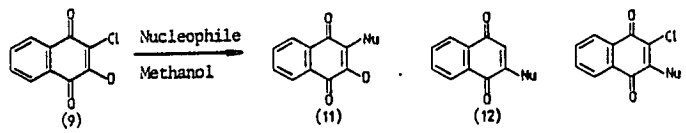
All reactions were routinely performed in the absence of light to suppress processes involving the excited state of the quinone; certain aminations of methoxy quinones have been shown to lead to different products depending on whether thermal or photochemical reaction conditions were used.[29] Air was deliberately not excluded since it was considered important to make adequate allowance for participation of the addition-oxidation mechanism outlined in Scheme 3 (p. 4).

The normalized results of addition of these nucleophiles to the deuterated quinone (9) are summarized in Table 1. The reaction of

"naked" fluoride with (9) was carried out under necessarily aprotic conditions.[30] The fluoro quinone that resulted was chiefly that which retained the label (18) indicating that *ipso* attack predominated. Its deuterium-free analogue (19) corresponding to vicinal attack was present in only a very small quantity.

TABLE 1

Reaction of Nucleophiles with the [^{2}H]Quinone (9)



(9) (11) (12)

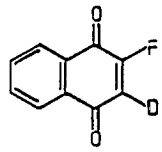
Nucleophile	Percentage Composition (11)	(12)	
⊖ F[a]	99	1	
⊖ OMe	15	85	
Aziridine	92	5	3
Morpholine[b]	82	12	3
Pyrrolidine	90	4	6
Pyrrolidine[c]	12	84	4

a. Acetonitrile was used as solvent.

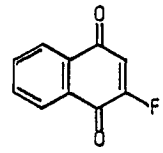
b. Ethanol was used as solvent, a fourth component (35) was isolated (3% of total product).

c. Benzene was used as solvent.

The ratio (18) : (19) was estimated by integration of the characteristic doublet at δ 6.66 in the ^{1}H n.m.r. spectrum of (19) assigned to the quinonoid proton.[30] In this, as in all other cases where such estimates



(18)

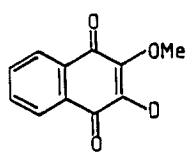


(19)

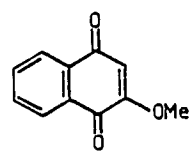
are made, account should be taken of the limits of accuracy of any quantitative procedure based on integration of n.m.r. spectra.[31] The values presented in Table 1 are normalized, representing the site of nucleophilic attack after adjustment for the residual proton content of the starting material.

It is recognized that in theory protonation of the intermediate resulting from vicinal attack must occur prior to formation of a stable product (Scheme 3). Under the strictly aprotic conditions necessary to achieve displacement with fluoride this is formally precluded. However, whether despite stringent precautions absolute exclusion of a catalytic amount of protic material can be guaranteed is questionable.

Reaction of the chloro quinone (9) with methoxide in methanol produced the methoxy quinones (20) and (21) in excellent yield overall. The ^{1}H n.m.r. spectrum of the mixture indicates a deuterium content of



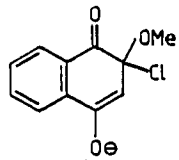
(20)



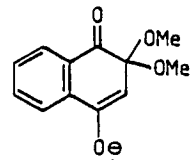
(21)

only 14% suggesting against expectation[6,10] that vicinal attack had prevailed. This seemingly anomalous result was clarified when it was

demonstrated that when either 2-chloro- or 2-methoxy-1,4-naphthoquinone (8) or (21) was treated with sodium methoxide in [*o*-^{2}H] methanol under the reaction conditions the recovered product consisting of (20) and (21), exhibited significant deuterium incorporation. This exchange may be rationalized by proton exchange involving the intermediate enolates (22) and (23), analogies for which exist in the



(22)

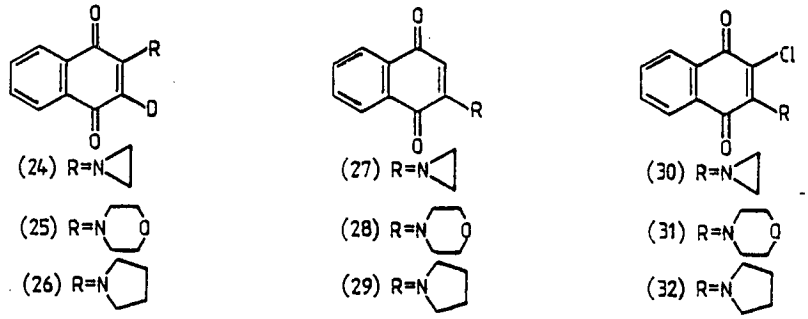


(23)

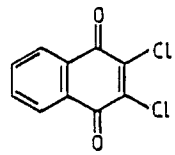
literature.[24] The exchangeable nature of the label under strongly alkaline conditions obviously limits the use of deuterated quinone (9) compared with carbon-labelled material (10) as a means of determining the mode of nucleophilic addition. As established in Section 2.2 the methoxide-catalysed displacement does indeed proceed substantially by *ipso* attack.

The amines when reacted with (9) in alcoholic media produced the same three types of substitution products; *ipso* displacement which in all cases predominated (Table 1) produced the deuterated amino quinones (24)-(26) respectively, together with minor proportions of the unlabelled amino quinones (27)-(29),[32,33] corresponding to vicinal attack and halo quinones (30)-(32)[34,35] presumably arising from oxidation of the dihydro intermediate (Scheme 3).

With the exception of the deuterated quinones and (32) all of these products are known compounds. The mass spectrum of (32) showed a molecular ion, *m/z* 263, 261, indicating retention of chlorine and



incorporation of the pyrrolidino moiety and its ^{1}H n.m.r. spectrum was fully consistent with the proposed structure. Confirmation was obtained by comparison of the product with an authentic sample derived from reaction between pyrrolidine and 2,3-dichloronaphthoquinone (33).

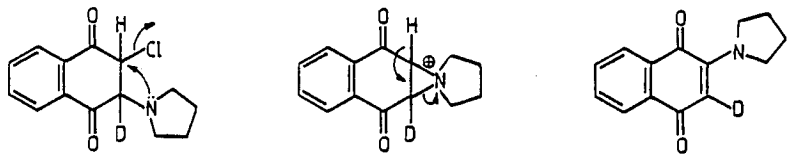


(33)

The addition of pyrrolidine to the deuterated quinone (9) in benzene was examined. The same three products (26), (29) and (32) were isolated; however, vicinal addition now predominated. This remarkable solvent effect is discussed more fully in conjunction with carbon-labelled material (Section 2.2). Nonetheless, some other mechanistic observations concerning the amine catalysed displacement can be appropriately made here.

It appears that reaction of pyrrolidine and (9) in the protic solvent methanol proceeds with *ipso* selectivity, though this process mechanistically does not require a proton source. Whereas in the aprotic solvent benzene, vicinal addition gave (29) as the major product in spite of the fact that a proton source is required. Proton transfer in this situation must therefore be rapid.

Vicinal addition has been considered by others[18] to possibly involve a spiro intermediate (34). If this intermediate species were present then initial vicinal attack might be expected to lead to retention of deuterium, as shown in Scheme 7, since operation of the deuterium isotope effect during decomposition of (34) should selectively produce

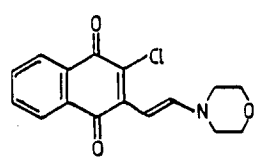


(34) (26)

Scheme 7

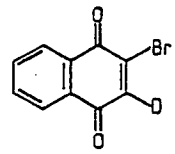
the deuterated quinone (26) rather than (29). Operation of this rearrangement to any significant extent is discounted by the fact that in benzene (29) is the major product. It is also worth noting that, unlike the reaction of (9) with the more strongly basic methoxide discussed earlier, the deuterium label was not exchangeable under the reaction conditions. In this context a similarly labelled amino benzoquinone was reported in the literature[26] as undergoing deuterium exchange rapidly though this occurred under very mildly acidic conditions.

In the case of reaction of (9) with morpholine in ethanol a fourth component, a blue compound, was isolated by Twaddle[27] but in quantities insufficient for identification. It is proposed that this substance is the enamino quinone (35) by analogy with the corresponding reaction of pyrrolidine which is discussed later. (p. 30).



(35)

Twaddle also studied the reactions of the labelled bromo quinone (36)[27] with the nucleophiles already discussed. Using ethanol



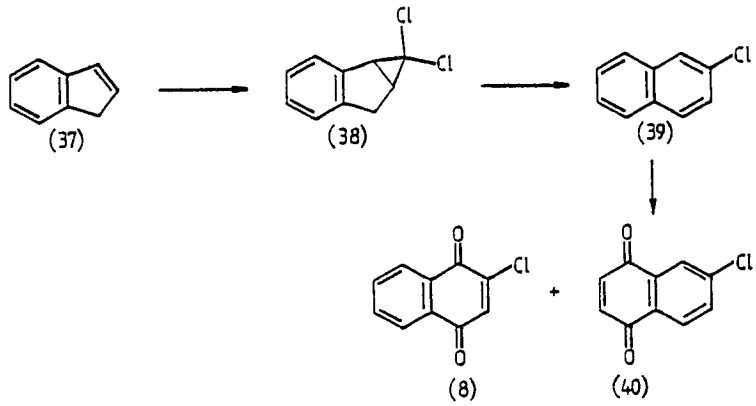
(36)

as solvent similar results to the chloro analogue (9) were obtained except for a preliminary reaction with aziridine which requires further work.

In summary results involving the chloro quinone (9) indicate that fluoride displaces a halogen from the quinonoid double bond almost exclusively by *ipso* attack. Reaction of the nitrogen nucleophiles appear to be solvent-dependent, attack occurring predominately *ipso* in alcoholic solvents, but with benzene as solvent vicinal addition is favoured. Addition of methoxide appeared ambiguous because of competitive exchange of isotope. This latter uncertainty taken together with the precedent for loss of the label from amino quinones,[17] led to the use of the ^{13}C-labelled chloro quinone (10) as a more suitable substrate. While the data derived from (10) are quantitatively in agreement where relevant with those from (9) reactions involving (10) have conveniently been developed to an apparently greater extent.

2.2 Reactions of 2-Chloro[2-^{13}C]-1,4-naphthoquinone

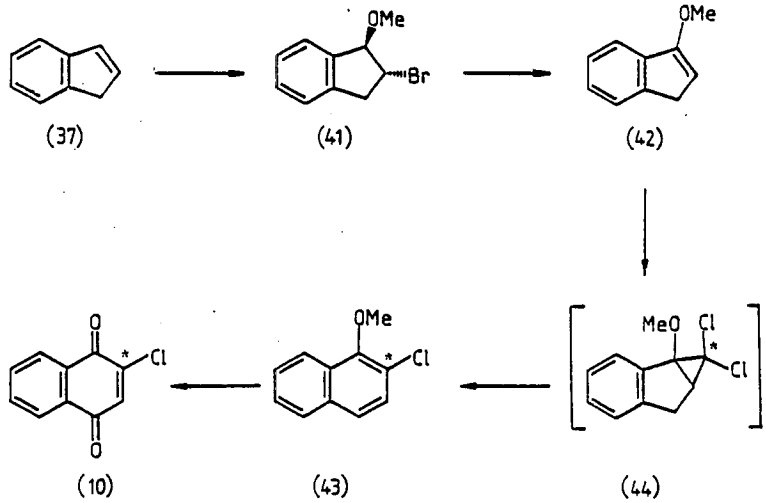
Synthesis of the carbon-labelled naphthoquinone (10) required both expeditious entry to the carbon skeleton and specific positioning of the labelled carbon and of the chlorine substituent. Dichlorocarbene addition to indene (37) is known to yield the tricyclic dichloride (38),[36] ring expansion of which furnishes 2-chloronaphthalene (39)[36] as outlined in Scheme 8. The naphthalene (39) has been oxidized with cerium (IV)[37] to give a mixture of the quinones (8) and (40).[38]



Scheme 8

This overall process using labelled dichlorocarbene would allow introduction of the label to (37) specifically as the chlorocarbon. The major shortcoming of a sequence based on this known work, the non-selective oxidation of (39) could potentially be overcome by commencing with an oxygenated indene. A new α-naphthol synthesis was devised, producing the labelled quinone (10) specifically (Scheme 9).

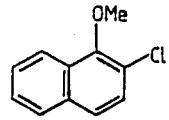
Indene (37) was treated with *N*-bromosuccinimide in methanol[39,40] yielding the *trans* bromohydrin methyl ether (41). Subsequent elimination of hydrogen bromide was achieved with 1,5-diazabicyclo[5.4.0]undecene to



Scheme 9

furnish (42) in 97% yield. This procedure is not only higher yielding but much easier to perform than the known elimination[40] mediated by potassium *t*-butoxide. Both of the products (41) and (42) were identical spectroscopically with the respective data reported in the literature.[39,40]

Addition of dichlorocarbene derived from ^{13}C-enriched chloroform (91.3%) under phase-transfer conditions proceeded with concomitant ring expansion to yield the naphthalene (43). Ring opening of the postulated intermediate (44) occurred without migration of the labelled carbon, to specifically enrich C2 of the aromatic nucleus. This was evident from the ^{13}C n.m.r. spectrum of (43) in comparison with the unlabelled analogue (45).[41] This spectrum and all subsequent ^{13}C n.m.r. spectra were measured using an inverse gated pulse sequence with a relatively long relaxation time, a procedure recommended for estimating peak area with suppression of the nuclear Overhauser enhancement.[42] In each case incorporation of the ^{13}C label was quantified by measurement

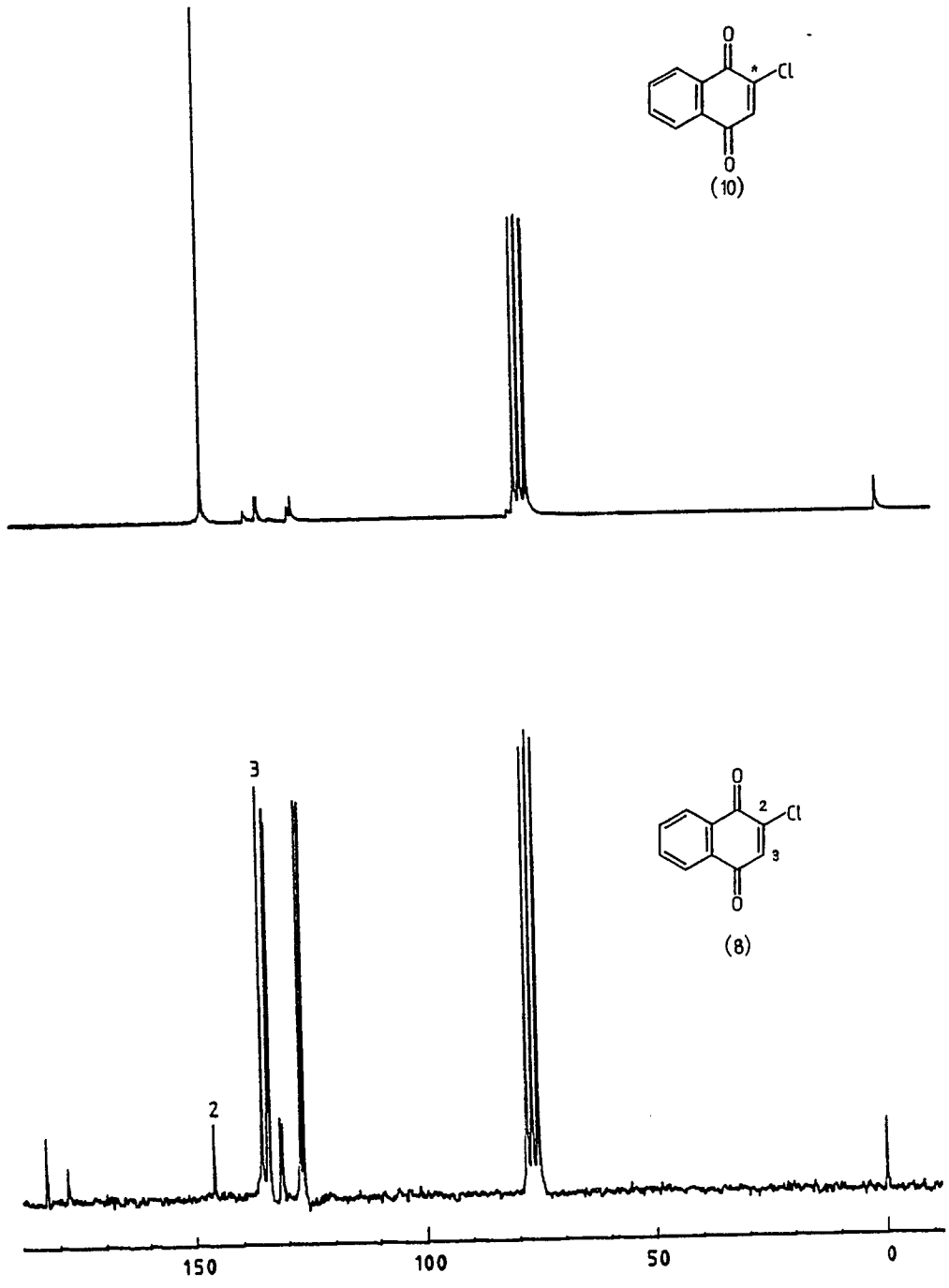


(45)

of the peak height,[43] which is proportional to the area, of the appropriate signal relative to that in the spectrum of the unlabelled compounds. The relative intensity of each pair of spectra was standardized using a signal for a carbon remote from the label.[44] Similar results where obtained when the relative area of the appropriate signals was estimated by using width at half height multiplied by height.[45] In the spectrum of (45) all carbons are distinguishable and signals at δ 61.3 and 123.1 are assigned to the methoxy carbon and C2 respectively. Using the intensity of the peak at δ 61.3 as reference, the relative areas of the signals at δ 123.1 in the unlabelled and labelled naphthalene indicate that C2 in the latter is 89% enriched with the isotope.

The naphthalene (45) could be obtained in yields up to 95% based on the indene (42) when excess chloroform was used in the carbene insertion. However, the high cost of ^{13}C-enriched chloroform precluded the use of more than one equivalent, when a lower but nonetheless workable yield (30%) of the labelled naphthalene (43) was obtained. Oxidative demethylation of the methyl ether (43) with ceric ammonium sulphate[37] afforded the labelled 2-chloro[2-^{13}C]-1,4-naphthoquinone (10) in good yield. The oxidation was directed specifically to the substituted aromatic ring, none of the alternative isomer corresponding to (40) being detected.

FIG. 1. ^{13}C N.m.r. Spectra of Labelled and Natural Abundance Chloro Quinones (8) and (10)



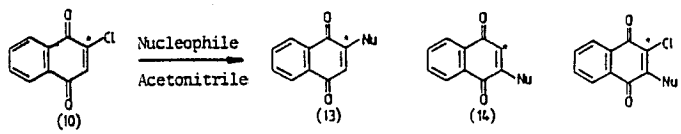
The ^{13}C n.m.r. spectra of the labelled and unlabelled 2-chloronaphthoquinones (8) and (10) are shown in Figure 1, together with the assignment of the two quinonoid carbons.[46] For the labelled quinone (10), the only peak showing measurable enhancement in comparison to unlabelled material(8) was the signal at δ 146.4 due to C2. The signal in the spectrum of the unlabelled compound at δ 135.9 assigned to C3, is replaced in the spectrum of the labelled compound by a doublet (J ~50Hz) centred at δ 135.9, consistent with natural abundance ^{13}C at C3 coupling with the isotopically enriched ^{13}C at C2. In the spectrum of (10) the higher field portion of the doublet is obscured by the signals of the aromatic carbons.

The mass spectrum of (10) indicated isotopic enrichment[28] of 90% without specifying the position of the label. The labelled quinone (10) was available in four steps beginning from indene (37) in an overall yield of 13%.

Use of the carbon-labelled quinone (10) as opposed to the deuterated substrate (9) has the added advantage that both of the quinonoid carbons can be substituted during reaction and the regiochemistry of addition can still be determined. This allows for investigation of annelation reactions such as Diels-Alder cycloadditions and nucleophilic addition of 1,1-dialkoxyethenes (2) as in the process (1) to (3). The latter process must necessarily be performed in dipolar aprotic solvents for 1:2 addition to take place.[3] A similar solvent restriction applies to fluoride as a nucleophile.[30] Accordingly, comparative reactions involving (10) were standardized as far as possible. Normalized results incorporating selected nucleophiles from the first row of the periodic table are summarized in Table 2.

TABLE 2

Reaction of Nucleophiles with the [^{13}C]Quinone (10)



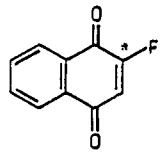
	Percentage Composition		
⊖F	100	0	
⊖OMe[a]	93	7	
Aziridine	25	70	5
Pyrrolidine	24	71	5
1,1-Dimethoxyethene	0	100	

a. Methanol was used as solvent.

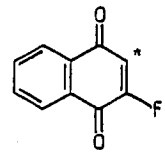
It is noteworthy that hard nucleophiles,[47] such as fluoride and methoxide, attack the chloro quinone (10) predominately *ipso*. Soft nucleophiles[47] (88), on the other hand displace chlorine through exclusive vicinal addition. The amines are borderline in hard/soft terms[47] and their lack of regioselectivity reflects this although vicinal addition predominates. This is consistent with reactions of hard nucleophiles, which are charge-controlled processes,[48,49] being directed to the more electron deficient quinonoid carbon C2.† However, soft nucleophiles are directed to attack the unsubstituted carbon C3 under orbital control.[48,49,51,52]

† *It is significant in this context that in the ^{13}C n.m.r. spectrum of (8) that C2 resonates downfield at δ 146.4 and C3 resonates at δ 135.9.*[50]

The charged nucleophiles, fluoride and methoxide attack the chloro quinone (10) predominately *ipso*. In the case of "naked" fluoride, the product (46) is formed exclusively. The ^{13}C n.m.r. spectrum of the labelled fluoro quinone (46) shows the doublet at δ 161.5 assigned as C2[17] to be enriched whilst no other peak exhibited any measurable enhancement. The fluoro quinone (47) was not observed.



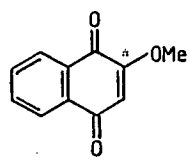
(46)



(47)

As discussed in the preceding section, whilst in principle vicinal attack is not possible under strictly aprotic conditions, in a practical sense this process cannot be precluded.

Methoxide also attacked the halo quinone (10) predominately *ipso*. This result indicates that loss of label in the reaction of methoxide with the deuterated quinone (9) was due to an exchange process as described earlier (see p. 12). Whilst predominate *ipso* attack of methoxide has been confirmed, the minor amount of vicinal attack is noteworthy. In the ^{13}C n.m.r. spectrum of the mixture of (48) and (49) the signals at δ 109.9 and δ 160.4 due to C3 and C2 respectively were



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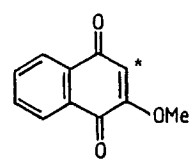
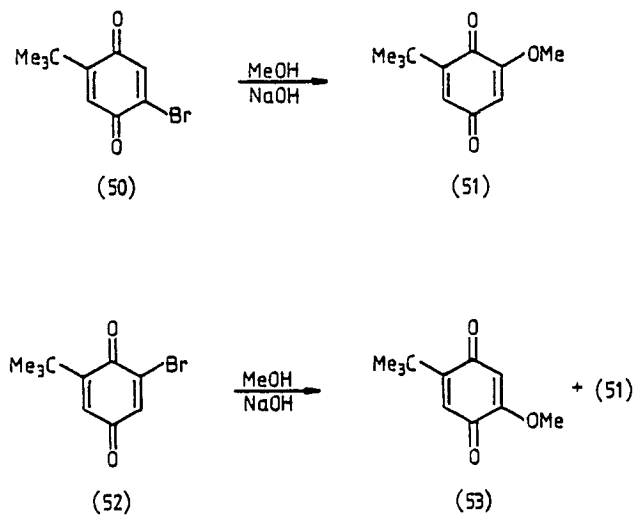


(49)

enhanced in a ratio of 7:93 relative to the unlabelled methoxy quinone (21).

In a synthetic context reaction between halo quinones and methoxide is generally taken for granted as proceeding with *ipso* specificity.[6,10] The most notable exception being described by Hewgill and Mullings[24] who showed that methoxide in methanol can displace a halogen through vicinal attack. Thus the bromo quinone (50) when treated with alkaline methanol produced only the methoxy quinone (51). The isomeric bromo quinone (52) under the same conditions gave a 2:1 mixture of (53) and (51) respectively, as shown in Scheme 10. However, in dimethylsulphoxide *ipso* displacement predominated in both cases.



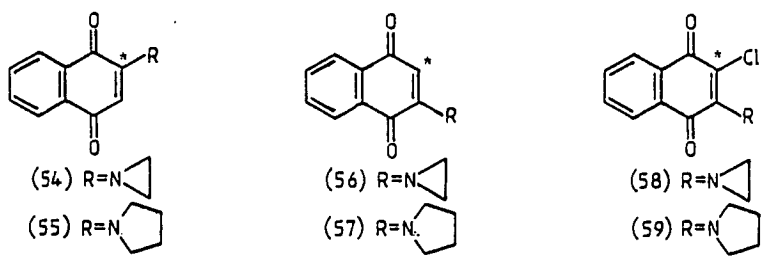
Scheme 10

Whatever the detailed mechanistic implications of this regioselectivity are, it is clear that the thermodynamics of these processes are finely balanced. It has to be assumed in the present work that variations in the quinonoid substrate, the leaving group and the sterically demanding *t*-butyl group are significant to the

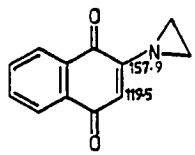
extent that factors which favoured vicinal attack in the case of (50) in methanol are suppressed in reaction of (10).

Attempted reaction of 2-chloronaphthoquinone (8) with methoxide in dipolar aprotic solvents such as acetonitrile, *N,N*-dimethylformamide or dimethylsulphoxide was surprisingly unsuccessful. However, it was found that the expected product 2-methoxynaphthoquinone (21) decomposed rapidly when treated with methoxide in these solvents. Whilst this instability precluded investigation of possible solvent dependence of the methoxide displacement, parallel to that described by Hewgill, a quite remarkable solvent dependence involving amine nucleophiles was observed.

As expected from the work on the deuterated quinone (9) reaction of (10) with the amines, aziridine and pyrrolidine using acetonitrile as solvent produced three products in each case; the amino quinones (54) and (55) from *ipso* substitution and the vicinal substitution products (56) and (57). Vicinal substitution also produced the amino chloro quinones (58) and (59) (Scheme 3). By



analogy with literature values for 2-mopholino-1,4-naphthoquinone (28)[46] signals in the ^{13}C n.m.r. spectrum of the aziridino quinone (27) at δ 119.5 and 157.9 were assigned to C3 and C2 respectively.



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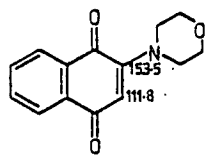
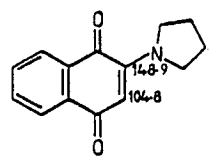


(28)



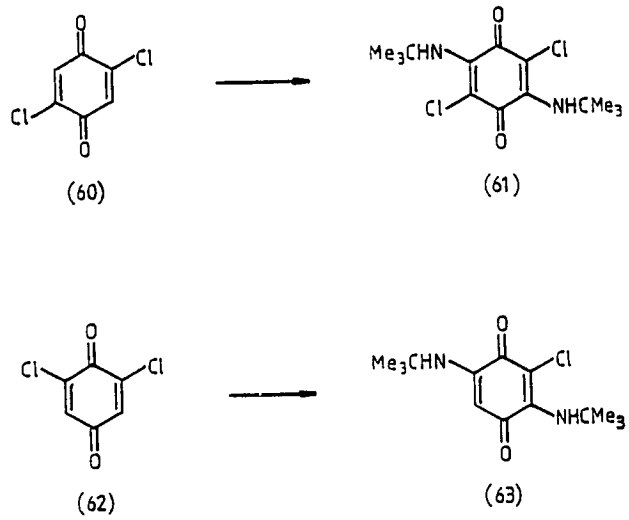
(29)

In the mixture of (54) and (56) the intensities of the signals at δ 119.5 and 157.8 relative to the signal of 27.7 due to C2' and C3' indicates enhancement in the ratio of 70:25 over natural abundance ^{13}C resulting from predominantly vicinal attack. Product (58) must also have resulted from vicinal attack and this was substantiated in its ^{13}C n.m.r. spectrum in which only the signal at δ 127.1 due to C2 was measurably enhanced relative to unlabelled material (30).

Reaction of (10) with pyrrolidine in acetonitrile gave the mixture of pyrrolidino quinones (57) and (59). In the ^{13}C n.m.r. spectrum of the unlabelled pyrrolidino quinone (29) signals at δ 104.8 and 148.9 were assigned to the unsubstituted quinonoid carbon C3 and the substituted C2 respectively. By the usual procedure comparing the intensity of these two peaks with reference to the signal at δ 50.9 due to C2' and C5' enrichment of C2:C3 with the isotope relative to the unlabelled material (29) was determined as 24:71. The product from vicinal attack (57) augmented by a relatively minor amount of the pyrrolidino chloro quinone (59) again indicates the predominance of this mode of attack in acetonitrile. In the ^{13}C n.m.r. spectrum of (59) only the signal at δ 111.5, attributed to the chlorinated carbon C2, was measurably enhanced.

The addition of amine nucleophiles to quinones has received considerable attention recently in respect to the synthesis of aminated quinones,[9] in particular the mitomycins.[26,53-55] The lack of regiospecificity in a number of examples and in the reaction of (10) with pyrrolidine and aziridine prompted a more detailed investigation of these processes.

The general topic of addition of nucleophiles has been studied extensively and the diversity of these reactions has been reviewed.[21] There is some evidence that amines attack the unsubstituted carbon of a halo quinone. For example,[56] addition of t-butylamine to 2,5-dichlorobenzoquinone (60) produced the diaminated quinone (61) albeit in modest yield, although reaction with 2,6-dichlorobenzoquinone (62) produced quinone (63) (Scheme 11). Formation of (63)

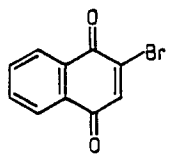


Scheme 11

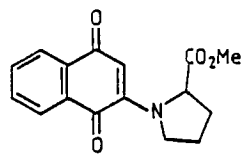
exemplifies the subtle nature of these additions. Irrespective of which amino group attacks the quinonoid nucleus of (62) its electronic

effect is such that addition of the second amine is directed to attack in the alternative mode (*ipso* or vicinal) to produce a 2,5-diaminated benzoquinone.

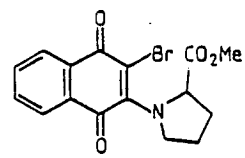
In the majority of the literature examples involving amine nucleophiles, alcohols (methanol or ethanol) are used as solvent. In one case, a reaction very closely analogous to reaction of (10) and pyrrolidine was carried out in benzene.[53] Reaction of 2-bromonaphthoquinone (64) with the methyl ester of proline gave the amino quinone (65) together with the disubstituted quinone (66) in a ratio of 12:1. Nothing can be deduced regarding the regiochemical origin of (65);



(64)



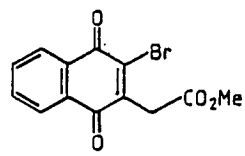
(65)



(66)

however, by analogy with results from (10) and the ratio of (55) and (57) it might be argued that the amount of (66) isolated could indicate predominately vicinal attack.

On the other hand it appeared from this same work, that the best conditions found to effect *ipso* attack by pyrrolidine on the mono halo quinone (67) used a mixture of methanol and toluene as solvent. This, together with the demonstration by Hewgill[24] that solvent played

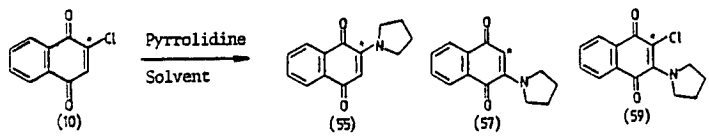


(67)

an important role in determining direction of attack of nucleophiles on benzoquinones (50) and (52), led to an examination of the reaction of (10) with pyrrolidine in a variety of solvents. The normalized results of these reactions are summarized in Table 3.

TABLE 3

Reaction of Pyrrolidine with the [^{13}C]Quinone (10)



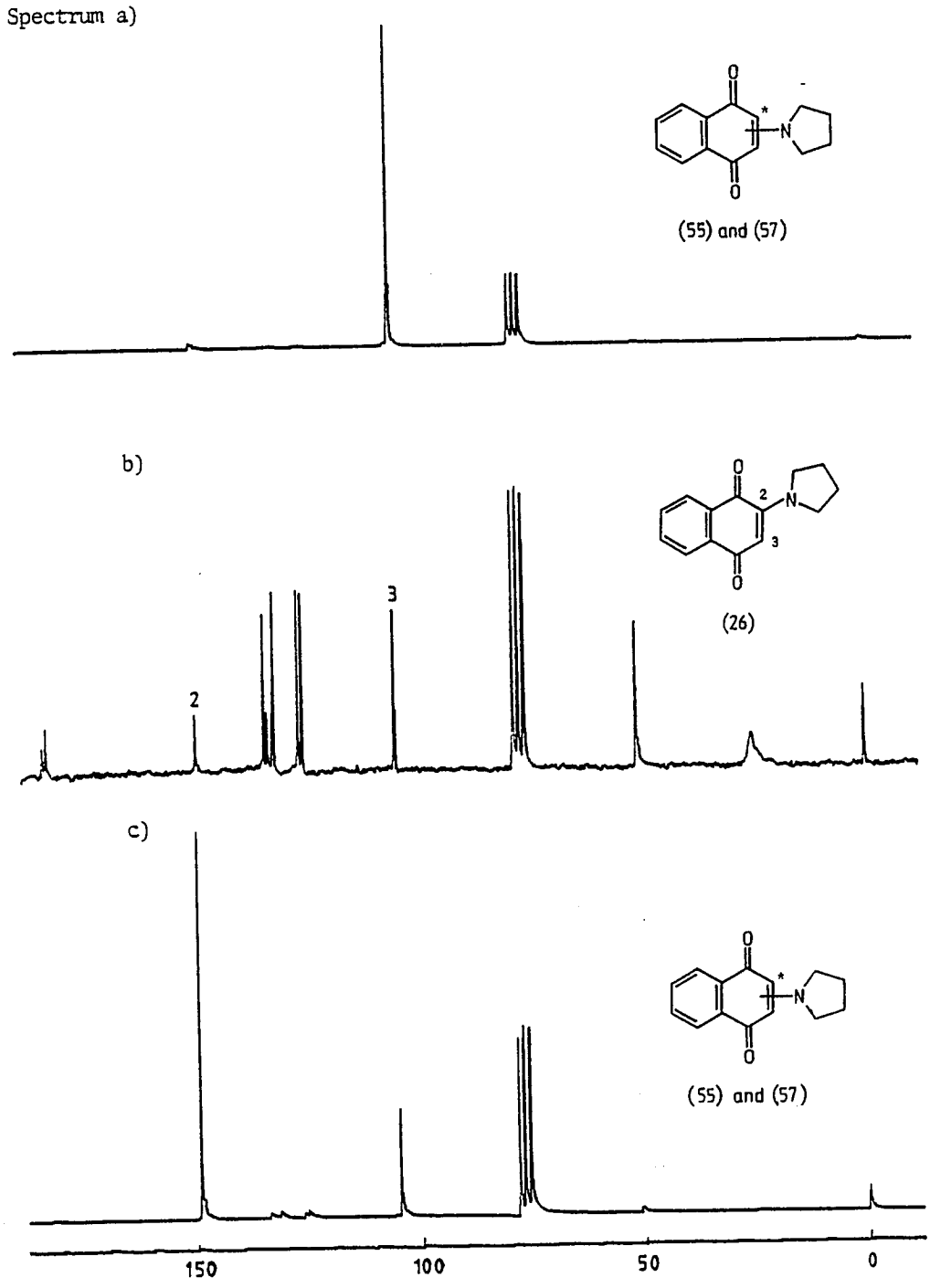
Solvent	Percentage Composition (55)	(57)	(59)
Benzene	8	80	12
Acetonitrile	25	70	5
Ethanol[a]	81	13	6
Methanol	84	10	6

a. Trace amounts of (68) were isolated.

The results indicate a reversal in the site of nucleophilic attack of pyrrolidine when the solvent is changed from aprotic to protic. The orientation of addition appears independent of polarity, non-polar benzene and dipolar acetonitrile give vicinal selectivity whilst in alcoholic solvents *ipso* substitution predominates.

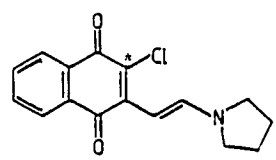
This is dramatically illustrated by the ^{13}C n.m.r. spectra of the product pyrrolidino naphthoquinones (55) and (57) from the reactions in a) benzene and c) methanol shown in Figure 2.

FIG. 2. ^{13}C N.m.r. Spectra of Labelled and Natural Abundance Pyrrolidino Quinones (29), (55) and (57)



Spectrum b) in Figure 2 is of the unlabelled quinone (29), assignment of the signals is made by analogy with those of 2-morpholino-1,4-naphthoquinone (31)[46] and is in accord with single frequency off-resonance measurements. In spectrum a) in Figure 2 marked enhancement of the resonance at δ 104.8 (C3) relative to that at δ 148.9 (C2) indicates predominantly vicinal attack in benzene. The reversal of the site of nucleophilic attack in methanol is evident from spectrum c) in which the signals for C2 and C3 are enhanced in the reverse sense. When the amount of product from vicinal attack is augmented by the amount of the disubstituted product (59), the ratio of vicinal to *ipso* attack is 92:8 in benzene whilst in methanol it is 16:84.

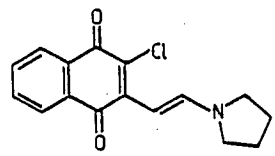
Analysis of the ^{13}C n.m.r. spectra of the labelled pyrrolidino quinones (55) and (57) from the reactions carried out in a dipolar aprotic solvent, acetonitrile, also showed a preference for vicinal attack, whilst in ethanol *ipso* attack predominated. A fourth component was isolated in low yield from reaction of (10) and pyrrolidine in ethanol, but not when any of the other solvents were used. The electron absorption of this blue compound (λ_{max} 594 nm) was similar to that reported by Henbest[56] for enamino quinones and on this basis structure (68) was tentatively assigned (compare with compound (35) p. 14).



(68)

The low yield of the blue compound precluded its identification directly, its structure was therefore confirmed by synthesis. Pyrrolidine

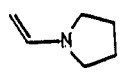
was allowed to react with acetaldehyde then 2,3-dichloronaphthoquinone (33) was added and the enamino quinone (69) was isolated. The ^1H n.m.r. spectrum showed two multiplets at δ 2.03 and 3.50 for the



(69)

pyrrolidinyl ring protons together with the characteristic aromatic pattern. In addition there were two olefinic doublets at δ 5.54 and 8.60 (J_{trans} 13Hz). The electronic spectrum of the synthetic sample was identical with that obtained for the by-product and the two samples were chromatographically indistinguishable.

The formation of (69) is postulated to result from nucleophilic attack of the enamine (70) in the vicinal mode by a mechanism similar to

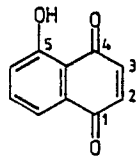


(70)

that in Scheme 3. The enamine is possibly formed by oxidation of ethanol under the reaction conditions or contamination of ethanol with acetaldehyde. Condensation of the amine and acetaldehyde would then furnish the enamine (70).

References in the literature to the solvent dependence of the site of nucleophilic addition to quinones are rare. It has been shown[57] that 5-hydroxy-1,4-naphthoquinone (juglone) (71) reacts with

piperidine to produce a mixture of 2- and 3-piperidino derivatives (72), (73). In neat piperidine (72) predominates whilst in ethanolic solutions (73) is the major product. The phenomenon was not investigated further. In addition to their work which demonstrated



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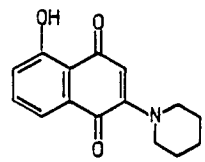
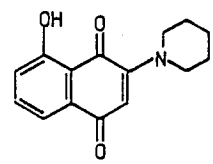
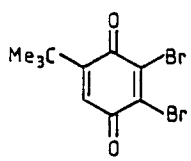


(72)

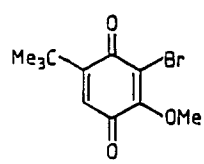


(73)

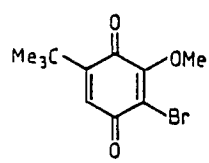
the solvent dependence of the orientation of addition of methoxide to the bromo quinones (50) and (52), Hewgill and Mullings[24] also showed that the dibromo quinone (74) when reacted with methoxide in dimethylsulphoxide produced (75) whilst in methanol formation of (76) was observed.



(74)

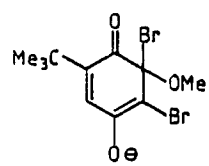


(75)



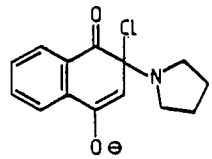
(76)

It was postulated[24] that under equilibrating conditions formation of the more readily solvated, less hindered enolate (77) in the protic medium would be favoured thus accounting for the



(77)

formation of (76) in methanol. Dimethylsulphoxide, a dipolar aprotic solvent which does not significantly solvate anions[58], would preferentially form (75) under the electronic influence of the t-butyl group. A similar argument could be used to account for the difference observed with reaction of pyrrolidine with the labelled quinone (10). The less hindered enolate (78) may be stabilized by solvation in protic



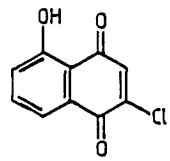
(78)

solvents and so direct *ipso* nucleophilic addition. The aprotic solvents, benzene and acetonitrile do not solvate anions and vicinal addition prevails.

As observed in earlier work[24] there remains a good deal of uncertainty about the mechanistic detail of these processes. It is interesting that attack of methoxide towards the bromo benzoquinones (50) and (52) should occur preferentially *ipso* to the halo substituent in dimethylsulphoxide and vicinal in methanol; whereas for the chloro naphthoquinone (10) the reverse should be the case. This difference cannot be rationalized in first-order terms, but is illustrative of the subtle factors which evidently control such processes, factors like the change of substrate from benzoquinonoid to naphthoquinonoid and the nature of the leaving group from bromide to chloride.

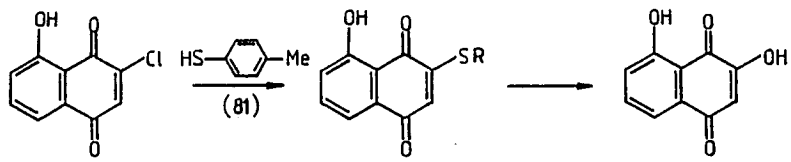
It is noteworthy that the chloro pyrrolidino quinone (59) is formed in greater amounts when the reaction is performed in benzene than in polar solvents. This presumably reflects the ease of elimination of hydrogen chloride in polar solvents.

Inasmuch as nucleophilic addition to juglone (71) and its derivatives has been widely studied,[11,18,22,23] and as the orientation of addition has regularly been inferred from subsequent displacement of the quinonoid substituent, it was decided to extend the present work to include a brief investigation of displacements on 2- and 3-chlorojuglone[11] (79) and (80). This deliberately superimposes on the chloro quinone system a substantial electronic perturbation.



(79)

An example of the published chemistry of chloro juglones[18] is shown in Scheme 12. Displacement of chloride from (80) by the



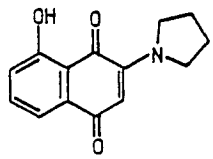
(80) (81) (82) (83)

Scheme 12

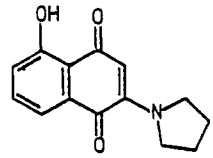
thiol (81) gave the thioether (82) whose structure followed from assumed *ipso* hydrolysis to the known (83). Whilst there is no suggestion that this conclusion is not correct, the results from the reaction of (80) with pyrrolidine counsel caution in assumptions of the regiochemistry of these precesses.

When 3-chlorojuglone (80) was made to react with pyrrolidine in methanol the isomeric pyrrolidino juglones (84) and (85) were

produced in good overall yield in the ratio 31:1. The two products

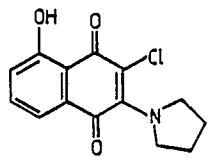


(84)

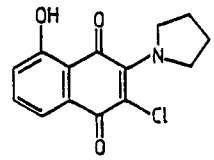


(85)

have very similar ^{1}H n.m.r. spectra, the only distinguishing feature being the chemical shift of the hydroxy protons *peri* to carbonyl. The chemical shift of hydroxy protons in juglones is known to be sensitive to electronic effects of the quinonoid substituents. It has been shown not to be concentration-dependent and has been used to differentiate isomeric juglones.[59,60] In 2-pyrrolidinojuglone (85) the mesomeric effect of the nitrogen is to cause a downfield shift of the hydroxy proton to δ 13.21 relative to 11.87 in juglone (74) itself. In 3-pyrrolidino juglone (84) on the other hand the hydroxy proton resonates at δ 11.95. A third component was also isolated from reaction of (80) with pyrrolidine. This unstable product is assumed to be the amino chloro juglone (86).



(86)



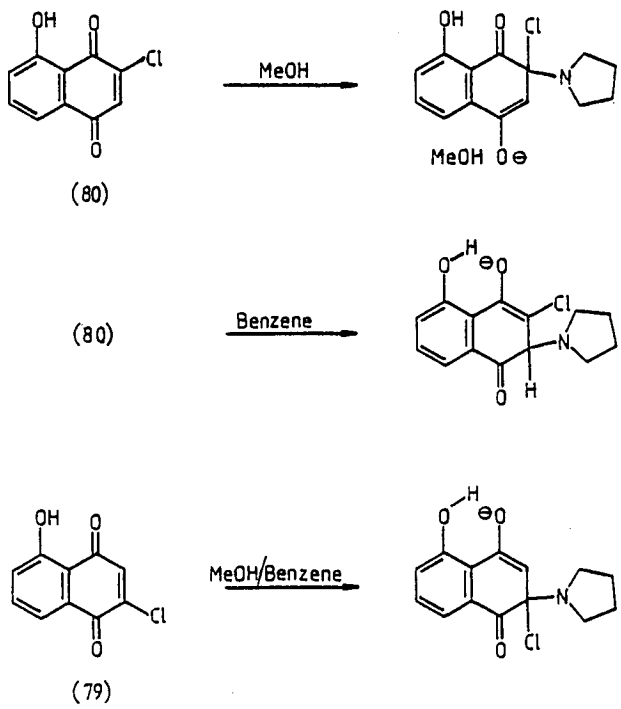
(87)

When the reaction was performed in benzene the same three products were observed in good overall yield. However, in this case the major product was 2-pyrrolidinojuglone (85), favoured in the ratio of 20:1 over its isomer (84). These results parallel the solvent effects observed with the labelled chloro naphthoquinone (10) and those

observed by Cameron and Samuel[57] for the reaction of juglone itself with piperidine.

Reaction of 2-chlorojuglone (79) with pyrrolidine in either benzene or methanol produced (85) from *ipso* substitution as the major product. Again a third component was observed and assumed to be the amino chloro juglone (87). The fact that reversal of orientation was not observed in this case upon changing solvent again emphasizes the subtle nature of factors controlling the regiochemistry of addition.

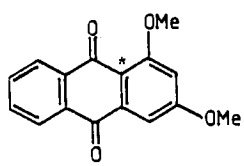
An argument analogous to that used earlier[24] based on solvation of the putative enolate intermediates in thermodynamically-controlled processes could be invoked (Scheme 13). In benzene intramolecular



Scheme 13

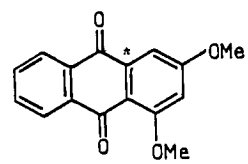
stabilization afforded by the *peri* hydroxy group favours formation of products from attack at the 2- position regardless of the location of the halogen. In methanol solvation of the less hindered enolate from (80) favours formation of products from *ipso* attack. However, the steric advantage of the enolate derived from vicinal attack on (79) is no longer obvious due to the proximity of the chloro group and solvation of the C4 enolate at the more polar region of the molecule. The regiochemical influence of the *peri* hydroxy group in the reactions of juglone itself has been shown previously.[23] Reactions of chloro naphthoquinones substituted in the benzenoid ring with less powerfully directing groups are currently under investigation in this Department.

Addition of carbon nucleophiles to the ^{13}C-labelled quinone (10) was next investigated. Addition of 1,1-dimethoxyethene (88) in a 1:2 process yielded 1,3-dimethoxyanthraquinone (89) by exclusive vicinal attack, the isomeric anthraquinone (90) not being detected.

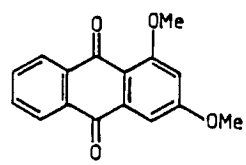


(89)

(88)

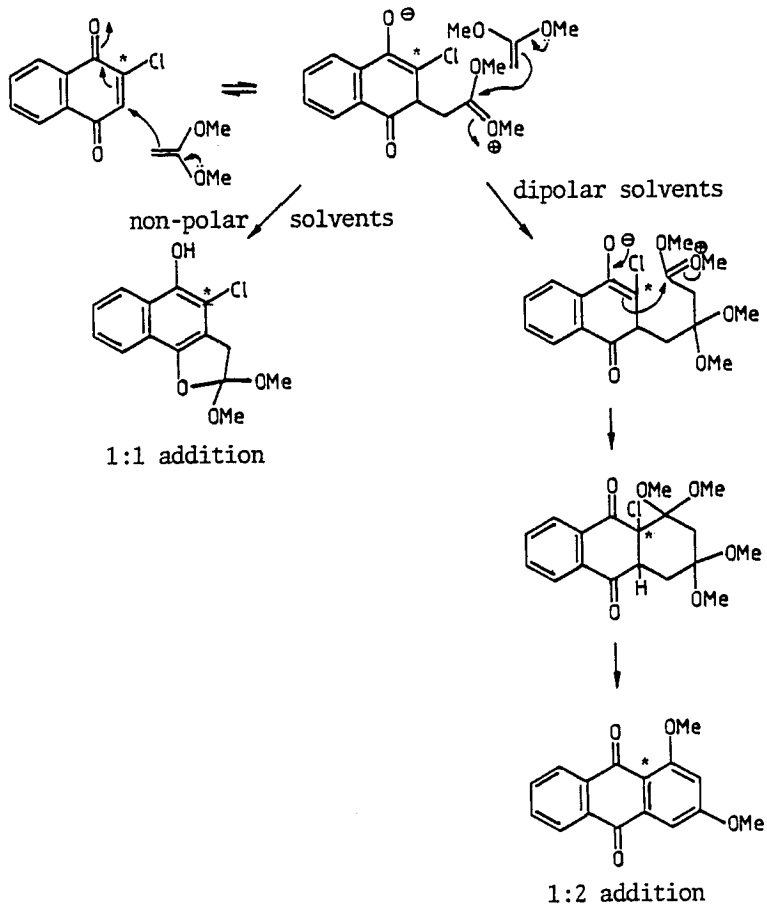


(90)



(91)

The postulated mechanism[3] for this process is outlined in Scheme 14.

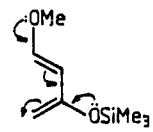


Scheme 14

In the ^{13}C n.m.r. spectrum of unlabelled 1,3-dimethoxyanthraquinone[61] (91) the signals at δ 116.1 and 137.5 were assigned to carbons 9a and 4a respectively. The only signal in the ^{13}C n.m.r. spectrum of the labelled product (89) exhibiting any enhancement over natural abundance

was that at δ 116.1. This result is further evidence for the vicinal specificity of the carbon nucleophile (88). Reactions of this nucleophile with chloro naphthoquinones substituted in the benzenoid ring have been thoroughly investigated,[3-6] and in all cases the process has been similarly regiospecific as noted earlier (p. 1).

There is a natural extrapolation from the behaviour of carbon nucleophiles such as (88) towards halo quinones, to the Diels-Alder annelation of the latter with polar butadienes (e.g.(4)[7]). This process has proved extremely useful in the synthesis of natural products.[62] Both oxygen substituents of (4) electronically reinforce one another rendering the unsubstituted terminus more electron rich.

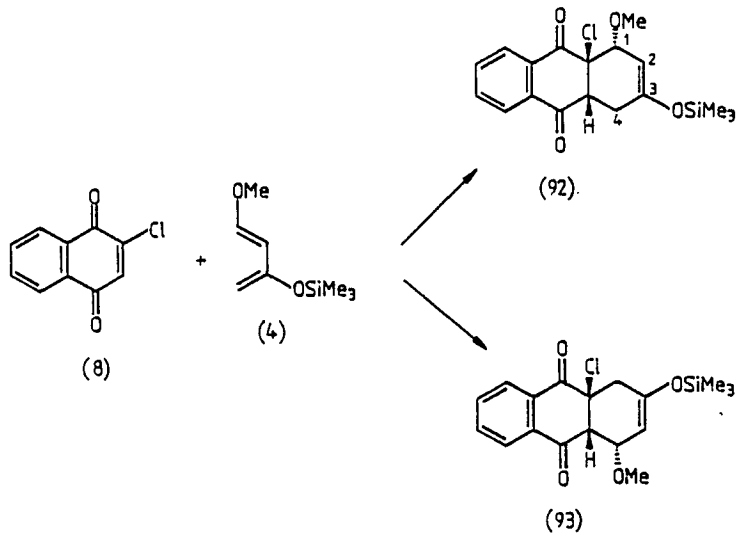


(4)

Recently, the Diels-Alder addition of (4) to quinonoid dienophiles has been investigated[8,63] and in all cases where the quinonoid double bond was substituted with either a chloro, acetoxy, methyl or methoxy group the addition had vicinal specificity.

Addition of the diene (4) to 2-chloronaphthoquinone (8) could produce either of the isomeric adducts (92) or (93) which retain the halogen (Scheme 15). The anticipated stereochemistry is consistent with *endo* selectivity, as has been established for simpler analogues.[8]

When the reaction with (8) was performed in acetonitrile the adduct (92) resulting from vicinal attack was isolated. Although unstable, the product was ammenable to characterization. Its ^{1}H n.m.r.



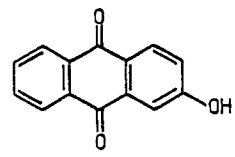
Scheme 15

spectrum confirmed the structure as (92). In particular, a doublet at δ 4.14 assigned to H1 showed a single vicinal coupling to the vinyl proton H2 (J_{vic} 5Hz). In the isomeric adduct (93), H1 would appear as a doublet of doublets vicinally coupled to both the vinyl proton and also to the proton at the ring junction H9a. The rest of the spectrum was fully consistent with the assigned structure (92) as were other spectral data.

Examination of the ^{1}H n.m.r. spectrum of the crude reaction mixture failed to show even a trace of the isomeric adduct (93). Use of the labelled quinone (10) was not necessary to distinguish the two adducts (92) and (93) as retention of the halogen unequivocally establishes the regiochemistry of the reaction. The latter is consistent with the more nucleophilic terminus of the diene attacking the halo quinone vicinally, as does the carbon nucleophile (88). This

directive influence of the halo substituent is apparently general for Diels-Alder additions of highly functionalized butadienes to chloro quinones and as such it is important to the work described in the next part of this Thesis.

Aromatization of the simple adduct (92) produced 2-hydroxy-anthraquinone (94) in excellent yield. Similar aromatizations involving more highly substituted systems are routinely employed in the work that follows where firm orientational control is required.



(94)

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage and are uncorrected. Microanalyses were carried out by AMDEL Australian Microanalytical Service, Melbourne.

Electronic spectra were recorded in ethanol using a Varian Super Scan 3 Spectrophotometer unless otherwise stated. Infrared spectra were recorded for solids in potassium bromide discs or as a film for liquids using a Perkin Elmer 457 Grating Spectrophotometer.

Proton nuclear magnetic resonance spectra were recorded at 100 MHz using a JEOL FX-100 Spectrometer. Deuterochloroform was used as solvent with tetramethylsilane as internal reference unless otherwise stated. Chemical shifts are quoted on the δ-scale followed by multiplicity, coupling constant(s) and assignment.

Carbon nuclear magnetic resonance spectra were recorded at 25 MHz using a JEOL FX-100 spectrometer. Where relevant, assignments were confirmed by single frequency off resonance decoupled spectra. For determining relative isotope incorporation an inverse gated pulse mode under double precision acquisition with a pulse delay of 4.2 sec. was used[41] for both labelled and unlabelled compounds. Integration of the appropriate signals was performed by measuring the peak heights of these signals.[42] Relative enrichment was determined by comparison[43] of the peak heights of the same signal in ^{13}C n.m.r. spectra of both the labelled and unlabelled compounds relative to a reference signal remote from the label.

Mass Spectra were recorded using a V.G. Micromass 7070F instrument at 70 eV unless otherwise stated. The mass of the ion

followed by the intensity are given, in general only those peaks greater than 20% are quoted. Where relevant, the isotope incorporation is given in brackets after the mass spectral data.

In reporting spectral data the following abbreviations have been used : sh, shoulder; s, singlet; d, doublet; t, triplet; q, quartet; br, broad; m, molecular ion.

Flash chromatography[64] was carried out using Merck Silica No. 9385. Thin layer chromatography (t.l.c.) was carried out on glass plates coated with a layer of silica gel (Merck Kieselgel GF_{254} or silica gel containing 2% oxalic acid). The separated compounds were extracted from the adsorbent using ethyl acetate or chloroform, oxalic acid was removed by washing the organic phase with water.

All solvents used were redistilled prior to use or were of analytical grade. Acetonitrile was distilled from phosphorous pentoxide and stored over 4Å molecular sieves. 1,2-Dimethoxyethane and tetrahydrofuran were freshly distilled from potassium benzophenone ketyl under nitrogen immediately prior to use. Dry ethanol and methanol were distilled from magnesium. Benzene, ether and pentane were all dried with sodium wire. Petrol refers to the hydrocarbon fraction boiling in the range 60-80°, light petrol refers to the boiling range 40-60°.

All organic extracts were dried over anhydrous sodium sulphate and filtered before evaporation.

[^{13}C]Chloroform was obtained from Novachem and used without purification.

[2,3-2H$_2$]-1,4-Naphthoquinone (17)

A solution of 1,4-naphthoquinone (16) (2 g) in ethanol (100 cm^3) was shaken over Adams catalyst (20 mg) under hydrogen (1 atm) until the yellow solution became clear. The solvent was evaporated and a solution of sodium methoxide (7 g) in deuterium oxide (25 cm^3) was added to the residue with exclusion of air. The reaction mixture was stirred at 90^o for 120 h, cooled to room temperature and diluted with acetic acid (30 cm^3). A solution of ferric chloride (8.0 g) in water (1000 cm^3) was added dropwise and the reaction mixture was stirred for 1 h. The mixture was then filtered and extracted with ether (3 x 150 cm^3). The ether extract was washed with water (3 x 100 cm^3), dried and evaporated. Recrystallization of the crude product from light petrol (charcoal) gave the *deuterated quinone* (17) (0.81 g, 42%)[27] as yellow needles (m.p. 126-127^o) *m/z* 160 (M, 100%). ($2H_2$ 89%, 2H, 8%). In the ^{1}H n.m.r. spectrum, the signal at δ 6.99 due to protons at C2 or C3 integrated for 0.17 protons.

2-Chloro[3-^{2}H]-1,4-naphthoquinone (9)

Chlorination of deuteronaphthoquinone (17) (200 mg) according to the procedure of Thomson[11] afforded the *deuterium-labelled chloro quinone* (9) (220 mg, 91%)[27] as yellow needles from methanol m.p. 115-116^o *m/z* 193 (M, 100%), 165 (21), 158 (54), 130 (91), 104 (34), 102 (36) 76 (62), 75 (29), 50 (37). (91% enriched). In the ^{1}H n.m.r. [$(CD_3)_2CO$] the signal at δ 7.36 due to protons at C3 integrated for 0.07 protons.

Trans *2-Bromo-1-methoxyindane (41)*

Indene (37) (16.0 g) was treated with *N*-bromosuccinimide (26 g) and sulphuric acid (5 drops) in methanol (60 cm^3) according to the method of Iovchev.[39] Distillation afforded the indane (41) (21.8 g, 70%) b.p. 108-110^o/3.5 mm (lit.[39] 105-6^o/3 mm) as a colourless liquid.

λ_{max} (log ε) 247 sh, 254 sh, 259, 266, 333 nm (2.68, 2.77, 2.88, 3.00, 3.02). ν_{max} 2920, 1605 cm^{-1}. δ 3.17 dd, *J* 17, 5 Hz, H3α or β; 3.55, s, OCH_3; 3.68, dd, *J* 17, 6.5 Hz, H3α or β; 4.45 ddd, *J* 6.5, 5, 3.5 Hz, H2; 4.94, d, *J* 3.5 Hz, H1; 7.20-7.40, m, 4 x ArH. *m/z* 228 (M[^{81}Br], 8%), 226 (M[^{79}Br], 8), 107 (12), 195 (12), 147 (100).

1-Methoxyindene (42)

A solution of *trans*-2-bromo-1-methoxyindene (41) (5.1 g) and 1,5-diazabicyclo[5.4.0]undecene (4.1 g) in dry acetonitrile (30 cm^3) was stirred under a nitrogen atmosphere for 20 h. The solvent was evaporated and the residue was distilled bulb-to-bulb yielding the indene (42) (3.2 g, 97%) as a colourless liquid b.p. 111-113°/14 mm (lit.[40] 101-104°/15 mm). λ_{max} (log ε) 251 nm (3.82). δ 3.25, d, *J* 2.5 Hz, CH_2; 3.81, s, OCH_3; 5.22, t, *J* 2.5 Hz, H2; 7.11-7.46, m, 4 x ArH. *m/z* 146 (M, 65%), 131 (68), 103 (67), 77 (31).

2-Chloro-1-methoxynaphthalene (45)

Aqueous sodium hydroxide (30 cm^3, 10 M) was added dropwise to a solution of 1-methoxyindene (42) (1.0 g) and benzyltriethylammonium chloride (0.10 g) in chloroform (20 cm^3). The reaction mixture was stirred vigorously for 20 h, then diluted with water (50 cm^3) and extracted with ether (4 x 50 cm^3). Flash chromatography of the residue with petrol afforded the naphthalene (45) (1.26 g, 95%) as a white solid. An analytical sample was recrystallized from light petrol m.p. 41-42° (lit.[41] 41-42°). λ_{max} (log ε) 211, 265 sh, 272, 278, 287 sh nm (4.38, 3.69, 3.75, 3.75, 3.61). ν_{max} 2938, 1574 cm^{-1}. δ ^{1}H 4.03, s, OCH_3; 7.37-8.18, m, 6 x ArH. ^{13}C 61.3, OCH_3; 123.1, C2; 128.9, C8a; 133.4, C4a; 151.8, C1; 121.9, 124.8, 126.4, 126.7, 127.6, 128.0, 6 x ArCH. *m/z* 194 (M[^{37}Cl], 30%), 192 (M[^{35}Cl], 96), 177 (60), 151 (32), 149 (100).

2-Chloro-1-methoxy[2-^{13}C]naphthalene (43)

Using the procedure for the preparation of naphthalene (45), 1-methoxyindene (42) (0.61 g) was made to react with [^{13}C]chloroform (0.49 g, 91.3% enriched) to yield the *labelled naphthalene* (43) (0.24 g, 30%). An analytical sample was recrystallized from light petrol as white needles m.p. 42-42.5°. *m/z* 195 (M[^{37}Cl], 31%), 193 (M[^{35}Cl], 100), 178 (67), 152 (25), 150 (82). (92% enriched). In the ^{13}C n.m.r. spectrum only the signal at δ 123.1 was measurably enhanced.

2-Chloro-1,4-naphthoquinone (8)

To a solution of the naphthalene (45) (104 mg) in acetonitrile (10 cm^3) was added a solution of ceric ammonium sulphate (1.78 g) in aqueous sulphuric acid (11 cm^3, 2 M). The reaction mixture was heated at 50° for 3 h, then diluted with water (50 cm^3). The ethyl acetate extract (2 x 50 cm^3) was washed with water (50 cm^3), dried and evaporated. Flash chromatography of the residue in toluene gave 2-chloro-1,4-naphthoquinone (8) (66 mg, 63%) as yellow needles from methanol m.p. 114-115° (lit.[65] 117-118°). δ ^{1}H 7.23, s, H3; 7.74-7.90, m, H6, H7; 8.05-8.24, m, H5, H8. ^{13}C[46] 126.7, C7; 127.5, C6; 131.3, C8a; 131.7, C4a; 134.2, C8; 134.5, C5; 135.9, C3; 146.4, C2; 177.9, C4; 182.6, C1. *m/z* 194 (M[^{37}Cl], 29%), 192 (M[^{35}Cl], 91), 157 (49), 129 (100), 104 (38), 101 (44), 76 (64), 75 (46), 74 (35), 53 (21), 52 (22), 50 (64).

2-Chloro[2-^{13}C]-1,4-naphthoquinone (10)

The labelled naphthalene (43) (170 mg) was made to react as for (45), flash chromatography afforded the *labelled naphthoquinone* (10) (104 mg, 61%) m.p. 115-116°. *m/z* 195 (M[^{37}Cl], 28%), 193 (M[^{35}Cl], 85), 158 (52), 130 (97), 104 (44), 102 (45), 76 (100), 75 (43), (90% enriched). In the ^{13}C n.m.r. spectrum only the signal at δ 146.4 exhibited measurable enhancement.

Addition of Naked Fluoride to Chloro Quinones (8), (9) and (10)

(i) Anhydrous potassium fluoride (9 mg) and 18-crown-6 (2 mg) was added to dry acetonitrile (6 cm^3). The reaction mixture was stirred at room temperature for 10 min with protection from atmospheric moisture. 2-Chloro-1,4-naphthoquinone (8) (15 mg) was added and the reaction mixture was refluxed in the dark for 16 h.[30] The solvent was evaporated and the residue chromatographed on silica in toluene/ethyl acetate (19:1). The only band, R_f0.65, afforded 2-fluoro-1,4-naphthoquinone (19) (10 mg, 73%) as golden needles from petrol m.p. 98.5-99.5° (lit.[30] 101-102°). δ ^1H 6.66, d, *J* 11 Hz, H3; 7.68-7.84, m, H6, H7; 8.04-8.18, m, H5, H8. ^{13}C[17] 117.4, C3; 126.6, C5, C8; 130.5, C4a; 131.8, C8a; 134.2, C6; 134.8, C7; 161.7, C2; 178.0, C4; 184.6, C1. *m/z* 176 (M, 100%), 148 (33), 120 (76), 76 (28), 50 (22).

(ii) The deuterium-labelled quinone (9) (15 mg) was made to react with the fluoride reagent as for (8). Chromatography afforded the *fluoro quinones* (18) and (19) (11 mg, 82%) m.p. 98-99°. *m/z* 177 (M, 97%), 149 (36), 121 (100), 76 (44), 74 (21), 50 (35). (92% enriched). The doublet at δ 6.66 in the ^1H n.m.r. spectrum integrated for 0.08 protons.

(iii) The carbon-labelled quinone (10) (16 mg) was made to react as for (8) with the fluoride reagent to yield *2-fluoro[2-^{13}C]-1,4-naphthoquinone* (46) (11 mg, 75%) m.p. 98-99.5°. *m/z* 177 (M, 100%), 149 (37), 121 (99), 76 (44), 50 (34). (92% enriched). In the ^{13}C n.m.r. spectrum only the doublet at δ 161.5 was measurably enhanced.

Addition of Methoxide to Chloro Quinones (8), (9) and (10)

(i) A solution of sodium methoxide (9 mg) in methanol (0.07 cm^3) was added to a solution of 2-chloro-1,4-naphthoquinone (8) (15 mg) in dry methanol (15 cm^3). The reaction mixture was stirred in the dark at room temperature for 45 min then acidified with aqueous hydrochloric

acid and diluted with water (50 cm^3). The ethyl acetate extract (2 x 25 cm^3) was washed with water (30 cm^3) dried and evaporated. The residue was subjected to chromatography on silica in toluene/ethyl acetate (3:1) to yield 2-methoxy-1,4-naphthoquinone (21) (14 mg, 93%) as yellow needles from methanol m.p. 184-185° (lit.[66] 184-185°) δ ^1H 3.92, s, OCH_3; 6.19, s, H3; 7.69-7.83, m, H6, H7; 8.05-8.19, m, H5, H8. ^{13}C[46] 56.4, OCH_3; 109.9, C3; 126.1, C5; 126.7, C8; 131.0, C8a; 132.0, C4a; 133.3, C7; 134.3, C6; 160.4, C2; 180.1, C1; 184.8, C4. *m/z* 188 (M, 74%), 173 (37), 159 (22), 158 (41), 102 (62), 89 (100), 76 (46), 75 (25), 74 (20), 69 (26), 50 (37).

(ii) The deuterium-labelled quinone (9) (15 mg) was made to react with sodium methoxide as for (8). Chromatography afforded the *methoxy quinones* (20) and (21) (14 mg, 92%) m.p. 183.5-184.5°. *m/z* 189 (M, 22%), 188 (100), 173 (40), 159 (29), 158 (48), 102 (67), 89 (98), 75 (22), 69 (27), 50 (33). (18% enriched). The singlet at δ 6.18 in the ^1H n.m.r. spectrum integrated for 0.86 protons.

(iii) The carbon-labelled quinone (10) (15 mg) was treated with sodium methoxide as for (8). Chromatography afforded the *carbon-labelled methoxy quinones* (48) and (49) (14 mg, 92%) m.p. 184-185°. *m/z* 189 (M, 100%), 174 (37), 160 (26), 159 (50), 103 (52), 89 (75), 76 (43), 50 (27). (91% enriched). In the ^{13}C n.m.r. spectrum the signals at δ 109.9 and 160.4 were enriched with the ^{13}C label in the ratio of 7:93 respectively.

Addition of Aziridine to Chloro Quinones (8), (9) and (10)

(i) A solution of 2-chloro-1,4-naphthoquinone (8) (15 mg) and aziridine (7 mg) in dry acetonitrile (6 cm^3) was stirred at room temperature in the dark for 2 h. The solvent was evaporated and the

residue was chromatographed on silica in toluene/ethyl acetate (9:1). The major band, R_f 0.29, afforded 2-aziridino-1,4-naphthoquinone (27) (14 mg, 87%) as orange plates from methanol m.p. 170-173° dec. (lit.[32] 170-178° dec) δ ^{1}H 2.29, s, 2 x CH_2; 6.29, s, H3; 7.61-7.83, m, H6, H7; 7.96-8.18, m, H5, H8. ^{13}C 27.7, C2', C3'; 119.5, C3; 126.0, C5; 126.4, C8; 131.8, C8a; 132.5, C4a; 133.1, C7; 134.1, C6; 157.9, C2; 182.0, C1; 185.2, C4. *m/z* 199 (M, 100), 172 (31), 144 (33), 116 (29), 115 (44), 105 (21), 104 (52), 76 (66), 75 (28), 50 (42). The minor band, R_f 0.50, afforded 3-aziridino-2-chloro-1,4-naphthoquinones (30) (1 mg, 7%) identical with an authentic sample described on the next page.

(ii) The deuterium-labelled quinone (9) (15 mg) was made to react with aziridine in dry methanol (15 cm^3) as for (8). Chromatography afforded the *aziridino quinones* (24) and (27) (14 mg, 93%) m.p. 162-165° dec. *m/z* 200 (M, 100%), 199 (21), 173 (30), 145 (31), 144 (22), 117 (29), 116 (44), 115 (21), 105 (20), 104 (56), 102 (21), 76 (76), 75 (22), 50 (40). (90% enriched). The signal at δ 6.29 in the ^{1}H n.m.r. integrated for 0.11 protons. The minor band afforded 3-aziridino-2-chloro-1,4-naphthoquinone (30) (1 mg, 3%).

(iii) The carbon-labelled quinone (10) (13 mg) was made to react with aziridine as for (8). Chromatography afforded the *carbon-labelled aziridino quinones* (54) and (56) (11 mg, 79%) m.p. 164-169° dec. *m/z* 200 (M, 80%), 173 (24), 145 (35), 144 (24), 117 (32), 116 (52), 115 (25), 105 (25), 104 (61), 102 (23), 76 (100), 75 (29), 50 (59), 42 (66). (90% enriched). In the ^{13}C n.m.r. spectrum the signals at δ 119.5 and 157.8 were enriched with the ^{13}C label in the ratio of 70:25 respectively. The minor band afforded *3-aziridino-2-chloro[2-^{13}C]-1,4-naphthoquinone* (58) (1 mg, 4%). *m/z* 236 (M[^{37}Cl], 32%), 234 (M[^{35}Cl],100), 207 (29), 199 (61), 178 (23), 172 (58), 149 (32), 116 (23), 115 (36), 105 (33),

104 (27), 76 (60), 57 (31), 50 (41), 43 (24), 42 (60). (90% enriched). In the ^{13}C n.m.r. spectrum only the signal at δ 127.1 exhibited measurable enhancement.

3-Aziridino-2-chloro-1,4-naphthoquinone (30)

A solution of 2,3-dichloro-1,4-naphthoquinone (33) (205 mg) in dry acetonitrile (20 cm^3) and aziridine (99 mg) was stirred at room temperature for 30 min. The solvent was evaporated and the residue was flash chromatographed in chloroform to yield 3-aziridino-2-chloro-1,4-naphthoquinone (30) (211 mg, 92%) as orange needles from methanol m.p. 130-131° (lit.[34] 129.5-130.5°). λ_{max} (log ε) 223, 257, 291, 336, 420 nm (4.15, 4.34, 4.14, 3.50, 3.46). ν_{max} 2950, 1677, 1654, 1589, 1560 cm^{-1}. δ ^1H 2.58, s, 2 x CH_2; 7.61-7.80, m, H6, H7; 8.04-8.18, m, H5, H8. ^{13}C 30.0, C2', C3'; 126.8, C5, C8; 127.1, C2; 130.8, C4a; 131.6, C8a; 133.4, C6; 134.2, C7; 152.4, C3; 177.4, C4; 179.4, C1. *m/z* 235 (M[^{37}Cl], 34%), 233 (M[^{35}Cl], 100), 206 (29), 198 (62), 177 (29), 171 (61), 149 (21), 143 (23), 115 (30), 114 (54), 105 (27), 104 (28), 76 (68), 75 (25), 74 (24), 50 (50).

Reaction of Morpholine with Chloro Quinones (8) and (9)

(i) A solution of 2-chloro-1,4-naphthoquinone (8) (20 mg) and morpholine (18 mg) in ethanol (20 cm^3) was allowed to stand at room temperature for a few minutes.[27] The solvent was evaporated and the residue chromatographed on silica in toluene/ethyl acetate (9:1). The major band, R_f 0.19, was recrystallized from water to give 2-morpholino-1,4-naphthoquinone (28) (16 mg, 62%) as golden brown needles m.p. 152-153° (lit.[33] 152.5-153.5°). λ_{max} (log ε) 222 sh, 236, 244 sh, 264 sh, 268, 332 sh, 454 nm (4.08, 4.11, 4.09, 4.18, 4.20, 3.45, 3.50). ν_{max} 2900, 1677, 1645, 1592, 1567 cm^{-1}. δ 3.45-3.54, m, 2 x H3', 2 x H5'; 3.82-3.92, m, 2 x H2', 2 x H6'; 6.02, s, H3; 7.64-7.73, m, H6, H7; 7.96-8.10,

m, H5, H8. *m/z* 243 (M, 100%). The minor band, R_f 0.40, afforded 2-chloro-3-morpholino-1,4-naphthoquinone (31)[35] (1 mg, 3%) as a dark red solid identical with an authentic sample in chromatographic behaviour. The blue band, R_f 0.30, is tentatively postulated to be the *enamino quinone* (35) (0.5 mg, 2%).

(ii) The deuterium-labelled quinone (9) (20 mg) was made to react with morpholine as for (8).[27] Chromatography afforded the *morpholino quinones* (25) and (28) (14 mg, 68%) m.p. 150.5-151°. *m/z* (10 eV) 245 (M, 24%), 244 (100), 243 (46). The signal at δ 6.03 in the ^{1}H n.m.r. spectrum integrated for 0.19 protons. The minor bands afforded 2-chloro-3-morpholino-1,4-naphthoquinone (31) (1 mg, 2%) and the *enamino quinone* (35) (0.5 mg, 2%).

Addition of Pyrrolidine to Chloro Quinones (8), (9) and (10)

(i) A solution of 2-chloro-1,4-naphthoquinone (8) (15 mg) and pyrrolidine (11 mg) in dry acetonitrile (6 cm^3) was stirred at room temperature in the dark for 30 min. The solvent was evaporated and the residue was chromatographed on silica in toluene/ethyl acetate (9:1). The major band, R_f 0.11, afforded 2-pyrrolidino-1,4-naphthoquinone (29) (16 mg, 89%) as bright red needles from methanol/water m.p. 157.5-158.5° (lit.[32] 158-159°) δ ^{1}H 2.00, m, 2 x H3', 2 x H4'; 3.67, brs, 2 x H2', 2 x H5'; 5.75, s, H3; 7.50-7.78, m, H6, H7; 7.97-8.11, m, H5, H8. ^{13}C 25.4, C3', C4'; 50.9, C2', C5'; 104.8, C3; 125.3, C5; 126.3, C8; 131.6, C7; 131.8, C8a; 133.1, C4a; 133.9, C6; 148.9, C2; 182.2, C1; 183.2, C4. *m/z* 227 (M, 100%), 226 (23), 104 (21), 70 (45). The minor band, R_f 0.42, afforded *2-chloro-3-pyrrolidino-1,4-naphthoquinone* (32) (1 mg, 5%) identical with an authentic sample described on p.54.

(ii)a The deuterium-labelled quinone (9) (16 mg) was made to react with pyrrolidine in dry methanol (15 cm^3) as for (8). Chromatography afforded the *pyrrolidino quinones* (26) and (29) (15 mg, 83%) m.p. 159-160°. *m/z* 228 (M, 100%), 227 (36), 104 (32), 76 (36), 70 (61). (88% enriched). The singlet at δ 5.75 in the ^1H n.m.r. spectrum integrated for 0.15 protons. The minor band afforded *2-chloro-3-pyrrolidino-1,4-naphthoquinone* (32) (1 mg, 5%).

(ii)b The deuterium-labelled quinone (9) (5.5 mg) was made to react with pyrrolidine in dry benzene (3 cm^3) as for (8). Chromatography afforded the *pyrrolidino quinones* (26) and (29) (5.5 mg, 85%) m.p. 159-160°. *m/z* 228 (M, 36%), 227 (100), 226 (22), 104 (28), 76 (31), 70 (58). (18% enriched). The singlet at δ 5.75 in the ^1H n.m.r. spectrum integrated for 0.88 protons. The minor band afforded *2-chloro-3-pyrrolidino-1,4-naphthoquinone* (32) (0.25 mg, 4%).

(iii)a The carbon-labelled quinone (10) (14 mg) was made to react with pyrrolidine as for (8). Chromatography afforded the *labelled pyrrolidino quinones* (55) and (57) (14 mg, 81%) m.p. 158-159°. *m/z* 228 (M, 100%), 227 (32), 199 (20), 104 (40), 103 (27), 102 (23), 76 (52), 70 (76). (92% enriched). In the ^{13}C n.m.r. spectrum the signals at δ 104.8 and 148.9 were enriched with the ^{13}C label in the ratio 71:24 respectively. The minor band afforded *2-chloro-3-pyrrolidino[2-^{13}C]-1,4-naphthoquinone* (59) (1 mg, 4%). In the ^{13}C n.m.r. spectrum only the signal at δ 111.5 exhibited any measurable enhancement.

(iii)b The carbon-labelled quinone (10) was made to react with pyrrolidine in the dry benzene (6 cm^3) as for (8). Chromatography afforded the *labelled pyrrolidino quinones* (55) and (57) (15 mg, 85%) m.p. 158.5-159.5°. *m/z* 228 (M, 100%), 227 (31), 104 (24), 76 (24), 70 (50). (92% enriched). In the ^{13}C n.m.r. spectrum the signals

at δ 104.8 and 148.9 were enriched with the ^{13}C label in the ratio of 80:8 respectively. The minor band afforded the *labelled chloro quinone* (59) (2 mg, 12%). *m/z* 264 (M[^{37}Cl], 35%), 263 (26), 262 (M[^{35}Cl], 100), 261 (30), 158 (25), 135 (36), 76 (22), 70 (65), 57 (24), 43 (28). (88% enriched). In the ^{13}C n.m.r. spectrum only the peak at δ 111.5 exhibited measurable enhancement.

(iii)c The carbon-labelled quinone (10) (14 mg) was made to react with pyrrolidine in dry ethanol (15 cm^3) as for (8). Chromatography afforded three bands. The major band gave the *labelled pyrrolidino quinones* (55) and (57) (13 mg, 84%) m.p. 158-159°. *m/z* 228 (M, 100%), 227 (30), 104 (21), 76 (21), 70 (40). (93% enriched). In the ^{13}C n.m.r. spectrum the signals at δ 104.8 and 148.9 were enriched with the ^{13}C label in the ratio 13:81 respectively. The minor band gave the *labelled chloro quinone* (59) (1 mg, 5%). The minor blue band afforded the *labelled enamino quinone* (68) (0.01 mg, 0.05%) identical with an authentic sample (p. 54) with respect to chromatographic behaviour and electronic spectra.

(iii)d The carbon-labelled quinone (10) (16 mg) was made to react with pyrrolidine in dry methanol (15 cm^3) as for (8). Chromatography afforded the *labelled pyrrolidino quinones* (55) and (57) (16 mg, 85%) m.p. 159-160°. *m/z* 228 (M, 100%), 227 (32), 104 (37), 103 (24), 76 (46), 70 (70). (90% enriched). In the ^{13}C n.m.r. spectrum the signals at δ 104.8 and 148.9 were enriched with the ^{13}C label in the ratio 10:84 respectively. The minor band afforded the *labelled chloro quinone* (59) (1 mg, 5%). *m/z* 264 (M[^{37}Cl], 17%), 262 (M[^{35}Cl], 52), 149 (73), 76 (31), 71 (45), 70 (58), 69 (36), 57 (81), 55 (50), 43 (100). (88% enriched). In the ^{13}C n.m.r. spectrum only the peak at δ 111.5 exhibited measurable enhancement.

2-Chloro-3-pyrrolidino-1,4-naphthoquinone (32)

A solution of 2,3-dichloro-1,4-naphthoquinone (33) (201 mg) and pyrrolidine (117 mg) in dry acetonitrile (20 cm^3) was stirred at room temperature for 30 min. The solvent was evaporated and the residue was flash chromatographed in chloroform to yield *2-chloro-3-pyrrolidino-1,4-naphthoquinone* (32) (221 mg, 95%) as red needles from methanol/water m.p. 87-90° dec. (Found: C, 64.3; H, 5.0; N, 5.3. $C_{14}H_{12}ClNO_2$ requires C, 64.3; H, 4.6; N, 5.4%). λ_{max} (log ε) 244 sh, 248, 259, 283, 333 sh, 488 nm (3.85, 3.87, 3.91, 4.03, 3.20, 3.31). ν_{max} 2920, 1680, 1619, 1590, 1531 cm^{-1}. δ ^1H 1.93, m, 2 x H3', 2 x H4'; 3.98, m, 2 x H2', 2 x H5'; 7.49-7.77, m, H6, H7; 7.88-8.15, m, H5, H8. ^{13}C 25.7, C3', C4'; 54.1, C2', C5'; 111.5, C2; 126.0, C5; 126.3, C8; 131.2, C4a; 132.1, C6, C8a; 134.0, C7; 149.3, C3; 177.0, C4; 183.0, C1. *m/z* 263 (M[^{37}Cl], 34%), 262 (21), 261 (M[^{35}Cl], 100), 71 (21), 70 (65), 69, (21), 57 (32), 55 (28).

Synthesis of Enamino Quinone (69)

A solution of pyrrolidine (32 mg) and acetaldehyde (10 mg) in dry benzene (15 cm^3) was stirred at room temperature for 10 min. 2,3-Dichloro-1,4-naphthoquinone (33) (50 mg) was added to the reaction mixture and stirring was continued for a further 30 min. The solvent was evaporated and the residue was flash chromatographed in chloroform to yield the *enamino quinone* (69) (36 mg, 57%) as dark blue needles from methanol m.p. > 180° dec. (Found: C, 66.7; H, 5.1; N, 5.2. $C_{16}H_{14}ClNO_2$ requires C, 66.8; H, 4.9; N, 4.9%). λ_{max} (log ε) 235, 316 sh, 427, 594 nm (4.08, 4.47, 4.52, 4.23). ν_{max} 2870, 1669, 1594, 1573 cm^{-1}. δ 2.03, brs, 2 x H3", 2 x H4"; 3.50, brs, 2 x H2", 2 x H5"; 5.54, d, *J* 13Hz, H2'; 7.51-7.74, m, H6, H7; 7.95-8.16, m, H5, H8; 8.60, d, *J* 13Hz, H1'. *m/z* 289 (M[^{37}Cl], 34%), 287 (M[^{35}Cl], 100), 252 (82),

251 (63), 250 (65), 224 (47), 223 (48), 184 (21), 183 (68), 127 (26), 126 (22), 77 (24), 76 (35), 70 (78).

Addition of 1,1-Dimethoxyethene to Chloro Quinones (8) and (10)

(i) A solution of 2-chloro-1,4-naphthoquinone (8) (15 mg) and 1,1-dimethoxyethene (88) (120 mg) in dry acetonitrile (6 cm^3) was stirred at room temperature in the dark for 17 h. The solvent was evaporated and the residue was dissolved in acetone (10 cm^3). Anhydrous potassium carbonate (500 mg) and dimethyl sulphate (0.5 cm^3) were added and the reaction mixture was refluxed for 2 h. The cooled reaction mixture was diluted with ethyl acetate (100 cm^3) and washed successively with water (50 cm^3), conc. aqueous ammonia (2 x 50 cm^3) and again with water (50 cm^3), dried and evaporated. Chromatography of the residue on silica in toluene/ethyl acetate (3:1) afforded 1,3-dimethoxy-9,10-anthraquinone (91) (19 mg, 88%) as yellow needles from methanol m.p. 164-165° (lit.[67] 164-165°). δ ^1H 3.99, 4.01, s, s, 2 x OCH_3; 6.79, d, *J* 2Hz, H2; 7.46, d, *J* 2Hz, H4; 7.62-7.84, m, H6, H7; 8.17-8.32, m, H5, H8. ^{13}C[61] 56.0, 3-OCH_3; 56.6, 1-OCH_3; 103.3, C4; 104.7, C2; 116.1, C9a; 126.5, C5; 127.2, C8; 132.3, C10a; 132.8, C6; 134.3, C7; 135.1, C8a; 137.5, C4a; 162.6, C1; 164.7, C3; 181.2, C9; 183.5, C10. *m/z* 268 (M, 100%), 239 (45), 139 (24).

(ii) The carbon-labelled quinone (10) (16 mg) was made to react with 1,1-dimethoxyethene (88) as for (8). Chromatography afforded *1,3-dimethoxy[9a-^{13}C]-9,10-anthraquinone* (89) (15 mg, 67%). m.p. 162-163°. *m/z* 269 (M, 100%), 268 (22), 240 (46), 140 (22). (90% enriched). In the ^{13}C n.m.r. spectrum only the signal at δ 116.1 exhibited measurable enhancement.

(1α,4aβ,9aβ)-9aβ-Chloro-1α-methoxy-3-trimethylsilyloxy-1,4,4aβ,9aβ-tetrahydro-9,10-anthraquinone (92)

A solution of 2-chloro-1,4-naphthoquinone (8) (15 mg) and (*E*)-1-methoxy-3-trimethylsilyloxy-1,3-butadiene (4) (30 mg) in dry acetonitrile (6 cm^3) was allowed to stand at room temperature for 2 h, then the solvent was evaporated. The ^1H n.m.r. spectrum of the crude adduct was consistent with the presence of a single isomer. The residue was recrystallized from dichloromethane/petrol to yield the *adduct* (92) (24 mg, 84%) as white needles m.p. 117-120° dec. (Found: C, 59.0; H, 6.1. $C_{18}H_{21}ClO_4Si$ requires C, 59.3; H, 5.8%). λ_{max} (log ε) (cyclohexane) 227, 253, 260 sh, 296, 305 nm (4.57, 4.04, 3.98, 3.30, 3.28). ν_{max} 2958, 1710, 1696, 1661, 1593 cm^{-1}. δ 0.30, s, $OSi(CH_3)_3$; 2.45, dd, *J* 18, 7Hz, H4β; 2.91, s, OCH_3; 3.19, d, *J* 18Hz, H4α; 3.61, d, *J* 7Hz, H4a; 4.14, d, *J* 5Hz, H1; 5.09, d, *J* 5Hz, H2; 7.60-8,24, m, 4 x ArH. *m/z* (12eV) (M, 41%), 269 (55), 172 (100).

2-Hydroxy-9,10-anthraquinone (94)

A solution of 2-chloro-1,4-naphthoquinone (8) (15 mg) and (*E*)-1-methoxy-3-trimethylsilyloxy-1,3-butadiene (4) (30 mg) was allowed to stand at room temperature for 2 h in acetonitrile (6 cm^3). The crude adduct (92) was treated with aqueous hydrochloric acid (1.6M, 1 cm^3). The reaction mixture was stirred at room temperature for 1 h, then diluted with water (50 cm^3) and extracted with ethyl acetate (3 x 25 cm^3). The combined organic phase was washed with water (25 cm^3), dried and evaporated. Flash chromatography in chloroform as eluant afforded 2-hydroxy-9,10-anthraquinone (97) (16 mg, 94%) m.p. 304-305° (lit.[68] 306°) identical with an authentic sample in chromatographic behaviour.

Reaction of Pyrrolidine with Chloro Juglones (79) and (80)

(i) A solution of 2-chloro-8-hydroxy-1,4-naphthoquinone (80)[11] (22 mg) and pyrrolidine (15 mg) in methanol (20 cm^3) was stirred at

room temperature for 30 min. The solvent was evaporated and the residue was chromatographed on silica in toluene/ethyl acetate (9:1). The least mobile band, R_f 0.18, afforded *8-hydroxy-2-pyrrolidino-1,4-naphthoquinone* (84) (16 mg, 62%) as red needles from methanol m.p. 191-192.5° (Found: C, 69.6; H, 5.5; N, 5.6. $C_{14}H_{13}NO_3$ requires C, 69.1; H, 5.4; N, 5.8%). λ_{max} (log ε) 239, 276, 303 sh, 417, 470 sh nm (4.24, 4.24, 3.83, 3.73, 3.67). ν_{max} 1636, 1624, 1590, 1554 cm^{-1}. δ 2.01, m, 2 x H3', 2 x H4'; 3.67, brm, 2 x H2', 2 x H5'; 5.72, s, H3; 7.13, m, H7; 7.58, m, H5, H6; 11.95, s, *peri*-OH. *m/z* 243 (M, 100%), 70 (45). The band, R_f 0.48, gave *5-hydroxy-2-pyrrolidino-1,4-naphthoquinone* (85) (0.5 mg, 2%) as red needles from methanol m.p. 161-162° (Found: C, 68.8; H, 5.3; N, 5.7. $C_{14}H_{13}NO_3$ requires C, 69.1; H, 5.4; N, 5.8%). λ_{max} (log ε) 240, 272, 305 sh, 405 sh, 492 nm (3.91, 3.94, 3.39, 3.07, 3.69). ν_{max} 1676, 1612, 1553 cm^{-1}. δ 2.01, m, 2 x H3', 2 x H4'; 3.69, brm, 2 x H2', 2 x H5'; 5.62, s, H3; 7.20, dd, *J* 2, 7Hz, H6; 7.43, t, *J* 7Hz, H7; 7.53, dd, *J* 2, 7Hz, H8; 13.21, s, *peri*-OH. *m/z* 243 (M, 100%), 242 (21), 70 (37). The most mobile red band, R_f 0.72, was unstable. It is presumed to be 2-chloro-8-hydroxy-3-pyrrolidino-1,4-naphthoquinone (86) (5 mg, 17%).

(ii) 2-Chloro-8-hydroxy-1,4-naphthoquinone (80) (24 mg) was made to react with pyrrolidine in benzene (10 cm^3) as described in the preceding reaction. Chromatography afforded *8-hydroxy-2-pyrrolidino-1,4-naphthoquinone* (84) (1 mg, 4%), *5-hydroxy-2-pyrrolidino-1,4-naphthoquinone* (85) (23 mg, 82%) and 2-chloro-8-hydroxy-3-pyrrolidino-1,4-naphthoquinone (86) (3 mg, 9%). These products were identical with those obtained previously.

(iii) 2-Chloro-5-hydroxy-1,4-naphthoquinone (79)[11] (18 mg) was made to react with pyrrolidine in methanol (10 cm^3) as for the isomeric

quinone (80). Chromatography afforded the *2-pyrrolidino quinone* (84) (2 mg, 8%), *2-pyrrolidino quinone* (85) (15 mg, 71%) and a third component, R_f 0.61, was unstable and presumed to be 2-chloro-5-hydroxy-3-pyrrolidino-1,4-naphthoquinone (87) (4 mg, 17%). These products, with the exception of (87), were identical with those obtained previously.

(iv) 2-Chloro-5-hydroxy-1,4-naphthoquinone (79) (13 mg) was made to react with pyrrolidine in benzene (5 cm^3) as for the isomeric quinone (80). Chromatography afforded the *2-pyrrolidino quinone* (84) (1 mg, 5%), *2-pyrrolidino quinone* (85) (9 mg, 60%), and 2-chloro-3-pyrrolidino quinone (87) (6 mg, 32%). These products were identical with those described in foregoing reaction.

PART II

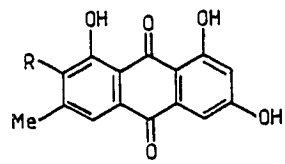
SYNTHESIS OF 1,3,8-TRIHYDROXY ANTHRAQUINONES

AND RELATED NAPHTHOQUINONES

CHAPTER 3

INTRODUCTION

Quinonoid pigments are widely distributed in Nature, and of these the anthraquinones are the largest group. The majority of these pigments are polyhydroxylated arising predominately from either the polyketide or shikimate pathways. Of the polyketide-derived anthraquinones a 1,3,8-trioxygenated skeleton is the most common and this substitution is typified by emodin (95) and endocrocin (96).



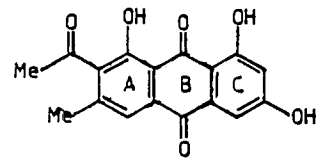
(95) R=H

(96) R=CO_2H

Emodin (95) is perhaps the most widely distributed naturally occurring anthraquinone; it has been isolated from over thirty different sources.[69] Often anthraquinonoid pigments can be seen to be biosynthetic variants of its basic octaketide skeleton. Examples exist in which there has been either introduction or loss of nuclear hydroxy groups, side-chain oxidation, *o*-methylation and nuclear chlorination during biogenesis.[1]

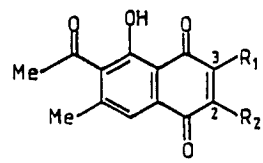
The terminal carboxylic acid group that is lost in the biosynthesis of emodin can, in some circumstances, also be retained. Endocrocin (96), isolated from fungal sources,[70] is the simplest natural 1,3,8-trioxygenated anthraquinone which possesses the intact octaketide skeleton.

2-Acetylemodin (97) is another structural variant of the basic emodin skeleton. This coccid pigment was isolated from the common gum tree scale *Eriococcus coriaceus* Maskell[71] in this Department and is the first example of this particular presumed nonaketide skeleton. Similar substitution patterns to the A-ring of (97)



(97)

have also been observed among naphthoquinonoid pigments. Examples include stypandrone (98), also isolated within this Department,[72] and the methoxylated analogue, orientalone, derived from the roots of *Rumex orientalis* Bernh.[73]



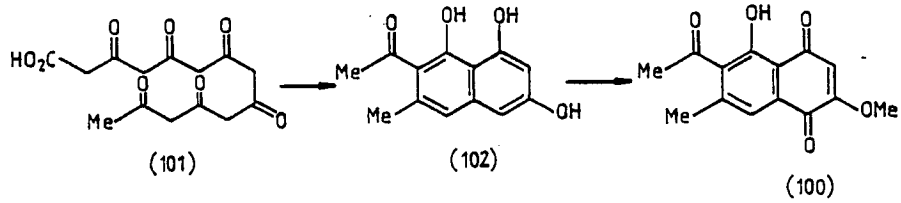
(98) $R_1=R_2=H$

(99) $R_1=OMe, R_2=H$

(100) $R_1=H, R_2=OMe$

The structure of orientalone was postulated to be (99),[73] placement of the methoxy group at C3 being based purely on spectroscopic grounds. Consideration of the probable polyketide origin of orientalone would, however, lead to preference for the methoxy group to be attached to C2 as in (100). Condensation of the putative polyketide precursor (101)[74] could produce the naphthalene (102).[75]

Subsequent oxidation and *o*-methylation would afford structure (100) as outlined in Scheme 16.

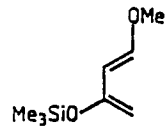


Scheme 16

In support of correction of the structure of orientalone to (100), Jung[76] reported a synthesis of (99) which appeared during the course of this work. The synthetic material had different spectral characteristics from natural orientalone.

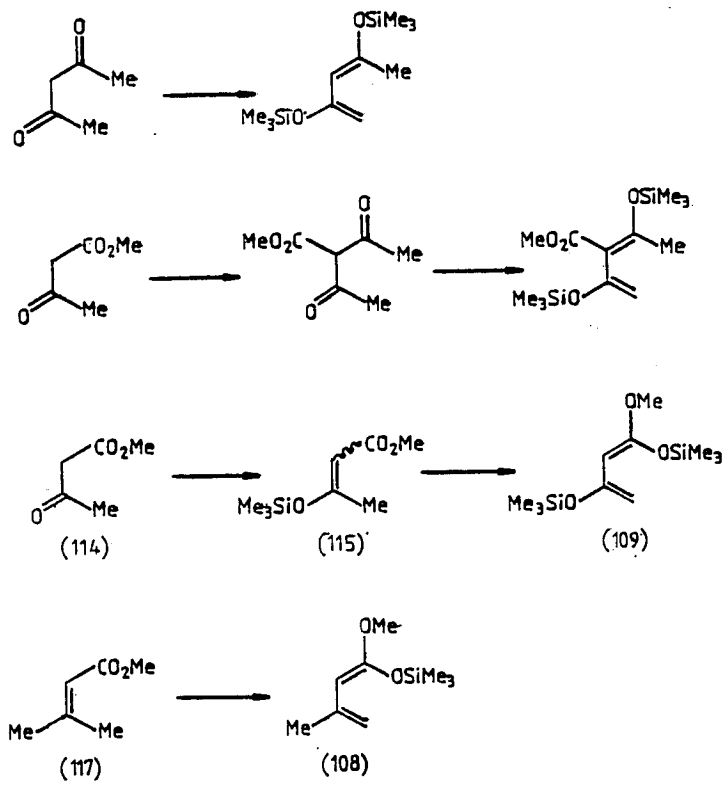
Whilst the anthraquinones (95),[3] (96)[77] and (97)[4,76,78] and stypandrone (98)[79] have previously been synthesized, the structure of orientalone has not been confirmed by synthesis. This Thesis, in part examines a general methodology applicable to the synthesis of the more commonly encountered 1,3,8-trioxygenated anthraquinones such as (95), (96) and (97). The versatility of the strategy also allows access to the naphthoquinones (98), (99), (100) and their derivitives.

The classical Friedel-Crafts syntheses of anthraquinones, for example emodin (95)[80] are plagued by regiochemical ambiguities as well as low yields. Considerable improvement has resulted from the recent application of the Diels-Alder reaction which has been used for the efficient construction of the carbon skeleton of a number of complex anthraquinones under mild conditions and with high regioselectivity.[81,82] This work received considerable impetus from the publication by Danishefsky[7] of the synthesis and use of diene (4). Natural extensions



(4)

of this work led to the preparation of numerous highly oxygenated butadienes pertinent to the synthesis of polyketide-derived pigments.[81-91]

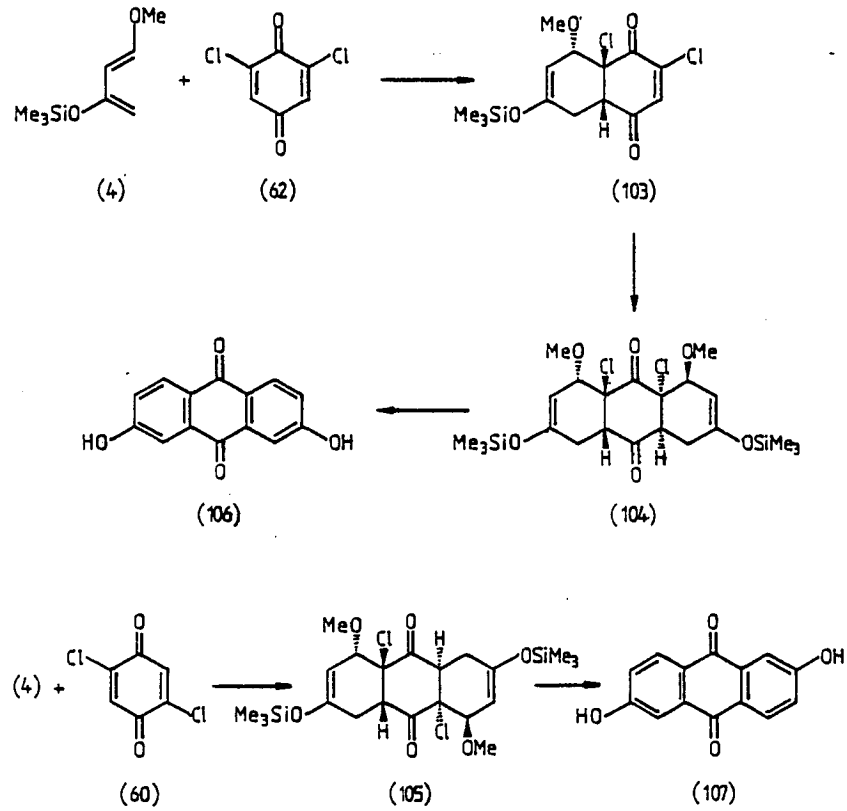


Scheme 17

Several reviews have appeared giving extensive accounts of the applicability of cycloaddition reactions of polar butadienes.[62,92-94]

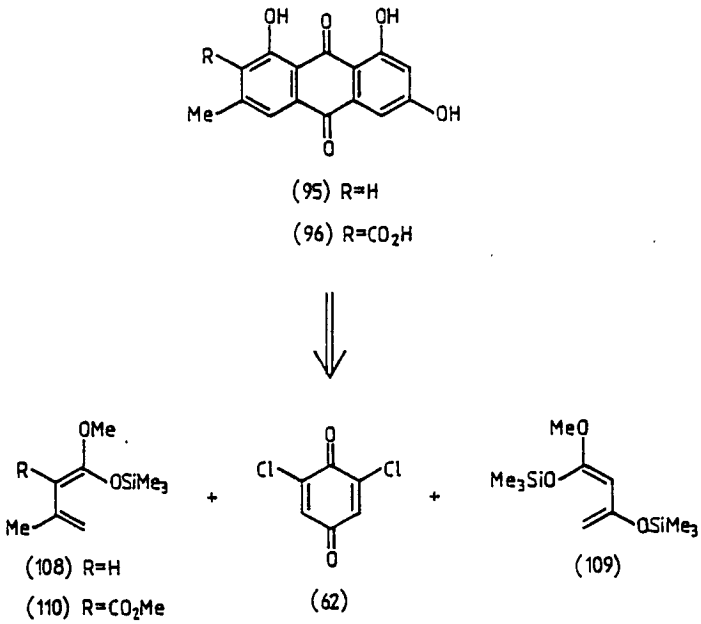
Perhaps the most versatile of the approaches to these dienes is summarized in Scheme 17. These methods all pivot on the capacity to trap enolates of ketones or esters by *O*-silylation. There is strong evidence, part of which is presented in Chapter 2 of this Thesis, that orientation of reaction of these polar dienes with quinonoid dienophiles is controllable by prior introduction of a halogen on the quinonoid double bond. This appears to be so regardless of the electronic effect of any remote substituent which may be present in the molecule. It has been shown that reaction of diene (4) with 2,6-dichlorobenzoquinone (62) occurs specifically such that the more nucleophilic terminus, C4, of the diene attacks the position vicinal to the chloro-substituted carbon to give the isolable *endo* adduct (103).[95] Under more forcing conditions the bis *endo* adduct (104) is formed exclusively as outlined in Scheme 18. The structure of (104) has been established by X-ray crystallography.[8] When the same process is repeated on 2,5-dichlorobenzoquinone (60) the isomeric bis *endo* adduct (105) is formed. Aromatization of (104) and (105) by elimination of hydrogen chloride and methanol and cleavage of the silyl ethers led to 2,7- and 2,6-dihydroxy-9,10-anthraquinone (106) and (107) respectively.

Thus prepositioning of the chloro substituents allows regio-specific construction of either isomeric anthraquinone. Since addition of the second mole of diene proceeds significantly more slowly than of the first, stepwise annelation using different dienes is readily contemplated. Conventionally the mono adduct is first aromatized to a chloro naphtho-quinone which can participate in a second cycloaddition or direct nucleophilic attack in the required fashion as discussed in Chapter 2.



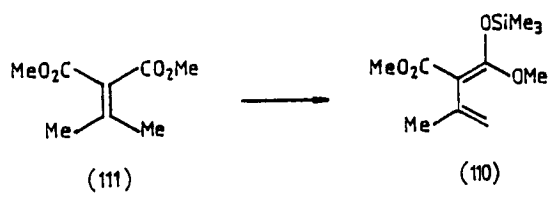
Scheme 18

Against this background syntheses were devised for emodin (95) and endocrocin (96). Retrosynthetic analysis of (95) through disconnection of the four bonds to the central quinonoid ring (Scheme 19) identified dienes (108)[81] and (109)[83] as the initial synthetic targets. Sequential reaction of these known compounds with 2,6-dichlorobenzoquinone would allow the complete carbon framework and oxygenation pattern of emodin (95) to be assembled. A similar strategy for the preparation

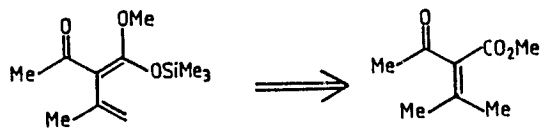


Scheme 19

of endocrocin (96) and its methyl ester requires reaction of (109) and the methoxycarbonyl diene (110) with (62). The complex diene (110) has not hitherto been reported, but it was anticipated that it would be accessible through *o*-silylation of the enolate of (111).



For the preparation of 2-acetylemodin (97) and related compounds, development of a synthon for diene (112) was required. Clearly preparation from (113) in a fashion analogous to the conversion of (111)



(112) (113)

to (110) requires suitable protection of the keto function to direct 1,4-enolization in favour of the ester enolate.

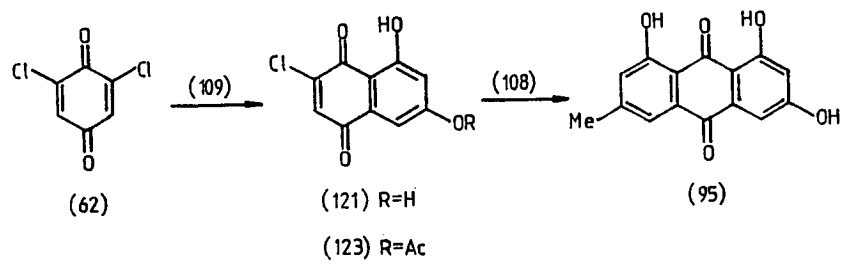
Inasmuch as this last-mentioned feature of selective enolization represents a variation from previous diene formations based on *o*-silylation of enolates, this section of work is treated separately. Hence Chapter 4 deals with the synthesis of emodin (95) and endocrocin (96) whilst Chapter 5 describes the synthesis of 2-acetylemodin (97), orientalone (100) and its isomer (99).

CHAPTER 4

RESULTS AND DISCUSSION

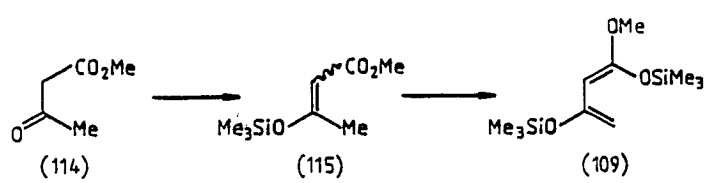
4.1 Synthesis of Emodin

Synthesis of emodin (95), the simplest natural 1,3,8-trioxygenated anthraquinone, was undertaken as a model study for the preparation of more complex analogues. The approach is outlined in Scheme 20.



Scheme 20

The 1,1,3-trioxygenated butadiene (109) was first reported by Yamamoto.[83] It is conveniently prepared by two successive silylations of methyl acetoacetate (114) as shown in Scheme 21.



Scheme 21

The enol tautomer of (114) is silylated using conditions described by Danishefsky[7] to yield the enol ether (115)[96] as a mixture of geometrical

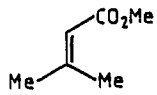
isomers. Subsequent 1,4-enolization of (115) with lithium diisopropylamide at -78° followed by quenching of the resulting dienolate with chlorotrimethylsilane affords only the (z)-butadiene (109). (z)-stereochemistry has been assigned by other workers in this Department.[97] The assignment is based upon the facility with which the diene undergoes thermally induced 1,5-sigmatropic migration of the silyl group from oxygen to carbon to produce the (*E*)-ester (116) (Scheme 22).[97] Other

(109) (116)

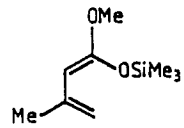
Scheme 22

groups have reported similar results in a variety of related systems.[98-103] Chan and Brownbridge[96] have concluded that diene formation results in a mixture of both (*E*)- and (z)- isomers with the former predominating. However, this view cannot be accepted without further work; partly because the basis for the authors' geometrical assignment is not clear and partly because the conclusions as to an isomeric mixture rests on gas chromatographic evidence which, given the thermal lability implicit in Scheme 22, has to be regarded as questionable. A mechanistic rationale for stereospecific diene formation has not been fully elucidated and falls outside the scope of this work, though arguably coordination constraints within the lithium dienolate are involved.[104] It appears however, that the enolization process involving bases such as lithium diisopropylamide is a general one as all other dienes mentioned in this Thesis were each formed as a single geometric isomer as indicated by n.m.r. spectroscopy. In all cases, except one (see p.76), stereochemistry has been assigned by analogy with (109).

The butadiene (108)[81] is easily prepared by *o*-silylation of the enolate of methyl 3-methyl-2-butenoate (117). Reaction of (108)

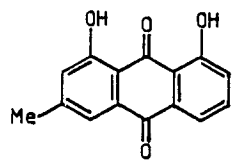


(117)



(108)

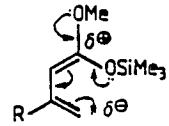
with both 2,6-dichlorobenzoquinone (62) and 2-chloro-8-hydroxy-1,4-naphthoquinone (80) has been reported.[81] The latter reaction furnished chrysophanol (118) regiospecifically in 63% yield.



(118)

Vinylogous ketene acetals such as (108) and (109) are highly polar; all substituents electronically reinforce one another rendering the unsubstituted terminus highly nucleophilic.[96] Evidence for this can be seen in the ^{13}C n.m.r. spectrum of (109)[97] where signals for

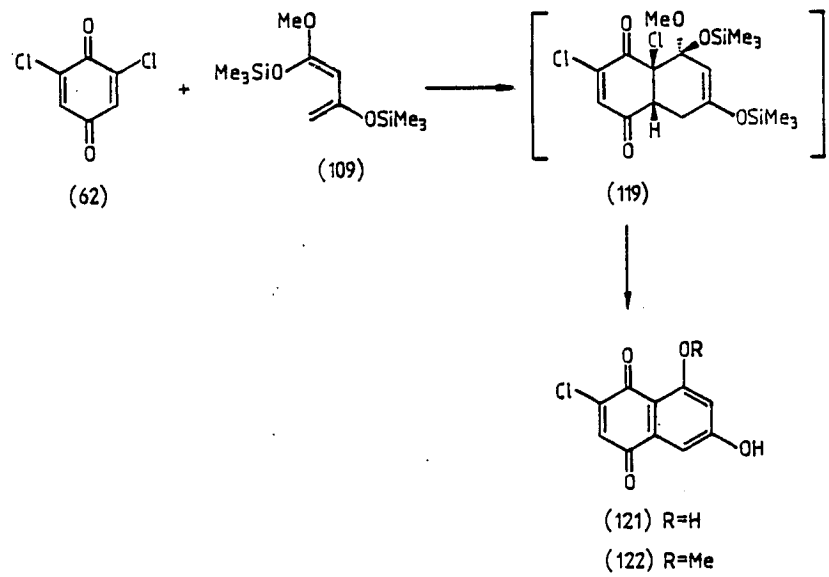
C2 and C4 (δ 77.57 and 89.22 respectively), imply considerable shielding relative to simple vinylic carbons. It has been established for a large number of examples that these highly polar butadienes react with chloro quinonoid dienophiles through the more nucleophilic terminus attacking the carbon adjacent to the chlorine-bearing carbon, i.e. vicinal attack (see p.39).[81,82,84-90]



(108) R=Me

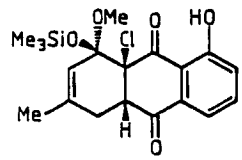
(109) R=$OSiMe_3$

Sequential reaction of (108) and (109) with 2,6-dichloro-benzoquinone (62) then resulted in a highly convergent synthesis of emodin.



Scheme 23

Reaction of (109) with (62) was presumed to proceed *via endo* addition of the butadiene to form the initial adduct (119) (Scheme 23). Formal characterization of Diels-Alder adducts from similar but less polar butadienes has been described in Chapter 2 of this Thesis. More recently within this Department adducts such as (120) have been observed and their structures have been concluded from spectral data.[105] The assignment of relative stereochemistry of the mixed acetal function is proposed by analogy with the earlier X-ray work[8] and from the stereochemistry of the butadiene.[97]



(120)

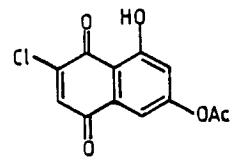
The adduct (119) was unstable; in principle it could be aromatized in a number of ways. Loss of hydrogen chloride followed by 1,4-elimination of methanol or hydrolysis of the mixed acetal moiety and cleavage of the remaining silyl group would yield the phenol (121). Alternatively elimination of hydrogen chloride and of trimethylsilanol together with cleavage of the remaining silyl group would give the methyl ether (122) (Scheme 23).

Under acidic conditions the adduct (119) decomposed to give a 6.5:1 mixture of (121) and (122) respectively in 75% overall yield. It is noteworthy that no regioisomeric products were obtained.

The ^{1}H n.m.r. spectrum of the unstable phenol (121) showed two *meta*-coupled doublets at δ 6.58 and 6.94 due to H7 and H5 respectively whilst the quinonoid proton resonated at δ 7.38. Placement of the chlorine at position 2 follows from the expected regiochemistry of the cycloaddition. The ^{1}H n.m.r. spectrum of the methyl ether (122)

exhibited similar resonances in addition to a singlet at δ 3.92 for the methyl ether.

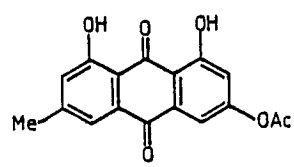
It is apparent from related work that the presence of a non-chelated aromatic hydroxy group in quinonoid dienophiles such as (121) is not compatible with reactions involving acid-sensitive dienes such as (108) and (109).[84,106] Selective esterification of the 6-hydroxy group of (121) was achieved with boron trifluoride and acetic anhydride[84] to yield the mono acetate (123). The ^{1}H n.m.r. spectrum of the product contained two *meta*-coupled doublets at δ 7.07 and 7.39



(123)

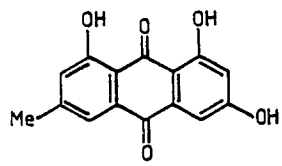
as well as an acetate resonance at δ 2.35. The selectivity of the acetylation of the β-hydroxy group was confirmed by the appearance of a singlet at δ 11.73 due to the chelated 8-hydroxy proton.

Reaction of the protected naphthoquinone (123) with the butadiene (108), proceeded readily at room temperature. The crude adduct was efficiently aromatized by slow elution down a column of silica. The dihydroxyanthraquinone (124) was the only product isolated (74% yield). Its ^{1}H n.m.r. spectrum showed two *meta*-coupled



(124)

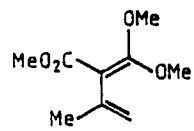
doublets at δ 7.06 and 7.56 assigned to H2 and H4 respectively. The remaining aromatic protons resonated at δ 7.11 and 7.65 and were broadened by allylic coupling to the adjacent methyl group. Sharp singlets at δ 11.97 and 12.20 indicated the presence of two intramolecularly-chelated hydroxy groups. The infrared spectrum exhibited only one chelated carbonyl at 1628 cm^{-1} whilst the non-chelated quinonoid carbonyl absorbed at 1677 cm^{-1}. This fixes the orientation of the two hydroxy groups *peri* to the same quinonoid carbonyl. Saponification of the acetate (124) then afforded emodin (95) in good yield. The synthetic material was identical in every respect to an authentic sample.[107]



(95)

4.2 Synthesis of Endocrocin

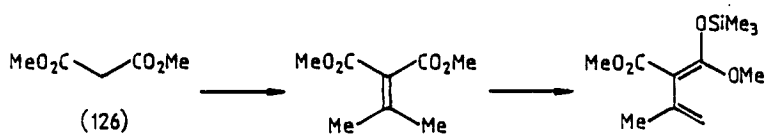
Extrapolation of this methodology to the synthesis of endocrocin (96) (Scheme 20) required preparation of the ester diene (110). The related 1,1-dialkoxybutadiene (125) is known and has been used in a synthesis of permethylated endocrocin.[108] However, the yield of diene in this case was low, and the subsequent Diels-Alder reactions were reported as requiring elevated temperatures.



(125)

The corresponding silyloxy butadiene (110) was expected to be more readily available through *o*-silylation of the ester (111), and to annelate chloro quinones under mild conditions in accordance with other trimethylsilyloxy butadienes.[81,82,84-90]

The ester (111)[109] was conveniently prepared by Knoevenagel condensation[110] of dimethyl malonate (126) and acetone (Scheme 24).

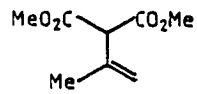


(126) (111) (110)

Scheme 24

The ^1H n.m.r. spectrum of (111) contained two singlets at δ 2.07 and 3.77. Unexpectedly under the standard conditions established for formation of dienes (108) and (109), and for a variety of similar dienes, quenching of the lithium dienolate of (111) with chlorotrimethylsilane

did not give the diene (110). Indeed generation of the lithium or potassium dienolate of (111) using a variety of bases in either tetrahydrofuran or 1,2-dimethoxyethane, followed by quenching with either chlorotrimethylsilane or *t*-butyldimethylsilyl chloride, gave mixtures which consisted chiefly of starting material (118), the deconjugated malonate (127), and at best trace amounts of the expected butadiene (110). Addition of metal cation sequestering agents[111] such as hexamethylphosphoramide did not affect the outcome of the reaction.

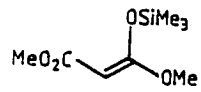


(127)

The reasons for this apparent reluctance to undergo silylation remain obscure. Isolation of (127) indicates that the dienolate was indeed formed at least to some extent. It is possible that this was due to similar factors to those recently observed by Beak[112] and Meyers.[113] These authors concluded that reaction between, for example, *n*-butyllithium and a formamidine involved initial formation of a base-substrate complex. The stability of this complex was highly solvent-dependent and in some solvents, notably tetrahydrofuran and 1,2-dimethoxyethane, the substrate could be recovered unchanged upon addition of D_2O.

That the dienolate which did form did not react with the silylating agents but simply gave the deconjugated ester (127) after work-up is also puzzling. However, it is quite consistent with the observed low reactivity of lithium and potassium enolates of malonate esters.[114-116]

On the other hand, anionic reactions involving analogous sodium enolates have been successful under certain specific conditions. Hanessian[115] and Ainsworth[116] among others have utilized the combination of sodium hydride in 1,2-dimethoxyethane for this purpose. Under these conditions, for example, dimethyl malonate can be *o*-silylated to produce (128).[116]



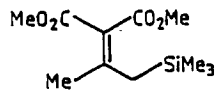
(128)

When the malonate (111) was treated with sodium hydride in refluxing 1,2-dimethoxyethane followed by quenching of the cooled reaction mixture with chlorotrimethysilane, the diene (110) could be obtained as the major product. Its ^{1}H n.m.r. spectrum indicated that it was isomerically pure. There appeared vinyl resonances of appropriate intensity at δ 4.69 and 4.99 along with singlets at δ 3.56 and 0.26 assigned to the methoxy group and *o*-trimethylsilyl moiety respectively.

(110)

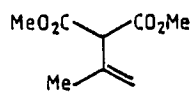
The appearance of a single methoxyl resonance is consistent with the fluxional behaviour of the silyl group rapidly migrating between the oxygen atoms as shown. Analogous migration has been established for the ketene acetal (128).[116] The stereochemistry of (110) is thus assigned with the silyloxy and isopropenyl groups *trans* to one another.

That is the opposite stereochemistry to that assigned to the corresponding groups in (108). Consistent with this conclusion the butadiene (110), although itself thermally unstable, does not rearrange to a C-silylated isomer (129) (see p.68).



(129)

The reaction mixture from preparation of 110 was persistently contaminated with the deconjugated malonate (127). The latter could be prepared exclusively by selective hydrolysis of diene (110) when the mixture was treated with methanol. Its ^{1}H n.m.r. spectrum exhibited vinyl resonances at δ 4.99 and 5.10 and a single methoxyl resonance at δ 3.76. The methine proton appeared as a broadened singlet at δ 4.13.

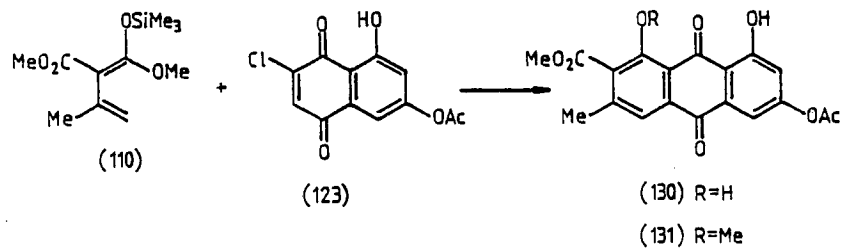


(127)

Attempts to fractionate the mixture were unsuccessful. Whether this was due in part to conversion of the diene (110) to (127) during distillation was not determined. In subsequent Diels-Alder additions the crude mixture of (110) and (127) typically in the ratio 2:1 was used in appropriate excess.

Reaction of the acetoxy naphthoquinone (123) with the diene (110) at room temperature overnight, followed by aromatization of the

initial adduct using sodium acetate in methanol, gave a 3:1 mixture of the hydroxy anthraquinone (130) and its methyl ether (131) in 75% overall yield (Scheme 25). The ^{1}H n.m.r. spectrum of (130) showed

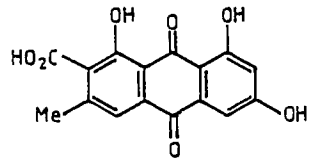


Scheme 25

two *meta*-coupled doublets at δ 7.08 and 7.57 due to H7 and H5 respectively and a singlet at δ 7.69 due to H4. Two downfield singlets at δ 12.04 and 12.32 were assigned to the two chelated hydroxy groups. The infrared spectrum indicated the presence of both aryl acetate and methyl ester groups 1779 and 1730 cm^{-1} respectively. It was apparent from absorbances of the quinonoid carbonyls that only one of them was chelated. The latter absorbed at 1640 cm^{-1}, the other at 1676 cm^{-1}. This establishes the orientation of the two hydroxy groups in (130) *peri* to the same carbonyl and thus confirms the regiochemistry of the cycloaddition of (110) to (123).

The ^{1}H n.m.r. spectrum of (131) was essentially the same as for (130), the major difference being the expected replacement of one hydroxy resonance by that of a three-proton singlet at ~ δ 4.0 due to the methoxy group.

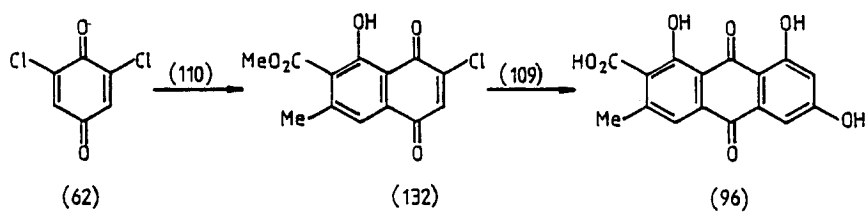
Both products (130) and (131) possess the substitution pattern observed for endocrocin (96). The acetoxy ester (130) was converted quantitatively to endocrocin (96) by alkaline hydrolysis.



(96)

Its ^{1}H n.m.r. spectrum in [$^{2}H_{6}$]dimethylsulphoxide exhibited a singlet at δ 2.40 assigned to the β-aryl methyl group, two *meta*-coupled doublets at δ 6.62 and 7.15 and a singlet at δ 7.59 attributed to the aromatic protons H7, H5 and H4 respectively, whilst only one hydroxy proton was observed at δ 12.02, consistent with structure (96).

One of the inherent advantages of the sequential Diels-Alder approach to anthraquinones lies in the capacity to reverse the order of the cycloaddition processes thereby altering the yield of the overall process. With this in mind, synthesis of endocrocin (96) was undertaken in the reverse sense as outlined in Scheme 26.



(62) (132) (96)

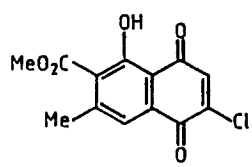
Scheme 26

Addition of the butadiene (110) to 2,6-dichlorobenzoquinone (62) followed by aromatization of the initial adduct on silica afforded the chloro naphthoquinone (132) in excellent yield. Conveniently, none of the corresponding methyl ether could be detected. The mass spectrum

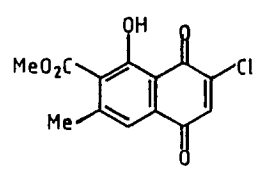
of (132) showed the characteristic monochloro isotope pattern for the molecular ion (*m/z* 280, 282). The compound absorbed in the infrared at 1640 and 1666 cm^{-1} corresponding to the chelated and non-chelated quinonoid carbonyl groups. Its ^{1}H n.m.r. spectrum showed resonances at δ 2.44 and 3.98 for the aryl methyl and methoxycarbonyl groups. The quinonoid proton and the aromatic proton resonated at δ 7.19 and 7.49 respectively whilst the chelated hydroxy proton resonated at δ 11.94.

At this point, it is appropriate to consider the isomeric chloro quinone (133) isomeric with (132). Its formation illustrates the directing influence of the halogen in Diels-Alder additions to halo quinones, which has been emphasized several times in this Thesis. Part of the procedure by which this was established for a wide variety of dienes was to show that reaction of a particular diene with either 2,5- or 2,6-dichlorobenzoquinone occurred regiospecifically, resulting in regioisomeric chloro naphthoquinones.[85] On this basis it was pertinent to examine reaction of (110) with 2,5-dichlorobenzoquinone (60).

The reaction was significantly slower than the analogous addition to the 2,6-isomer (62) already described. However, acid catalysed aromatization of the initial adduct gave a single naphtho-quinone (133) in good yield. Though this product was chromatographically



(133)

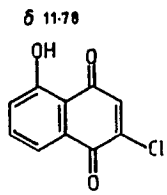


(132)

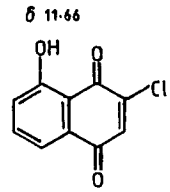
indistinguishable from (132), the isomers had significant spectroscopic

differences. In particular in the ^{1}H n.m.r. spectrum of (133) the aromatic proton and the hydroxy proton resonated at δ 7.57 and 12.07 respectively, in each case deshielded by about 0.1 ppm relative to the respective resonances in the spectrum of (132).

The observed deshielding of the hydroxy resonance of (133) relative to (132) is of structural value since chemical shifts of chelated hydroxy protons have been shown to be sensitive probes for differentiation of isomeric naphthoquinones[59,60] and anthraquinones.[118] Lillee and Musgrave[59] have shown that for isomeric derivatives of juglone the hydroxy shift in deuterochloroform is dependent on the nature and position of quinonoid substituents. Of particular relevance to the present work are 2- and 3-chlorojuglones (79) and (80). The sharp singlet for the hydroxy proton in the 2- chloro compound is deshielded by 0.08 ppm relative to that of the 3-chloro isomer. This



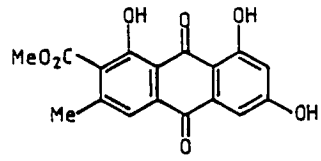
(79)



(80)

correlates with the comparative data obtained for (132) and (133) and is taken as further evidence for the structure of these compounds.

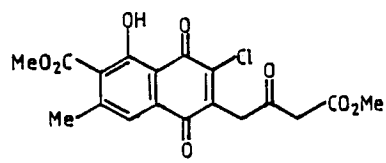
The 3-chloro quinone (132) was then made to react with the 1,1,3-trioxygenated butadiene (109). Whilst consumption of starting material was observed, under a variety of aromatization conditions endocrocin methyl ester (134) was produced as only a minor component of the reaction product. Its electronic spectrum resembled that of



(134)

endocrocin itself with a long wavelength maximum at 448 nm. Its ^{1}H n.m.r. spectrum [$^{2}H_{6}$]dimethsulphoxide exhibited two *meta*-coupled doublets at δ 6.62 and 7.13 and a singlet at δ 7.57 for the three aromatic protons along with singlets at δ 11.47 and 12.53 for the three hydroxy protons.

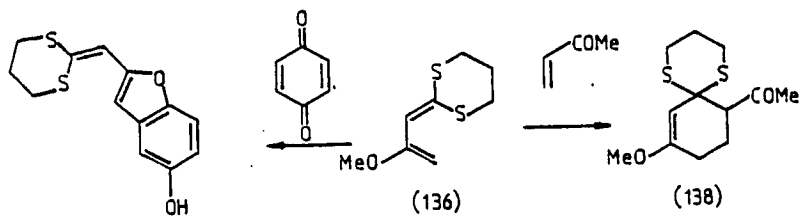
The major component from this reaction was not anthraquinoid but rather the naphthoquinonyl acetoacetate (135). The mass spectrum



(135)

of (135), which showed ions at *m/z* 394, 396 ascribed to the molecular ion, indicated that the chlorine had been retained. The infrared spectrum indicated an unconjugated ester absorbing at 1757 cm^{-1}. A broad stretch at 1725 cm^{-1} was ascribed to the carbonyls of the aromatic ester and the ketone moieties. The ^{1}H n.m.r. spectrum which lacked the singlet at δ 7.19 from the spectrum of (132) but there were three new singlets at δ 3.65 and 4.11, assigned to the two methylene groups, and at δ 3.79 due to the aliphatic methoxycarbonyl protons.

Formation of (135) is believed to be the first example of a Michael addition between a quinone and a silyloxbutadiene. There have been a number of examples cited in the literature however, where competition between Diels-Alder and Michael reactions of polar dienes has been observed. In these cases it appears that more electron-deficient substrates tend to favour Michael products. It was reported for example[119] that diene (136) reacted with benzoquinone to give the benzofuran (137), presumably through Michael attack with subsequent cyclization of the initial adduct (Scheme 27). On the other hand, reaction of (136) with methyl vinyl ketone gave the cycloadduct (138).



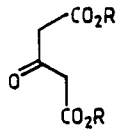
(137) (136) (138)

Scheme 27

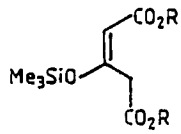
The comparative outcomes of reacting diene (109) with either 2,6-dichlorobenzoquinone (62), which gave products of cycloaddition, or with the chloro juglone (132), which gave mainly the product (135) from Michael addition, are consistent with this trend. It is expected that the intramolecular hydrogen-bonding in (132) would render this a more electron-demanding ene dione system than that in (62) and hence it should be more susceptible to Michael additions.

A procedure developed to avoid unwanted Michael reactivity in the synthesis of endocrocin will be described later. However, parallel work illustrates that this competitive process is a limitation to the generality of the Diels-Alder reaction.

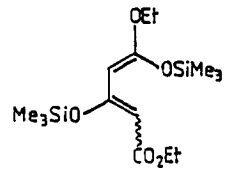
As part of a program designed to investigate the synthetic utility of acyl dienes, compound (139) was prepared (Scheme 28).



(140) R=Et
(143) R=Me



(141) R=Et
(142) R=Me

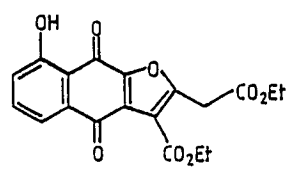


(139)

Scheme 28

It was obtained through a similar route to the synthesis of (109). The keto diester (140) was converted to the enol ether (141) as a mixture of *E/Z* isomers in high yield. The corresponding dimethyl ester (142) was also prepared but this offered no advantage over the cheaper diethyl series. The very sensitive butadiene (139) was obtained by *o*-silylation of the product of 1,4-enolization of (141) with lithium diisopropylamide. The ^{1}H n.m.r. spectrum of the crude diene showed two silyl resonances coincident at δ 0.25 and broad singlets at δ 4.75 and 5.98 for the two vinyl protons together with overlapping multiplets for the two ethoxy groups.

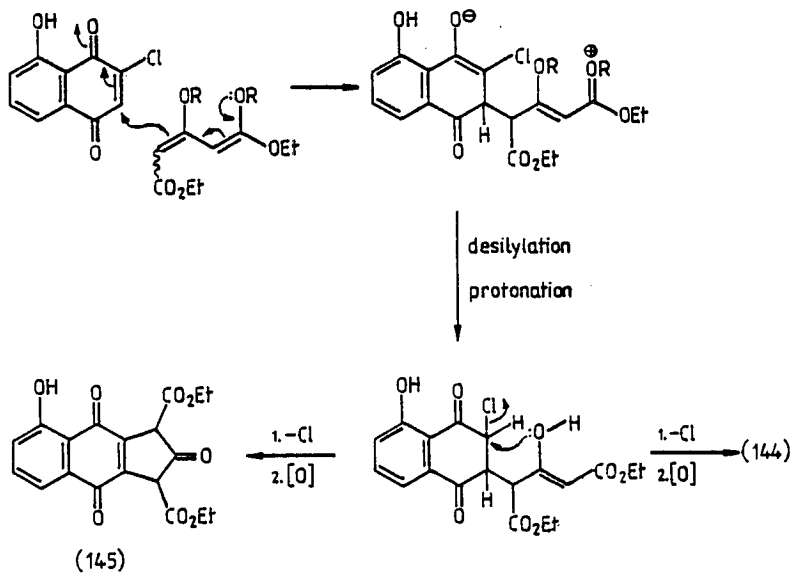
When the diene (139) was made to react with 3-chlorojuglone (80) under a variety of conditions no anthraquinones could be isolated. The major product in modest yield was found to be the naphthofuran (144). The mass spectrum of the product gave a molecular ion at *m/z* 372, which



(144)

suggested loss of the chlorine atom from (80). Its infrared spectrum showed the presence of two ester carbonyls, one of which was conjugated (1714 cm^{-1}) and the other not (1743 cm^{-1}). The ^1H n.m.r. spectrum of (144) exhibited multiplets due to the two ethyl ester groups and three characteristic signals for the aromatic protons of a juglone system; two *ortho-, meta*-coupled doublets at δ 7.26 and 7.76 and an *ortho*-coupled "triplet" at δ 7.62. The only remaining signals were attributed to the chelated hydroxy proton at δ 11.82 and a deshielded methylene resonance at δ 4.16.

The formation of (144) is postulated to arise from Michael addition, followed by the processes outlined in Scheme 29, though not necessarily in the sequence indicated. According to Baldwin's

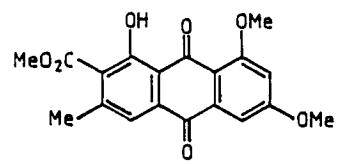


Scheme 29

guidelines for ring closure[120-123] the cyclization to form the furan ring is a 5-*Exo* -Tet process. For such closures, formation of the cyclic enol ether is favoured over carbon-carbon bond formation to the cyclic keto diester (145).

It appears therefore, that reaction of highly polar 1,1,3-trioxygenated butadienes such as (109) and (139) with reactive electrophiles such as (80) and (132) favour Michael addition over Diels-Alder cycloaddition. The basis of the relatively subtle factors[124] which control competition between these processes remains unidentified.[119] Some approaches have taken advantage of the greater negative volume of activation of the Diels-Alder process so as to maximize the products of cycloaddition by carrying out reactions at extremely high pressure.[124-127] However, these conditions are not routinely available.

In the specific case of the synthesis of endocrocin (96), the problem of competing Michael addition can be overcome in two ways. Firstly by reversing the order of the two Diels-Alder reactions, as has already been described (see p.78). Alternatively, elaboration of the 1,3-dioxygenated ring of (96) could be achieved by reaction of an appropriate chloro naphthoquinone with 1,1-dimethoxyethene (88). Such processes, outlined on p.38 of this Thesis, are known to occur regiospecifically by attack of the carbon nucleophile vicinal to the quinonoid halogen.



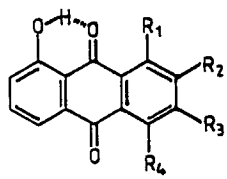
(146)

Reaction of (88) and the chloro naphthoquinone (132) in *N,N*-dimethylformamide afforded a single anthraquinone (146) in moderate yield. Its ^{1}H n.m.r. spectrum showed resonances consistent with the assigned structure, in particular the chelated hydroxy proton resonated at δ 13.45. The latter chemical shift is potentially useful in structural assignment, investigation of its applicability to substituted 1-hydroxy anthraquinones, but it is developed here to only a limited extent because of appearance of a partially overlapping publication[118] during progress of the work.

The difficulty of differentiating regioisomers using spectroscopic techniques has been alluded to earlier (p. 2). For this reason, it was decided to investigate the possibility that the shift of chelated hydroxy protons in the ^{1}H n.m.r. spectra of regioisomeric anthraquinones might be used diagnostically as they have been for naphthoquinones.[59,60] Relevant chemical shift data for a number of 1-hydroxy anthraquinones are listed in Table 4. These shifts were found to be independent of concentration.

TABLE 4

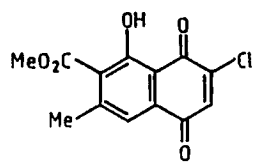
Chemical shifts of chelated hydroxy protons in anthraquinones



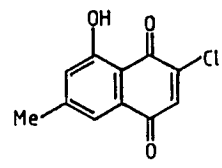
Compound	R_1	R_2	R_3	R_4	δ *peri*-OH
(147)	H	H	H	H	12.62
(148)	OMe	H	H	H	12.94
(149)	H	OMe	H	H	12.49[117]
(150)	H	H	OMe	H	12.69[117]
(151)	H	H	H	OMe	12.46
(152)	OMe	H	OMe	H	13.14
(153)	H	OMe	H	OMe	12.40

From these limited data it appears that when an electron donating methoxy group is conjugated with the chelated carbonyl as in (150) the hydroxy proton is deshielded relative to the unconjugated isomer (149). A similar difference is seen for the isomeric pair (148) and (151). If two methoxy groups conjugate with the chelated carbonyl the effect is more dramatic as seen for the isomeric (152) and (153). In all cases values for the regioisomeric pairs straddle the value for the unsubstituted (147). Therefore, in cases where both isomers are available, regiochemistry can be assigned with some confidence.

With data for only one isomer, as in the case of (146), some useful extrapolation can probably be made. In the first instance, comparison with compounds (123) and (152) (below) suggests the second ester carbonyl adjacent to the chelated hydroxy group has a deshielding effect of about 0.3 ppm compared with (152).[81,105]

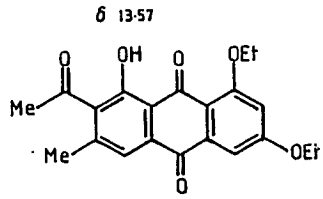


(132)

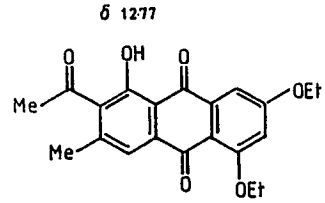


(154)

Superimposing that deshielding effect on the shifts for the chelated hydroxy protons in (152) and (153) (Table 4) is compatible only with the two methoxy groups in (146) being conjugated with the chelated carbonyl, the hydroxy proton in (146) resonating at δ 13.45. There is close correlation too, with similarly substituted (155) and (156).[128] In both these cases the acetyl carbonyl exerts a slightly stronger deshielding effect than the methoxycarbonyl group of (146).



(155)



(156)

The anthraquinone (144) was converted to endocrocin (96) by dealkylation in an aluminium chloride melt. However, under these conditions dealkylation of the ester moiety was sluggish presumably due to steric hindrance. Thus the methyl ester (134) was formed as the major product. This type of behaviour has been reported previously for similar esters.[85] Saponification of (134) afforded the natural pigment (96) quantitatively. The synthetic material obtained in this manner was identical to that obtained previously.

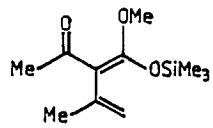
Although the latter procedure (132) to (146) to (96) was not as efficient as the process outlined in Scheme 25 (p.78), the combination of the approaches offers considerable flexibility in the construction of complex anthraquinonoid pigments.

CHAPTER 5

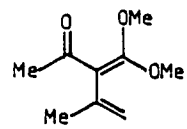
RESULTS AND DISCUSSION

5.1 Synthesis of a Protected Acetyl Butadiene

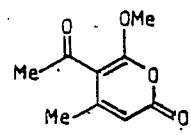
Extension of the methodology developed in Chapter 4 to the synthesis of 2-acetylemodin (97) and of related naphthoquinones (99) and (100) requires preparation of a synthon for the butadiene (112). Possible examples of such a synthon include the 1,1-dialkoxybutadiene (157) and the α-pyrone (158) which have been used for the



(112)



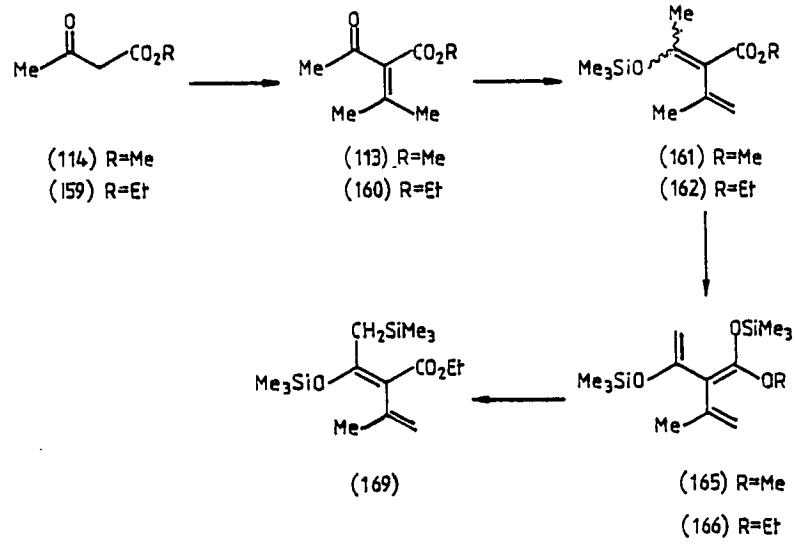
(157)



(158)

synthesis of (97)[76,78] and also in the case of the latter for the preparation of the incorrect structure for orientalone (99). However, both of these compounds (157) and (158) are tedious to prepare and require elevated temperatures for reaction with quinonoid dienophiles and further, procedures which employ their use lack flexibility. Whilst the 1,1-dialkoxybutadiene (157) was used to prepare stypandrone methyl ether, the approach could not be modified to afford stypandrone (98) itself. *o*-Demethylation of such naphthoquinone methyl ethers is not straightforward, significantly detracting from the synthesis. For similar reasons it is difficult to conceive how either (157) or (158) could be used successfully for a synthesis of orientalone (100).

A similar approach to that used for the synthesis of the methoxycarbonyl diene (110) was planned for the preparation of a synthon for (112). The carbon framework was prepared by Knoevenagel condensation of the acetoacetates (114) and (159) with acetone to yield the α,β-unsaturated esters (113)[129] and (160)[130] respectively (Scheme 30).



(114) R=Me
(159) R=Et

(113) R=Me
(160) R=Et

(161) R=Me
(162) R=Et

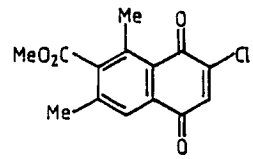
(169)

(165) R=Me
(166) R=Et

Scheme 30

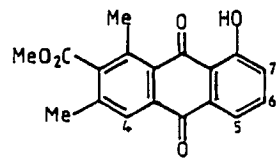
1,4-Enolization of these known esters (113) and (160) was expected to favour formation of the ketone dienolate. Indeed, silylation using Danishefsky's conditions[7] afforded the diene esters (161) and (162) respectively as a mixture of geometrical isomers. The ^{1}H n.m.r. spectrum of methyl ester (163) showed resonances in accordance with the structure and its infrared spectrum exhibited an α,β-unsaturated ester carbonyl absorbance at 1723 cm^{-1}. The ethyl ester (162) displayed similar spectral data, allowing for the different alkoxy group.

The methyl ester diene (161) was further characterized through its Diels-Alder addition products. Addition of (161) to 2,6-dichloro-benzoquinone (62) in refluxing toluene followed by aromatization of the initial adduct with sodium acetate afforded the dimethyl naphthoquinone (163) in excellent yield. Its ^{1}H n.m.r. spectrum showed singlets at δ 2.41, 2.66 and 3.98 for the β-, α- and ester-methyl groups respectively. Resonances at δ 7.18 and 7.87 were assigned to H2 and H8 respectively.



(163)

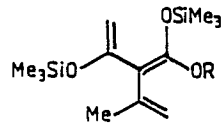
Placement of the chlorine at position 3 follows from the expected regiochemistry of cycloaddition. Similarly addition of (161) to 3-chlorojuglone (80) proceeded smoothly in refluxing toluene. Aromatization of the initial adduct afforded in 98% yield an anthraquinone formulated as (164). Its ^{1}H n.m.r. spectrum showed appropriate methyl



(164)

resonances along with signals with appropriate multiplicity at δ 7.30 and 7.99 assigned to H7 and H5, and at δ 7.63 and 8.08 due to H6 and H4 respectively.

The substitution pattern of the products (163) and (164) while usefully validating the structure of the diene (161) is not appropriate to the synthesis of polyketide-derived natural products. However, the carbon skeletons of (113) and (160) can be converted to a possible synthon for (112) by 1,4-enolization of the dienes (161) and (162) with lithium diisopropylamide followed by quenching of the enolates. This afforded the unstable trienes (165) and (166) in excellent yield. The ^{1}H n.m.r. spectrum of the methoxy triene (165) showed vinyl resonances

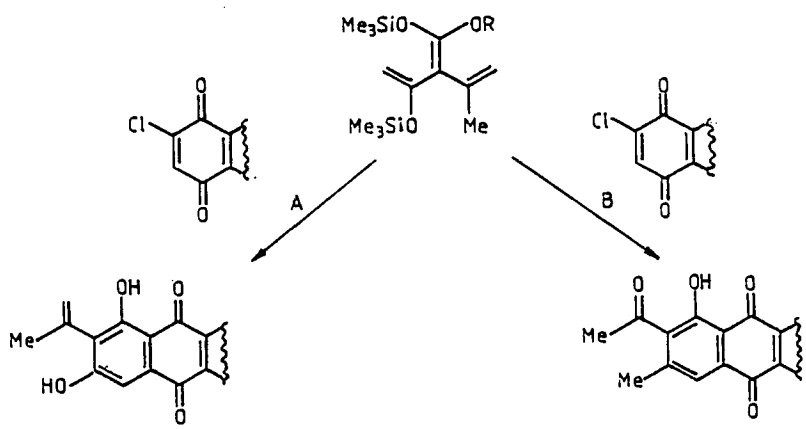


(165) R=Me

(166) R=Et

at δ 3.63 and 4.90 together with a methoxy resonance at δ 3.56 and a broad singlet at δ 1.88 due to the methyl group. This compound decomposed rapidly at room temperature and was used without further purification. The analogous ethoxy triene (166) showed similar spectral data. On one occasion careful distillation of the crude reaction mixture afforded a sample amenable to combustion analysis.

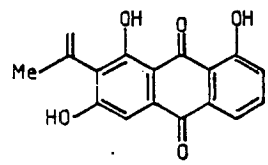
Both of these trienes (165) and (166) possess two cross-conjugated butadiene systems, either of which could participate in a Diels-Alder cycloaddition.[131] The 1,1-dioxy-3-methyl diene would generate the required substitution pattern of the A-ring of



Scheme 31

2-acetylemodin (97) after aromatization and hydrolysis (Scheme 31, path A). However, the alternative mode of cycloaddition *via* the 1,1,3-trioxygenated diene could not produce the desired substitution pattern (Scheme 31, path B).

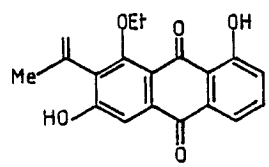
Reaction of the methoxy triene (165) with 3-chlorojuglone (80) in a model study gave a low yield of the anthraquinone (167) as the major product. Its formation is consistent with path B, that is, reaction of the more electron-rich butadiene with the dienophile. The ^{1}H n.m.r. spectrum of (167) exhibited multiplets at δ 5.21 and



(167)

5.64 due to the methylene protons as well as a broad singlet at δ 2.16 assigned to the vinyl methyl group.

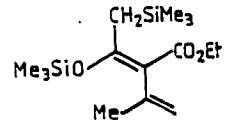
When a similar reaction was performed using the ethoxy triene (166), the ethyl ether (168) was isolated, also in poor yield.



(168)

This compound had similar spectral data to that of its trihydroxy analogue (167). The Diels-Alder additions of both the trienes (165) and (166) not only proceeded in the undesired manner, but gave disappointing conversions to aromatic products. By analogy with diene

(109) (p.68) the stereochemistry of (165) and (166) was assigned as shown when it was found that the ethoxy triene (166) rearranged slowly at room temperature and at higher temperatures was converted stereospecifically to its *C*-silylated isomer (169). Its ^{1}H n.m.r. spectrum

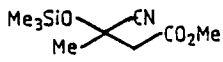


(169)

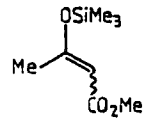
showed two nine-proton singlets at δ 0.06 and 0.19 for the *C*- and *O*-trimethylsilyl groups respectively. The allylic methylene protons resonated at δ 2.41. This shift closely correlates with the analogous protons in (116) indicating a *cis* relationship of the ester and *C*-silylated methylene groups.

Whilst the reactions in Scheme 30 (p. 91) served to construct the carbon skeleton of the desired synthon (112), the formation and behaviour of compounds (161)-(168) make it evident in order to obtain the reactivity implicit in (112) prior protection of the keto group would be required so as to direct enolization towards the ester enolate. A number of protecting groups were considered for the purpose, a major consideration in the selection being stability towards the strongly basic conditions required for enolization of the ester function.

Masking of a carbonyl group as the corresponding *O*-silyl cyanohydrin has been reported to afford protection from unwanted reaction in basic media.[132,133] In a model study reaction of methyl acetoacetate (114) with cyanotrimethylsilane gave a mixture of the cyanohydrin (170) and the known enol ether (115).[97] In the ^{1}H n.m.r. spectrum of the former product singlets at δ 1.72 and 2.79 were assigned



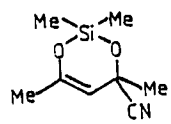
(170)



(115)

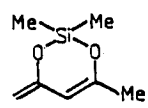
to the methyl and methylene groups. The reaction mixture upon distillation produced only the enol ether (115), ready elimination of hydrogen cyanide precluding isolation of the cyanohydrin (170). An analogous result has been reported in a similar process derived from acetylacetone.[134]

The same publication by Murai[134] reports the reaction of dicyanodimethylsilane with various β-diketones to produce silicon-containing heterocycles such as (171). This report suggested that



(171)

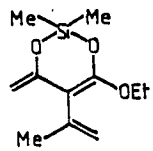
protection of the ketone and concurrent silylation of the ester could with the appropriate substrate generate a suitably protected diene. In an attempt to evaluate the utility of such a bridged protecting group, acetylacetone was made to react with dichlorodimethylsilane. The product which was assigned structure (172) could not be purified without considerable decomposition nor could it be stored, even at low temperature,



(172)

for any length of time. The ^{1}H n.m.r. spectrum of the material indicated that its purity was greater than 90%. A singlet at δ 0.37 was ascribed to the silyl methyl groups and a broad singlet at δ 1.86 to the vinyl methyl group. The exocyclic methylene protons appeared at δ 3.93, 4.10 and the remaining vinyl proton at δ 5.11.

The cyclic diene (172) cannot participate in a Diels-Alder cycloaddition as it is locked into an *S-trans* configuration. Similar treatment of the acetoacetate (160) might be expected to yield the triene (173). Unlike the trienes (165) and (166) the cyclic triene

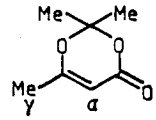


(173)

(173) has only one butadiene system suitably orientated to react by cycloaddition.

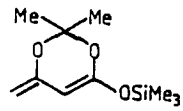
Treatment of (160) with lithium diisopropylamide and dichlorodimethylsilane produced a yellow viscous oil. The ^{1}H n.m.r. spectrum exhibited resonances consistent with the structure (173) though the signals were significantly broadened. Preliminary experiments directed towards cycloaddition of this unstable product to a variety of quinonoid dienophiles were unsuccessful. The intractable nature of this substance and its unsatisfactory spectral behaviour suggested that it may not have been a discrete molecular species. It has been reported previously that use of dichlorodimethylsilane in synthesis is limited by the propensity of this reagent to participate in the formation of dimers or oligomers.[135]

The shortcoming of this approach could potentially have been overcome by using the carbocyclic analogue (174).[136] This



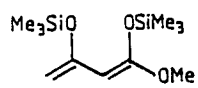
(174)

material is readily available from reaction of diketone and acetone. 1,4-Enolization of (174) with lithium diisopropylamide followed by quenching with chlorotrimethylsilane afforded the diene (175). Although this too was unstable, its ^{1}H n.m.r. spectrum showed three



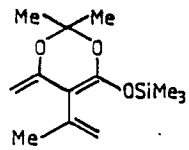
(175)

vinyl resonances at δ 3.93, 4.03 and 4.60 along with a singlet at δ 0.24 due to the silyl methyl groups. Unlike its acyclic analogue (109) the cyclic diene (175) is locked into an *s-trans* configuration and



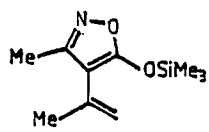
(109)

cannot participate in a Diels-Alder cycloaddition. However, conversion of (174) to a synthon for (112) such as (176) was frustrated by the inability to appropriately alkylate the dioxolenone (174) in the α-position, alkylation occurring predominately in the γ-position.[137]

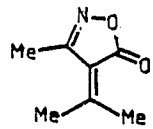


(176)

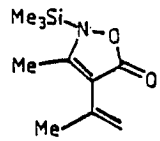
An alternative approach to the desired synthon (112) could be offered by the vinyl isoxazole (177). 1,4-Enolization of the known



(177)



(178)



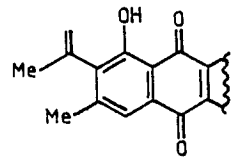
(179)

(178)[138] with lithium diisopropylamide followed by quenching with chlorotrimethylsilane gave a product which could be formulated as either the *O*-silylated (177) or *N*-silylated isomer (179). However, the material proved to be unstable having a limited lifetime at room temperature and decomposing very quickly when exposed to the atmosphere. Its ^{1}H n.m.r. spectrum showed a vinyl methylene resonance at δ 4.90 and methyl resonances at δ 1.97 and 2.20 as well as a singlet at δ 0.33 assigned to the silyl methyl groups. The chemical shift of the methyl resonance (δ 2.20) is more consistent with this substituent being attached to an isoxazole ring and on this basis structure (179) is tentatively preferred.

However, attempted Diels-Alder reaction between this diene and quinonoid dienophiles, though resulting in consumption of the starting quinone, invariably failed to give any tractable products.

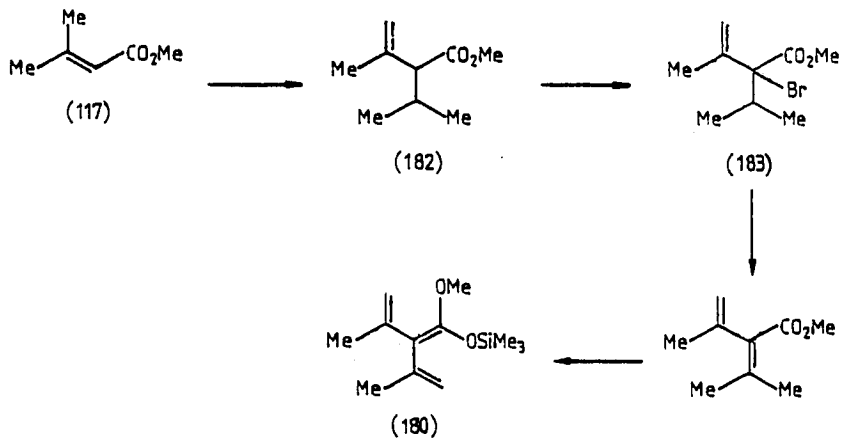
The seemingly general instability of the various bridged acetoacetate synthons (173), (175) and (177) led to this particular

approach being abandoned. As an alternative it was anticipated that reaction of the symmetrical triene (180) with appropriate dienophiles would generate quinonoid products with the substitution pattern shown in (181). Oxidative cleavage of the side chain would produce the



(181)

desired acetyl function. The planned synthesis of (180) is outlined in Scheme 32.

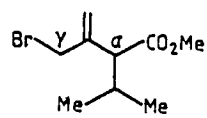


Scheme 32

The ester (117) was deconjugatively alkylated[139,140] using lithium diisopropylamide and isopropyl bromide to give the β,γ-unsaturated ester (182) in good yield. The ^{1}H n.m.r. spectrum of (182) showed doublets at δ 0.85 and 0.91 due to the methyl groups of the isopropyl residue, the methine proton of which resonated as a multiplet centred at δ 2.09. The 3-methyl resonance at δ 1.75 was broadened by

allylic coupling (J 1Hz) to the terminal methylene moiety at δ 4.90. A doublet at δ 2.68 (J 11Hz) was assigned to H2 and a singlet at δ 3.67 to the methoxycarbonyl group.

Allylic bromination of (182) with *N*-bromosuccinimide in carbon tetrachloride afforded, instead of the expected α-bromo ester (183), the isomeric γ-bromo ester (184). Its ^{1}H n.m.r. spectrum was

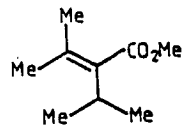


(184)

similar to that of (182) apart from the resonance due to the vinyl methyl group in the starting material being replaced by a deshielded two-proton singlet at δ 4.01. The vinyl methylene protons, also resonated downfield relative to the analogous signals in (182) at δ 5.31 and 5.44. In the mass spectrum of (184) the molecular ion was not visible, the base peak in the spectrum, corresponding to the loss of bromine, appeared at *m/z* 155.

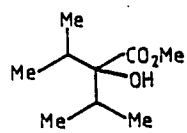
Despite the facile elimination of bromine in the mass spectrum of (184) an analogous process could not be achieved in the laboratory. 1,4-Elimination of hydrogen bromide from (184) formally requires prior conjugation of the double bond with the ester group. All attempts to do this under acidic or basic conditions failed. This presumably reflects the reluctance of this compound to form a sterically demanding tetrasubstituted double bond. Similarly (182) could not be isomerized to form its α,β-unsaturated isomer (185).

In an alternative approach to (180) addition of isopropylmagnesium bromide to dimethyl oxalate produced the alcohol (186). Its



(185)

^{1}H n.m.r. spectrum showed a doublet at δ 0.90 assigned to the methyl groups and a mutually coupled septet at δ 2.08 due to the methine protons. The hydroxy proton could be seen at δ 3.23 and the methoxycarbonyl group at δ 3.79.

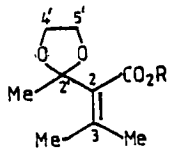


(186)

Preliminary experiments indicated that (186) could indeed be dehydrated with phosphoryl chloride to yield (185). However, the approach was discontinued at this stage in favour of a more promising one that was being pursued concurrently and that ultimately proved successful. This latter approach is developed in the remainder of this Section and is applied in Section 5.2.

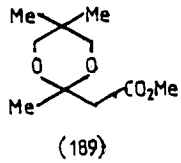
The use of a base-stable acetal[141] as a protecting group for the keto function of (112) suggested itself at an earlier stage and accordingly compounds (187)-(191) were progressively explored.

Reaction of ethylene glycol with the methyl ester (113) in the presence of trimethyl orthoformate and *p*-toluenesulphonic acid gave the ethylene acetal (187). Its infrared spectrum contained a single carbonyl stretching absorbance at 1730 cm^{-1} attributed to the

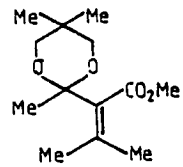


(187) R=Me

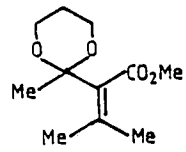
(188) R=Et



(189)



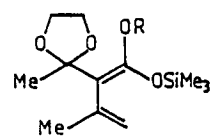
(190)



(191)

α,β-unsaturated ester group. Its ^{1}H n.m.r. spectrum showed methyl resonances at δ 1.66, 1.70 and 1.89 as well as a singlet due to the ester methyl at δ 3.74. A broad singlet at δ 3.90 was assigned to the methylene groups of the acetal. The corresponding ethyl ester (188) was prepared by a similar procedure.

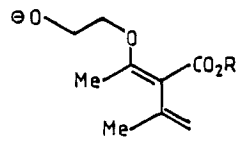
1,4-Enolization of either of the acetals (187) or (188) with lithium diisopropylamide or sodium hydride followed by quenching of the reaction mixture with a silylating agent did not produce the butadienes (192) or (193). The reaction mixture consisted mainly of



(192) R=Me

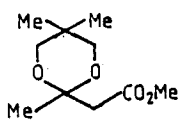
(193) R=Et

the respective starting materials. As discussed earlier (see p.75) both the nature of the base and of the solvent can alter the course of these types of reactions.[112,113] The reaction in this case may be complicated by the reversible formation of (194), analogies for which have been reported.[142,143]



(194)

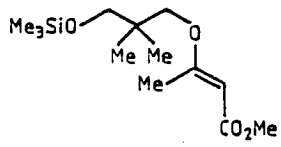
Neopentylene acetals are more stable than their ethylene or propylene counterparts.[141] The β-gem-dialkyl effect manifests itself by greatly enhancing the rate of ring closure of such systems.[145,146] If ring opening had been a contributing factor in the failure of (187) and (188) to enolize, this minor modification could possibly overcome this difficulty. In a model study the neopentylene acetal of methyl acetoacetate (189) was prepared under Dean-Stark conditions. Its mass spectrum did not show a molecular ion, a feature common to the acetals



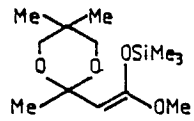
(189)

prepared in this Thesis. The ^{1}H n.m.r. spectrum of (189) exhibited singlets at δ 0.97 and 1.54 assigned to the gem-dimethyl group and to the 4-methyl group respectively. Resonances appeared at δ 2.80 and 3.70 due to the acyclic and cyclic methylene protons respectively, whilst a singlet at δ 3.54 was attributed to the methyl ester group.

Treatment of (189) with lithium diisopropylamide and chlorotrimethylsilane gave a single product in good yield. However, its structure was formulated as the enol ether (195) and not the ketene acetal (196). Its infrared spectrum showed an absorbance for the



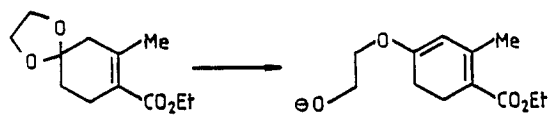
(195)



(196)

α,β-unsaturated carbonyl group (1720 cm^{-1}). Its ^{1}H n.m.r. spectrum exhibited resonances in accord with the assigned structure (195), in particular, the methyl group resonated as a broad singlet at δ 2.29, coupling to the vinyl proton (δ 5.03). The chemical shift of the methyl group suggested that it was in the deshielding zone of the ester carbonyl, and therefore (195) is assigned as the (*E*)-isomer.

Preparative cleavage of acetals under basic conditions although uncommon has been reported previously. Attempted enolization of Hagemann's ester (197) led to the formation of (198)[142] likewise the chloromethyl acetal (199) underwent ring opening to give (200)[143] (Scheme 33). Paquette also recognized the possibility in such



(197) (198)

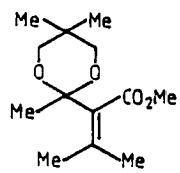
(199) (200)

Scheme 33

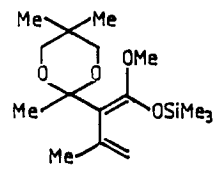
circumstances that acetals may be in equilibrium with the ring-opened form[144] (see p.103).

Despite the possibility of ring opening occurring as in the formation of (195), the isopropylidene acetals (190) and (191) were prepared using standard Dean-Stark conditions. The infrared spectrum of (190) showed an absorbance at 1730 cm^{-1} due to the α,β-unsaturated ester carbonyl. Its ^1H n.m.r. spectrum showed singlets at δ 0.72 and 1.17 assigned to the gem-dimethyl groups, and three other methyl resonances at δ 1.62, 1.76 and 1.87. The resonances of the methylene groups of the acetal were not first order and were observed as multiplets at δ 3.23 and 3.69. The methyl ester resonated at δ 3.74 as a sharp singlet.

Treatment of (190) with lithium diisopropylamide followed by quenching of the reaction mixture with chlorotrimethylsilane gave the butadiene (201) in which pleasingly the acetal ring remained intact. However, the compound was unstable and was freshly prepared prior to use.



(190)

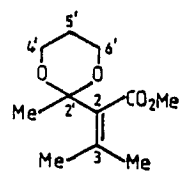


(201)

The ^1H n.m.r. spectrum of (201) showed a singlet at δ 0.21 assigned to the silyl methyl groups. Methyl resonances at δ 1.60 and 1.93, the latter being broadened by allylic coupling, were assigned as corresponding to the ethylidene and isopropenyl methyl groups respectively. The methoxycarbonyl protons resonated at δ 3.55 and appropriate signals for the intact acetal moiety were observed.

The corresponding propylene acetal (191) was also prepared. Its spectral data were similar to that of (190). The ^{1}H n.m.r. spectrum of (191) showed resonances appropriate to the butenoate moiety, the resonances of the acetal group were however, not first order appearing as multiplets at ~δ 2.00 and 3.85.

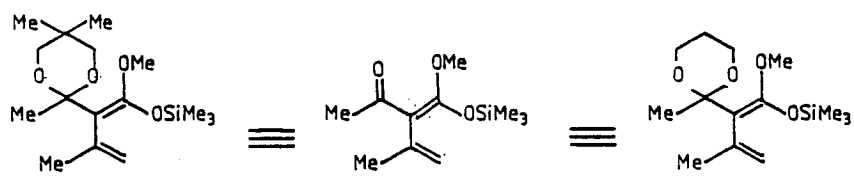
Treatment of (191) with lithium diisopropylamide and chlorotrimethylsilane gave the butadiene (202) analogous to (201). Like (201) this compound was also unstable and it too was freshly prepared prior to use. The ^{1}H n.m.r. spectrum of the crude product indicated that its purity was greater than 85%. The resonances at δ 1.56 and



(191)

1.94 were assigned to the ethylidene and isopropenyl methyl groups respectively, the latter being broadened by allylic coupling.

Both the butadienes (201) and (202) are suitably functionalized to act as synthons for (112). It was anticipated that deacetalization following cycloaddition would unmask the acetyl group. The

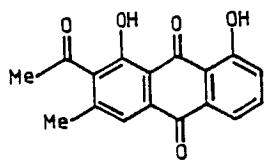


(201) (112) (202)

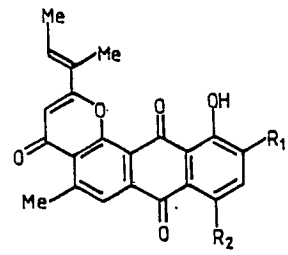
next Section describes the cycloaddition reactions of (201) and (202) in the synthesis of acetyl-substituted polyketide pigments.

5.2 Synthesis of 2-Acetylemodin and Related Quinones

The availability of dienes (201) and (202) has afforded synthetic access to 2-acetylemodin (97), orientalone (100) and its isomer (99), and to the anthraquinone (203). This last compound represents the basic quinonoid chromophore of the antitumor antibiotic kidamycin (204).[147] Development of these syntheses, which involved some adaption of the approach originally envisaged is discussed in this section.

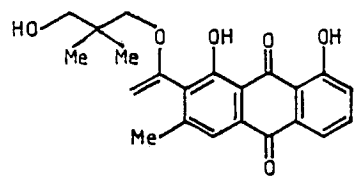


(203)



(204) R_1,R_2=amino sugars

To investigate the utility of diene (201) it was made to react with 3-chlorojuglone (80). Even in the presence of excess diene, the reaction was very sluggish. After acidic treatment of the crude reaction mixture the only tractable product appeared to be the enol ether (205). The mass spectrum of this product showed a



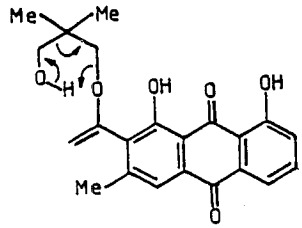
(205)

molecular ion (*m/z* 382) confirming retention of the neopentyl residue. In addition to signals characteristic of the quinonoid nucleus, the ^1H n.m.r. spectrum showed multiplets at δ 4.98 and 5.45 assigned to the

terminal methylene protons. The two aliphatic methylene groups appeared as a singlet at δ 3.99 and a doublet at 3.55. Addition of D_2O to the sample converted this last signal into a singlet and resulted in the disappearance of a triplet at δ 1.90 ascribed to the aliphatic hydroxy proton. The remaining singlets at δ 1.05 and 2.08 were attributed to the gem-dimethyl and the β-aryl methyl groups respectively.

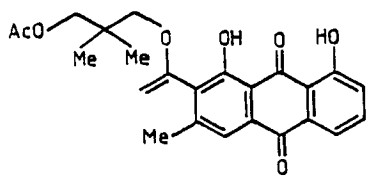
Isolation of the enol ether rather than the cyclic acetal is puzzling. Indeed it was not expected that either of these two acid-labile functions would survive the acidic work-up to which the reaction mixture was subjected. Still more surprising was the quite remarkable stability of the enol ether to deliberate attempts at hydrolysis. Compound (205) could be isolated unchanged after being refluxed in acidic ethanol for periods up to a month. Treatment with boron trichloride or neat trifluoromethanesulphonic acid also left (205) intact. Treatment with molten aluminium chloride (180^{o}) caused considerable decomposition but none of the desired quinone (203) was detected in the reaction mixture.

The mass spectrum of (205) showed a base peak (*m/z* 295) corresponding to loss of the neopentyl residue, possibly in the form of isobutylene and formaldehyde, and a hydrogen. Such a fragmentation has synthetic analogy with the fission of γ,δ-unsaturated alcohols.[148] All attempts to take advantage of this behaviour, schematically represented on p. 110, on a preparative scale by extrusion of these fragments under pyrolytic conditions were unsuccessful. The compound (205) sublimed unchanged at temperatures up to 200^{o} whilst flash vacuum pyrolysis at > 400^{o} resulted in extensive decomposition.



(205)

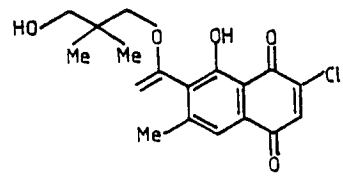
Attempted cleavage of the enol ether (205) with hydrobromic acid in acetic acid gave as the major product, the acetate (206). This assignment was supported by the presence of a molecular ion at



(206)

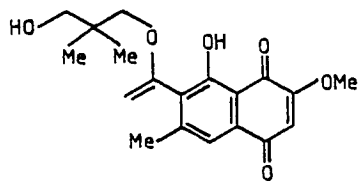
m/z 424 in its mass spectrum. Its ^{1}H n.m.r. spectrum was similar to that of (205) except that the signal for the hydroxy proton was absent, being replaced by an acetate resonance at δ 2.06 overlapping with the resonance due to the aryl methyl group. Introduction of the acetate group also resulted in deshielding of the adjacent methylene protons by about 0.4 ppm relative to the corresponding protons of the alcohol (205).

A further stable enol ether resulted from addition of diene (201) to 2,6-dichlorobenzoquinone (62). Its structure (207) was clear from its ^{1}H n.m.r. spectrum which showed sharp singlets at δ 7.13 and δ 7.23 for H3 and H5 respectively and a singlet at δ 11.97 for the chelated hydroxy proton. This product resisted hydrolysis under mildly acidic conditions and when harsher conditions were employed extensive

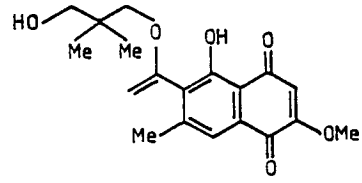


(207)

decomposition occurred. This last result was not unexplained given the known instability of halo quinones towards extremes of pH. It was expected on the other hand that the corresponding methoxy quinone (208) would be considerably more stable. Displacement of the halogen by methoxide ion as described in Chapter 2 of this Thesis gave chiefly (208), the product from *ipso* substitution. Its ^{1}H n.m.r. spectrum showed resonances at δ 3.91 and 12.07 due to the methoxy and hydroxy protons respectively.



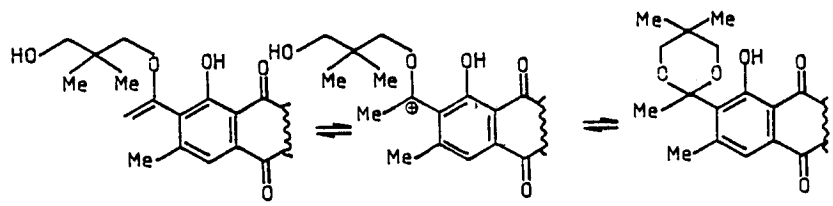
(208)



(209)

The second, minor product (9%) from this reaction was the isomeric (209) arising from vicinal substitution. Identification of the two isomers was usefully elucidated by comparison of the shifts of the H-bonded hydroxy protons in their ^{1}H n.m.r. spectra. In (208) in which the methoxy group is in conjugation with the chelated carbonyl this proton (δ 12.49) is deshielded by 0.42 ppm relative to the analogous proton in (209). This is in good agreement with isomeric differences reported previously[59,60] and referred to earlier in this Thesis (p. 87).

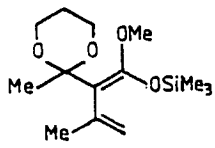
For neither isomer were conditions found for removal of the enol ether function. Therefore, while use of diene (201) successfully generated aromatic products with a substitution pattern, appropriate the target molecules (97), (99), (100) and (203) it quite unexpectedly had to be abandoned because of inability to unmask the protected keto group at the end. This is all the more ironic since the neopentylene acetal had been resorted to in the first place in recognition of the likely advantageous effect of the gem-dimethyl group on rate of formation and stability of the cyclic acetal system.[141] Arguably in the sterically compressed systems (205)-(209), the ring-opened form, the enol ether, is thermodynamically favoured; in attempted acid-catalysed hydrolysis, protonation of this form merely sets up a highly favoured internal equilibrium between ring-opened and ring-closed forms, with attack by an external nucleophile, which must arise at some stage for keto formation to occur, being excluded (Scheme 34).



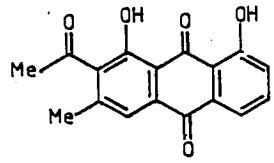
Scheme 34

For simpler systems omission of β,β-dialkyl substituents leads to striking kinetic and thermodynamic effects,[145,146] and so the possibility that the problem implicit in the stability of compounds (205)-(209) could be overcome by using diene (202) was investigated. Reaction of this diene with 3-chlorojuglone (80), like the reactions of diene (201) proceeded slowly at room temperature. However, treatment of the crude adduct from (202) with refluxing

methanolic hydrochloric acid gave the acetyl quinone (203) as the major product. Its infrared spectrum showed absorptions for the



(202)

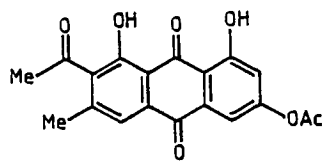


(203)

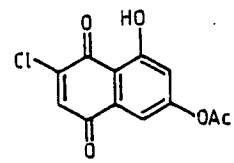
acetyl group out of planarity with the ring system and two quinonoid carbonyl groups (1703, 1673 and 1620 cm^{-1} respectively, the fact that one of the latter was evidently non-chelated served as confirmation of the orientation of the cycloaddition. In the ^{1}H n.m.r. spectrum resonances at δ 2.41 and 2.62 were assigned respectively to the aryl- and acetyl-methyl groups and singlets at δ 11.99 and 12.36 to the two chelated hydroxy protons.

Preparation of the anthraquinone (203) represents the first synthesis of the basic quinonoid chromophore of kidamycin (204). A considerably lengthier synthesis of *o*-methylkidamycinone has been reported earlier.[149]

Similar addition of the diene (202) to the acetoxy naphthoquinone (123) and treatment of the crude adduct with 1,5-diazabicyclo [5.4.0]undecene gave 2-acetylemodin acetate (210). The infrared spectrum of this compound showed carbonyl absorptions for the acetate

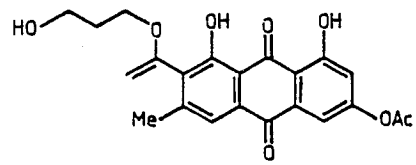


(210)



(123)

and methyl ketone groups (1777 and 1691 cm^{-1} respectively) and two quinonoid carbonyl groups (1675 and 1621 cm^{-1}) one of which again showed evidence of non chelation. The ^1H n.m.r. spectrum contained singlets for the acetate-, aryl- and acetyl-methyl groups (δ 2.36, 2.40 and 2.62) and *meta*-coupled doublets at δ 7.09 and 7.57 due to H7 and H5 respectively. A broad singlet at δ 7.69 was assigned to H4 and singlets at δ 12.06 and 12.31 were attributed to the chelated hydroxy protons.

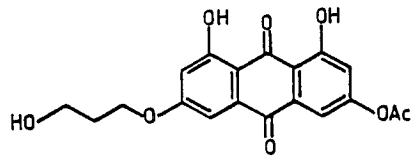


(211)

The enol ether (211) was also isolated in almost equal amount from the reaction of (202) with (123). Its mass spectrum gave a molecular ion at *m/z* 412 indicating retention of the hydroxypropyl residue. Its ^1H n.m.r. spectrum was consistent with structure, in particular vinyl resonances at δ 5.00 and 5.44, showing the presence of the enol ether. Like its counterpart (205), compound (211) resisted attempts to deprotect the carbonyl group by acid catalysis.

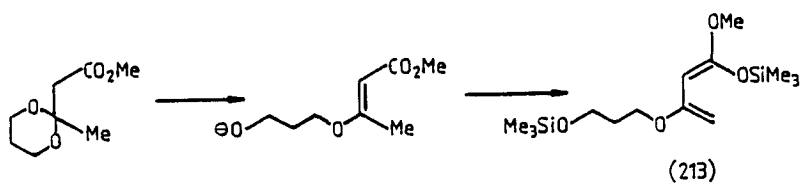
The question as to why hydrolysis of the acetal to give (203) and (210) occurred, albeit only partially is not clear. Cleavage must have occurred prior to aromatization as indicated by the stability of (211) yet in the case of (203) this cleavage was brought about under acidic conditions whilst formation of (210) was realized by base-treatment of the adduct. Although some non-aromatized adducts from reaction of dienes and quinonoid dienophiles have been observed,[105] in the present work these were not sufficiently tractable to allow for their

isolation and for deliberate hydrolysis to be examined.



(212)

On one occasion when impure diene (202) was used a third anthraquinone (212) was isolated. Four *meta*-coupled doublets in the ^{1}H n.m.r. spectrum indicated tetrasubstitution. Triplets (J 6Hz) at δ 3.89 and 4.26 and a multiplet at δ 2.10 suggested the presence of a hydroxypropyloxy group. The infrared spectrum showed one non-chelated quinonoid carbonyl band (1676 cm^{-1}). Formation of this product possibly arose from some methyl acetoacetate impurity retained after the formation of (113); this was then carried through the ketone protection step. Treatment with lithium diisopropylamide presumably then resulted in cleavage of the cyclic acetal, with further ionization to the ester dienolate and silylation giving diene (213) the precursor to (212) (Scheme 35).

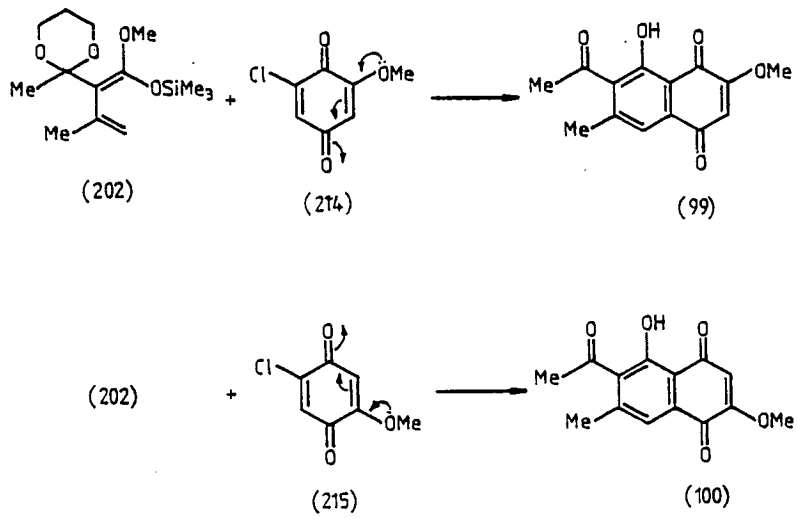


(213)

Scheme 35

While compounds (210) and (211) possess the requisite carbon-framework only (210) could be converted to (97). Base-catalysed hydrolysis of the acetoxy quinone (210) gave a quantitative yield of 2-acetylemodin (97).

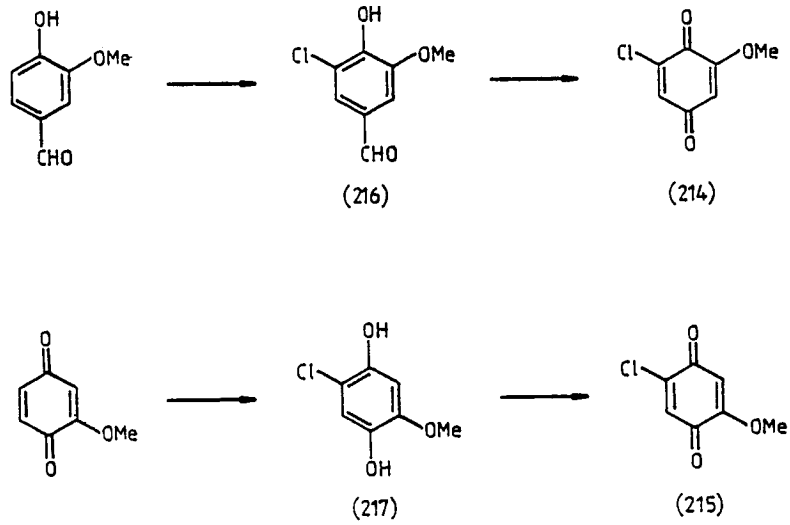
Direct synthesis of orientalone (100) and its isomer (99) were planned as outlined in Scheme 36. In each case addition of the



Scheme 36

polar diene (202) was expected to occur to the chlorinated quinonoid double bond in preference to the more electron-rich methoxy-substituted alternative. The orientation of addition was expected to parallel that of other chloro quinones already discussed. It was also anticipated that addition to (214), where the chloroenone system is essentially unimpeded by the electronic effect of the methoxy group, would be smoother than to (215) where this is not so. Both benzoquinones (214) and (215) were known[150] and were prepared according to Scheme 37.

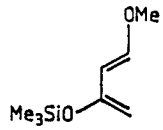
2-Chloro-6-methoxy-1,4-benzoquinone (214) was available through Dakin oxidation of 4-chlorovanillin (216).[151] The ^{1}H n.m.r. spectrum of (214) showed a methoxy resonance at δ 3.86 and two doublets at δ 5.96 and 6.93, assigned to H5 and H3 respectively, coupling to each other across the quinonoid ring (J 2Hz).[152]



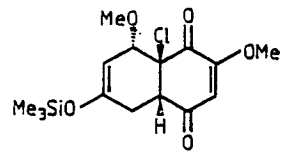
Scheme 37

The isomeric 2-chloro-5-methoxy-1,4-benzoquinone (215) could be prepared in two steps from methoxybenzoquinone. Hydrochlorination of the latter though Michael addition according to the modified method of Miller and Stewart[13] afforded the quinol (217).[150] Subsequent oxidation with silver (1) oxide gave the isomeric quinone (215) in good yield. Its ^{1}H n.m.r. spectrum contained singlet resonances at δ 3.87, 6.08 and 6.95 assigned to the methoxy group, H6 and H3 respectively.

The regiochemistry of cycloaddition of the benzoquinones (214) and (215) with the butadiene (4) was then investigated as a model study. Addition to (214) proceeded readily in refluxing benzene to yield the adduct (218). Although this was unstable, its ^{1}H n.m.r. spectrum was amenable to first order analysis. A doublet at δ 4.08 was assigned to H8β coupling to the vinyl proton H7 at δ 5.05 (J_{vic} 5Hz). The remaining signals in the ^{1}H n.m.r. spectrum were in accordance with the assigned structure. This example confirms the expected regiochemistry of the cycloaddition.

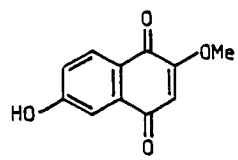


(4)



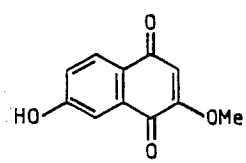
(218)

Aromatization of (218) in acidic methanol gave the known naphthoquinone (219)[153] in excellent yield. Its spectral data were in good agreement with those reported.



(219)

Addition of diene (4) to the isomeric benzoquinone (215) proceeded sluggishly in refluxing benzene. However, aromatization of the crude adduct in acidic methanol gave the naphthoquinone (220) in excellent yield. This compound was chromatographically

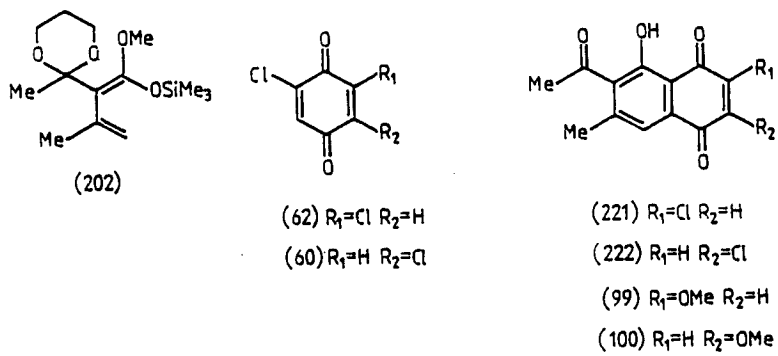


(220)

distinguishable from its isomer (219). The mass spectrum of (220) gave a molecular ion at *m/z* 204. Its ^{1}H n.m.r. spectrum showed resonances at δ 3.81 due to the methoxy group while the quinonoid proton H3 resonated as a singlet at δ 6.02. Three aromatic resonances at δ 7.14, 7.29 and 7.82 of appropriate multiplicity were assigned to

H6, H8 and H5 respectively, whilst a broad singlet at δ 10.85 was attributed to the hydroxy proton.

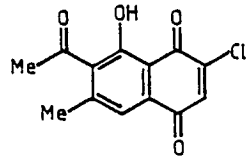
Although it has been demonstrated that the benzoquinones (214) and (215) undergo regiospecific Diels-Alder additions, the comparative slowness of addition to (215) detracts from its use for reaction with comparatively unstable diene (202). Indeed it was found that neither of the dienes (201) or (202) reacted with (215) at room temperature. To overcome this difficulty an alternative approach to the isomeric quinones (99) and (100) was explored using the more reactive dichlorobenzoquinones (60) and (62) (Scheme 38).



Scheme 38

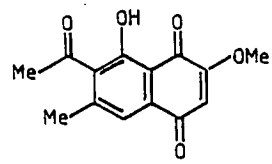
Addition of (202) to (62) proceeded readily at room temperature, treatment of the crude adduct with acidic methanol affording the chloro quinone (221). Its mass spectrum gave a molecular ion (*m/z* 266, 264) showing the characteristic monochloro isotope pattern. The presence of a small quantity of its methyl ether (*m/z* 280, 278) was also evident presumably arising from competitive elimination of trimethylsilanol from the initial adduct as described on p. 71 of this Thesis. The ^{1}H n.m.r. spectrum of purified (221) showed singlets at δ 2.38 and 2.59 due to the aryl- and acetyl-methyl groups respectively.

The aromatic protons H3 and H5 resonated at δ 7.19 and 7.49 respectively while the chelated hydroxy proton resonated as a sharp singlet at δ 11.94.



(221)

Treatment of (221)† with sodium methoxide effected predominately *ipso* displacement of the chloro-substituent. By this process a 13:1 mixture of the naphthoquinones (99) and (100) respectively were isolated in excellent overall yield. The ^{1}H n.m.r. spectrum of (99) showed resonances in accordance with the proposed structure. Singlets at δ 2.37, 2.59 and 3.92 were assigned to the aryl-, acetyl- and methoxy- methyl groups respectively. While the signals at δ 6.14, 7.48 and 12.03 were ascribed to the H3, H5 and the chelated hydroxy proton respectively.

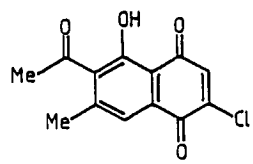


(99)

† *Preliminary experiments towards reductively removing*[154] *the quinonoid halogen of (221) to give stypandrone (98) were unsuccessful, a difficulty experienced elsewhere for a related chloro quinone.*[6] *A potentially more direct approach to (98) involving addition of diene (202) to chlorobenzoquinone was not explored, addition being expected to occur preferentially to the non-halogenated side of the quinone.*[155]

Structure (99) is the structure originally assigned to orientalone. However, the physical data for compound (99) as isolated here were different from those reported by Rangaswami for orientalone,[73] and as stated earlier (p. 60), the structure for orientalone must accordingly be revised to (100). In a preliminary communication Jung[76] has also described a synthesis of (99) different from the one reported here. But data for this product were limited and unsatisfactory and efforts are currently in progress to obtain a sample and/or spectra of this material. Jung does, however, also conclude that the published structure for orientalone is incorrect.

The minor component (100) from the reaction of (221) and sodium methoxide displayed spectral data similar to those reported by Rangaswami for orientalone.[73] However, compound (100) was more conveniently prepared from the isomeric chloro quinone (222).



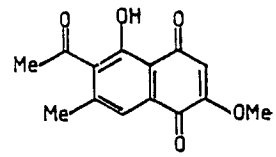
(222)

Compound (222) was obtained from addition of the butadiene (202) to 2,5-dichlorobenzoquinone (60) followed by acid-catalysed aromatization of the cycloadduct. Its mass spectrum gave a molecular ion (*m/z* 266, 264) and also showed the presence of small quantities of the corresponding methyl ether which proved difficult to remove by chromatography.

The regiochemical assignment for the two chloro products (221) and (222) was supported by chemical shifts of the resonances for

their chelated hydroxy protons. Although the difference between the shifts is small (Δ δ 0.14 ppm) it closely correlates with analogous figures for 2- and 3-chlorojuglones (79) and (80).[59] A more pronounced, but qualitatively similar, effect was observed for the methoxy quinones (99) and (100) (Δ δ 0.48) and for the correspondingly isomeric pair (208) and (209) (Δ δ 0.42), consistent with assigned structure.

Treatment of (222) with sodium methoxide efficiently gave the product now formulated as orientalone (100). Its ^{1}H n.m.r. spectrum



(100)

exhibited resonances at δ 2.35, 2.57 and 3.93 due to the acetyl-, aryl- and methoxy-methyl groups respectively. The singlets at δ 6.11 and 7.52 were ascribed to H3 and H8 respectively while the singlet at 12.51 was attributed to the chelated hydroxy proton.

The process converting (222) to (100) involved predominate *ipso* substitution as was observed for the isomeric chloro quinone (221). Whilst a direct comparison cannot be made with natural orientalone[73] as this sample and associated spectra are reported to have been lost[76] and independent enquiry has confirmed their unavailability, there is good evidence for their being identical. This evidence is detailed in the Experimental Section. It is therefore concluded that the structure of orientalone should be revised to (100) and that the work described here constitutes its synthesis for the first time.

EXPERIMENTAL

Synthesis of Emodin

1-Methoxy-3-methyl-1-trimethylsilyloxy-1,3-butadiene (109)

The butadiene (109) was prepared according to the known method[81] as a colourless liquid (57%) b.p. 30-32°/0.8 mm (lit.[81] 43°/0.1 mm) δ 0.23, s, $OSi(CH_3)_3$; 1.93, brs, CH_3; 3.57, s, OCH_3; 4.26, s, H2; 4.54, 4.78, brs, brs, $=CH_2$.

2,6-Dichloro-1,4-benzoquinone (62)

The quinone was prepared by the method of Ling[156] with modifications by Conn.[106] 2,2,4-Trichlorophenol (20 g) was added over 5 min to fuming nitric acid (200 cm^3) at 0-5°. After a further 15 min at 5° the reaction mixture was poured into ice-water (800 cm^3). After 10 min the aqueous solution was extracted with chloroform (2 x 250 cm^3). The organic phase was washed with water (2 x 250 cm^3) dried and evaporated. The residue was recrystallized to give the quinone (62) (7.0 g, 39%) as yellow needles from methanol m.p. 120-121° (lit.[156] 121°).

Addition of Diene (109) to 2,6-Dichloro-1,4-benzoquinone (62)

2,6-Dichloro-1,4-benzoquinone (62) (150 mg) was added to a solution of 1,3-bis(trimethylsilyloxy)-1-methoxy-1,3-butadiene (109)[82] (230 mg) in dry tetrahydrofuran (2 cm^3) at 0°. The reaction mixture was stirred at room temperature for 2 h, then the solvent was evaporated and the residue was dissolved in methanol (20 cm^3) and treated with aqueous hydrochloric acid (6.4M, 10 cm^3). The reaction mixture was stirred at room temperature for 2 h then it was diluted with water (50 cm^3) and extracted with ethyl acetate (3 x 50 cm^3). The combined

organic phase was washed with water (3 x 50 cm^3) dried and evaporated. Chromatography of the residue on silica containing 2% oxalic acid in toluene/ethyl acetate (3:1) gave two yellow bands. The more polar band, R_f 0.53, yielded *2-chloro-6,8-dihydroxy-1,4-naphthoquinone* (121) (151 mg, 65%) as red needles from methanol m.p. > 180° dec. (Found: C, 53.4; H, 2.3. $C_{10}H_5ClO_4$ requires C, 53.5; H, 2.2%). λ_{max} 219, 232 sh, 261, 274, 284 sh, 444 nm (4.41, 4.05, 4.07, 4.07, 3.96, 3.46). ν_{max} 3408, 1630, 1605, 1586 cm^{-1}. δ [$(CD_3)_2SO$] 6.58, d, *J* 2Hz, H7; 6.94, d, *J* 2Hz, H5; 7.38, s, H3; 11.96, brs, OH. *m/z* 226 (M[^{37}Cl], 33%), 224 (M[^{35}Cl], 100), 189 (33), 168 (21), 161 (81), 136 (21), 108 (22), 69 (38).

The minor yellow band, R_f 0.76, gave *2-chloro-6-hydroxy-8-methoxy-1,4-naphthoquinone* (122) (19 mg, 10%) as orange needles from ethyl acetate/petrol. m.p. 169-170° (Found: C, 5.55; H, 3.1. $C_{11}H_7ClO_4$ requires C, 55.4; H, 3.0%). λ_{max} (log ε) 217, 271, 282 sh, 435 nm (4.45, 4.11, 4.00, 3.61). ν_{max} 3420, 3052, 1662, 1634, 1596 cm^{-1}. δ 3.92, s, OCH_3; 6.67, d, *J* 3Hz, H7; 7.13, s, H3; 7.19, d, *J* 3Hz, H5; 11.92, s, OH. *m/z* 240 (M[^{37}Cl], 33%), 238 (M[^{35}Cl], 100), 203 (26), 175 (59).

6-Acetoxy-2-chloro-8-hydroxy-1,4-naphthoquinone (123)

The dihydroxy naphthoquinone (121) (201 mg) was suspended in acetic anhydride (6 cm^3), boron trifluoride diethyl etherate (160 mg) was added and the bright red solution was stirred at room temperature for 10 min. The reaction mixture was poured into ice-water (50 cm^3) and stirred for 30 min, then extracted with ethyl acetate (3 x 50 cm^3). The combined extract was washed with water (50 cm^3) dried and evaporated. The residue was chromatographed on silica containing 2% oxalic acid in toluene/ethyl acetate (9:1) to yield the *acetate* (123) (154 mg, 63%) as

orange needles from benzene/petrol m.p. 158-159.5° (Found: C, 53.8; H, 2.8; Cl, 13.7. $C_{12}H_7ClO_5$ requires C, 54.1; H, 2.7; Cl, 13.3%). λ_{max} (log ε) 212, 256 sh, 265, 421 nm (4.46, 3.96, 4.08, 3.61). ν_{max} 3065, 1770, 1663, 1644, 1592 cm^{-1}. δ 2.35, s, $OCOCH_3$; 7.07, d, *J* 2Hz, H7; 7.20, s, H3; 7.39, d, *J* 2Hz, H5; 11.73, s, *peri*-OH. *m/z* 268 (M[^{37}Cl], 2%), 266 (M[^{35}Cl], 7%), 226 (21), 224 (66), 43 (100).

3-Acetoxy-1,8-dihydroxy-6-methyl-9,10-anthraquinone (124)

To a solution of the acetate (123) (52 mg) in dichloromethane (4 cm^3) was added a solution of 1-methoxy-3-methyl-1-trimethylsilyloxy-1,3-butadiene (108) (54 mg) in dichloromethane (1 cm^3). The reaction mixture faded to pale yellow after stirring at room temperature for 2 h. It was then applied to a silica column and eluted sequentially with dichloromethane and then ethyl acetate at a slow flow rate. The eluant was evaporated and the residue was chromatographed on silica containing 2% oxalic acid in toluene/ethyl acetate (9:1). The major yellow band, R_f 0.64, afforded *emodin acetate* (124) (45 mg, 74%) as orange/yellow needles from benzene/petrol m.p. 183-185° (Found: C, 65.4; H, 3.9. $C_{17}H_{12}O_6$ requires C, 65.4; H, 3.9%). λ_{max} (log ε) 220, 253, 272 sh, 412 sh, 426, 437 nm (4.43, 4.29, 4.03, 3.95, 4.00, 3.97). ν_{max} 3060, 2920, 1772, 1677, 1628, 1559 cm^{-1}. δ 2.36, s, $OCOCH_3$; 2.46, s, $ArCH_3$; 7.06, d, *J* 2.5Hz, H2; 7.11, brs, H7; 7.56, d, *J* 2.5Hz, H4; 7.65, brs, H5; 11.97, 12.20, s, s, 2 x *peri*-OH. *m/z* 312 (M, 12%), 270 (100), 43 (57).

Emodin (95)

A solution of emodin acetate (124) (12 mg) in aqueous sodium hydroxide (1 M, 10 cm^3) was gently refluxed for 30 min. The purple solution was then cooled, acidified and extracted with ethyl acetate (2 x 25 cm^3). The extract was washed with water (25 cm^3), dried and evaporated. The residue was recrystallized from methanol to yield

emodin (95) (5 mg) as orange needles m.p. 254-255° (lit.[69] 255°). Chromatography of the mother liquor on silica containing 2% oxalic acid in toluene/ethyl acetate (9:1) gave a emodin (95) (3 mg, total yield 77%). The synthetic sample was indistinguishable (m.m.p., UV, IR and t.l.c.) from an authentic sample.[107]

Synthesis of Endocrocin

Dimethyl 2-(2'-propylidene)malonate (111)

Condensation of dimethyl malonate (126) (66 g) with acetone according to the method of Lenhert[110] with stirring for 48 h afforded the product (111) (38 g, 44%) b.p. 98-100°/18 mm (lit.[109] 116°/18 mm). δ 2.07, s, 2 x CH_3; 3.77, s, 2 x CO_2CH_3.

Formation of Diene (110)

The ester (111) (1.72 g) was added dropwise to a suspension of sodium hydride [(0.87 g, 80% dispersion in oil) washed with pentane (3 x 15 cm^3)] in dry 1,2-dimethoxyethane (20 cm^3) under nitrogen. The reaction mixture was refluxed for 45 min, cooled to room temperature, then chlorotrimethylsilane (1.63 g) was added and the solution was stirred for a further 2 h. The solvent was evaporated (1 mm) and the solid was filtered off and washed with carbon tetrachloride. The filtrate was concentrated and the residue was distilled to yield a colourless liquid (1.79 g) b.p. 40-43°/< 0.001 mm. The ^1H n.m.r. spectrum of the product indicated it was a mixture of *methyl(Z)-3-methoxy-2-(2'-propenyl)-3-trimethylsilyloxypropenoate* (110): δ 0.26, s, $OSi(CH_3)_3$; 1.78, brs, CH_3; 3.56, s, 2 x OCH_3; 4.69, 4.99, m, m, = CH_2; and *dimethyl 2-(2'-propenyl)malonate* (127) δ 1.89, brs, CH_3; 3.76, s, 2 x CO_2CH_3; 4.13, s, H2; 4.99, 5.10, m, m, =CH_2; in the ratio 2:1. Fractional distillation could not separate the two compounds.

Dimethyl 2-(2'-propenyl)malonate (127)

The ester (111) (0.86 g) was added dropwise to a suspension of sodium hydride [(0.23 g, 80% in oil) washed with pentane (3 x 10 cm^3)] in dry 1,2-dimethoxyethane (10 cm^3) under nitrogen. The suspension was refluxed for 1 h, cooled to room temperature, then chlorotrimethylsilane (0.81 g) was added. After 15 min methanol (0.4 cm^3) was added dropwise and the reaction mixture was stirred at room temperature for a further 1 h. The solvent was evaporated (1 mm) and the solid filtered off, and washed with diethyl ether. The filtrate was evaporated and the residue was distilled to yield *the deconjugated malonate* (127) (0.71 g, 83%) b.p. 28-30°/< 0.001 mm (Found: C, 55.8; H, 7.0. $C_8H_{12}O_4$ requires C, 56.1, H, 7.3%). ν_{max} 2978, 1740, 1649 cm^{-1}. δ 1.89, brs, CH_3; 3.76, s, 2 x CO_2CH_3; 4.13, s, H2; 4.99, 5.10, m, m, = CH_2. *m/z* 141 (M-31, 8%), 113 (100).

Addition of Diene (110) to the Acetoxy Quinone (123)

A solution of the acetate (123) (61 mg) and the crude diene (110) (252 mg) in dichloromethane (4 cm^3) was stirred at room temperature for 18 h. The solvent was evaporated and the residue was dissolved in methanol (10 cm^3) containing anhydrous sodium acetate (100 mg). The reaction mixture was then stirred at room temperature for 30 min. The orange solution was diluted with water (100 cm^3), acidified and extracted with ethyl acetate (2 x 50 cm^3). The combined organic phase was washed with water (2 x 100 cm^3), dried and evaporated. The residue was chromatographed on silica containing 2% oxalic acid in toluene/ethyl acetate (9:1) to give two major bands. The less polar band, R_f 0.48 afforded *methyl 6-acetoxy-1,8-dihydroxy-3-methyl-9,10-anthraquinone-2-carboxylate* (130) (40 mg, 47%) as yellow needles from methanol m.p. 199-200° (Found: C, 61.3; H, 4.2. $C_{19}H_{14}O_8$ requires C, 61.6; H, 3.8%).

λ_{max} (log ε) 223, 253, 278 sh, 426 nm (4.47, 4.29, 4.02, 3.99). ν_{max} 1779, 1730, 1679, 1634, 1602 cm^{-1}. δ 2.36, s, $OCOCH_3$; 2.47, s, $ArCH_3$; 4.00, s, CO_2CH_3; 7.08, d, *J* 2Hz, H7; 7.57, d, *J* 2Hz, H5; 7.69, s, H4; 12.04, 12.32, s, s, 2 x *peri*-OH. *m/z* 370 (M, 20%), 328 (20), 297 (25), 296 (100). The more polar band, R_f 0.42, gave *methyl 6-acetoxy-8-hydroxy-1-methoxy-3-methyl-9,10-anthraquinone-2-carboxylate* (131) (24 mg, 28%) as yellow microneedles from methanol m.p. 159-160° (Found: C, 62.5; H, 4.2. $C_{20}H_{16}O_8$ requires C, 62.5; H, 4.2%). λ_{max} (log ε) 214, 263, 271 sh, 369 sh, 400 nm (4.40, 4.36, 4.12, 3.70, 3.82). ν_{max} 2954, 1760, 1728, 1676, 1640, 1586 cm^{-1}. δ 2.35, s, $OCOCH_3$; 2.44, s, $ArCH_3$; 3.97, 3.99, s, s, CO_2CH_3 and OCH_3; 7.07, d, *J* 2Hz, H7; 7.52, d, *J* 2Hz, H5; 7.98, s, H4; 12.93, s, *peri*-OH. *m/z* 384 (M, 32%), 310 (41), 297 (100), 254 (29).

Hydrolysis of Anthraquinone (130)

The acetoxy ester (130) (11 mg) was dissolved in aqueous sodium hydroxide (1 M, 10 cm^3) and gently refluxed for 1 h. The purple solution was cooled, acidified with aqueous hydrochloric acid and extracted with ethyl acetate (3 x 30 cm^3). The extract was washed with water (2 x 30 cm^3), dried and evaporated. The residue was chromatographed on silica containing 2% oxalic acid in toluene/ethyl acetate (7:3) to give *endocrocin* (96) (11 mg, 100%) as an orange solid which precipitated from ethyl acetate/petrol m.p. > 300° (lit.[71] > 300°). The synthetic sample was identical in chromatographic behaviour with authentic material.[71,117] λ_{max} (log ε) 228, 260 sh, 277, 288 sh, 305 sh, 445 nm (4.26, 4.00, 4.13, 4.00, 3.76, 3.79) [lit.[70] λ_{max} (log ε) 274, 287 sh, 311 sh, 442 nm (4.32, 4.18, 3.92, 4.02)]. ν_{max} 3400, 2925, 1720, 1668, 1620 cm^{-1} (lit.[70] ν_{max} 3390, 1718, 1666, 1615 cm^{-1}). δ [$(CD_3)_2SO$] 2.40, s, $ArCH_3$; 6.62, d, *J* 2Hz, H7; 7.15, d, *J* 2Hz, H5; 7.59, s, H4; 12.02, s, OH.

Addition of Diene (110) to 2,6-Dichloro-1,4-benzoquinone (62)

2,6-Dichlorobenzoquinone (62) (406 mg) was added to a solution of the crude diene (110) (880 mg) in dichloromethane (2 cm^3) at 0^o. The reaction mixture was stirred at room temperature for 2 h then slowly eluted down a column of silica with dichloromethane. The eluant was concentrated and the residue was chromatographed on silica containing 2% oxalic acid in toluene/ethyl acetate (19:1). The major orange band, R_f 0.44, afforded *methyl 3-chloro-5-hydroxy-7-methyl-1,4-naphthoquinone-6-carboxylate* (132) (480 mg, 79%) as orange needles from ethyl acetate/petrol m.p. 163-4^o (Found: C, 55.9; H, 3.4; Cl, 12.4. $C_{13}H_9ClO_5$ requires C, 55.6; H, 3.2; Cl, 12.6%). λ_{max} (log ε) 216, 256, 279, 426 nm (4.50, 3.91, 4.04, 3.66). ν_{max} 1732, 1666, 1640, 1590 cm^{-1}. δ 2.44, s, $ArCH_3$; 3.98, s, CO_2CH_3; 7.19, s, H2; 7.49, s, H8; 11.94, s, *peri*-OH. *m/z* 280 (M, 15%), 250 (38), 249 (38), 248 (100), 185 (25).

Addition of Diene (110) to 2,5-Dichloro-1,4-benzoquinone (60)

A solution of 2,5-dichlorobenzoquinone (60) (112 mg) and the crude diene (110) (155 mg) in dichloromethane (4 cm^3) was stirred at room temperature for 17 h. The solvent was evaporated and the residue was dissolved in methanol (20 cm^3) and aqueous hydrochloric acid (3.2 M, 5 cm^3). The reaction mixture was stirred at room temperature for 2 h then diluted with water. The ethyl acetate extract (2 x 50 cm^3) was washed with water (50 cm^3) dried and evaporated. The residue was chromatographed on silica containing 2% oxalic acid in toluene/ethyl acetate (19:1). The less polar band, R_f 0.75, afforded 2,5-dichloro-benzoquinone (60) (77 mg) and the more polar band, R_f 0.43, afforded *methyl 2-chloro-5-hydroxy-7-methyl-1,4-naphthoquinone-6-carboxylate* (133) (33 mg, 60%) as orange needles from ethyl acetate/petrol m.p. 158-159^o (Found: C, 55.5; H, 3.3; Cl, 12.9. $C_{13}H_9ClO_5$ requires C, 55.6; H,

3.2; Cl, 12.6%). λ_{max} (log ε) 216, 249, 274, 421 nm (4.58, 4.03, 4.11, 3.71). ν_{max} 3050, 1718, 1686, 1656, 1592 cm^{-1}. δ 2.44, s, $ArCH_3$; 3.98, s, CO_2CH_3; 7.20, s, H3; 7.57, s, H8; 12.07, s, *peri*-OH. *m/z* 282 (M[^{37}Cl], 7%), 280 (M[^{35}Cl], 19), 250 (36), 249 (44), 248 (100).

Addition of Diene (109) to Quinone (132)

(i) To a stirred solution of the diene (109) (100 mg) in dry tetrahydrofuran (2 cm^3) at -30° was added the chloronaphthoquinone (132) (80 mg). The reaction mixture was warmed to room temperature and stirred for 2 h. The pale yellow reaction mixture was treated with tetrahydrofuran (20 cm^3) and aqueous hydrochloric acid (6.4 M, 10 cm^3) and stirred for a further 2 h at room temperature then diluted with water and extracted with ethyl acetate. The extract was concentrated and the residue was chromatographed on 2% oxalated silica in toluene/ethyl acetate (3:1). The broad orange band, R_f 0.63, was isolated and rechromatographed on 2% oxalated silica in chloroform/ethyl acetate (19:1) giving two yellow bands.

The less polar band, R_f 0.67, afforded *methyl 4-(6'-methoxycarbonyl-3'-chloro-5'-hydroxy-7'-methyl-1',4'-naphthoquinone-2'yl)-3-oxobutanoate* (135) (64 mg, 57%) as orange needles from ethyl acetate/petrol m.p. 131.5-133° (Found: C, 54.9; H, 4.1; Cl, 8.7. $C_{18}H_{15}ClO_8$ requires C, 54.8; H, 3.8; Cl, 9.0%). λ_{max} (log ε) 216, 269, 323 sh, 448 nm (4.43, 4.13, 3.42, 4.09). ν_{max} 2960, 1757, 1725, 1660, 1612, 1598 cm^{-1}. δ 2.43, s, $ArCH_3$; 3.65, s, 2 x H2; 3.79, s, CO_2CH_3; 3.98, $ArCO_2CH_3$; 4.11, s, 2 x H4; 7.50, s, H8'; 11.96, s, *peri*-OH. *m/z* 394 (M, 1%), 296 (33), 294 (22), 264 (33), 263 (23), 262 (100).

The more polar band, R_f 0.30, yielded *endocrocin methyl ester* (134) (12 mg, 13%) as orange needles from methanol m.p. 274-275° (Found:

C, 62.2; H, 4.0. $C_{17}H_{12}O_7$ requires C, 62.2; H, 3.7%). λ_{max} (log ε) 220,251, 266, 287, 439 nm (4.47, 4.30, 4.22, 4.33, 4.07). ν_{max} 3450, 1704, 1678, 1624, 1610 cm^{-1}. δ [$(CD_3)_2SO$] 2.36, s, $ArCH_3$; 3.90, s, CO_2CH_3; 6.62, d, *J* 2Hz, H7; 7.13, d, *J* 2Hz, H5; 7.57, s, H4; 11.47, 11.93, 12.47, s, s, s, 3 x OH. *m/z* 328 (M, 30%), 297 (32), 296 (100), 268 (32).

(ii) To a stirred solution of the diene (109) (120 mg) in dry tetrahydrofuran (2 cm^3) at -30° was added the chloronaphthoquinone (132) (81 mg). After 2 h at room temperature, the reaction mixture was treated with benzene (50 cm^3) containing silica (BDH 60-120 mesh, 10 g) and acetic acid (2 cm^3) and stirring was continued overnight. The silica was filtered and washed with several portions of hot ethyl acetate. The filtrate was evaporated and the residue chromatographed as in part (i) to yield the *naphthoquinonylbutanoate* (135) (43 mg, 39%) and *endocrocin methyl ester* (134) (16 mg, 17%).

(iii) The diene (109) (125 mg) and the chloronaphthoquinone (132) (80 mg) were allowed to react as in parts (i) and (ii). The pale yellow solution which resulted was diluted with tetrahydrofuran (20 cm^3) and treated with aqueous sodium carbonate (2%, 10 cm^3). The solution darkened rapidly, after 30 min at room temperature the reaction mixture was poured into water, acidified and extracted with ethyl acetate. The organic extract was washed with water, dried and evaporated. The residue was chromatographed as in part to afford *endocrocin methyl ester* (134) (8 mg, 9%) as the only tractable product.

Diethyl (E) and (Z)-3-Trimethylsilyloxypen-2-en-1,5-dioate (141)

A solution of diethyl acetone-1,3-dicarboxylate (140) (10.0 g), triethylamine (6.0 g), anhydrous zinc chloride (0.1 g) and chlorotrimethylsilane (6.5 g) in benzene (70 cm^3) was stirred under nitrogen at

45° for 45 h. The reaction mixture was cooled, dry ether was added and the suspension filtered. The filter cake was washed with several portions of dry ether. The filtrate and washings were evaporated and the residue distilled to give the *silyl enol ether* (141) (10.7 g, 79%) as a colourless liquid b.p. 109-111°/2 mm (Found: $M^{+\cdot}$ 274.1234. $C_{12}H_{22}O_5Si$ requires $M^{+\cdot}$ 274.1236). ν_{max} 2980, 1743, 1714, 1631 cm^{-1}. δ 0.26, s, $OSi(CH_3)_3$; 1.23, t, *J* 7Hz, 2 x $CO_2CH_2\underline{CH_3}$; 3,58, s, (*Z*)-CH_2; 3.79, s, (*E*)-CH_2; 4.10, 4.13, q, q, *J* 7Hz, 2 x $CO_2\underline{CH_2}CH_3$; 5.12, s, (*Z*)-CH; 5.19, s, (*E*)-CH. *m/z* 274 (M, 4%), 259 (47), 229 (33), 185 (23), 115 (43), 75 (33), 73 (70), 69 (23), 43 (38), 42 (21), 20 (100), 27 (38).

Dimethyl (E) *and* (Z)*-3-Trimethylsilyloxypent-2-en-1,5-dioate (142)*

A solution of dimethyl acetone -1,3- dicarboxylate (143) (10.0 g), triethylamine (7.0 g), zinc chloride (0.1 g) and chlorotrimethylsilane (7.5 g) in dry benzene (50 cm^3) was stirred at 60° for 45 h under nitrogen. The reaction mixture was cooled, diluted with dry ether and filtered. The filter cake was washed with several small portions of ether then the combined filtrate was evaporated and the residue was distilled to yield the *silyl enol ether* (142) (11.8 g, 83%) as a colourless liquid b.p. 86-88°/1 mm (Found: C, 48.6; H, 7.5. $C_{10}H_{18}O_5Si$ requires C, 48.8; H, 7.4%). ν_{max} 2956, 1746, 1714, 1632 cm^{-1}. δ 0.20, 0.22, s, s, (*E*) and (*Z*)-$OSi(CH_3)_3$; 3.60, 3.64, s, s, 2 x OCH_3; 3.68, s, (*Z*)-CH_2; 3.77, s, (*E*)-CH_2; 5.18, s, (*E*) and (*Z*)-H2. *m/z* 246 (M, 5%), 321 (100), 199 (27).

Ethyl-3,5-Bis(trimethylsilyoxy)-5-ethoxypenta-2,4-dienoate (139)

A solution of the silyl enol ether (141) (0.69 g) in dry tetrahydrofuran (1 cm^3) was added to a solution of lithium diisopropylamide (3 mmole) in dry tetrahydrofuran (5 cm^3) under nitrogen at -78°. After 15 min chlorotrimethylsilane (0.33 g) was added and the reaction

mixture was stirred at -78° for 10 min then at 0° for 20 min. The solvent was evaporated *in vacuo* then dry pentane was added and the suspension was quickly filtered. Evaporation of the solvent gave the *diene* (139) as a pale yellow liquid (0.76 g, 88%). Its purity was greater than 95% by ^{1}H n.m.r. spectroscopy but it could not be distilled without considerable decomposition (Found: $M^{+\cdot}$ 346.1628. $C_{15}H_{30}O_5Si_2$ requires $M^{+\cdot}$ 346.1632). δ 0.25, brs, 2 x $OSi(CH_3)_3$; 1.23, 1.31, t, t, *J* 7Hz, *J* 7Hz, 2 x $OCH_2\underline{CH_3}$; 3.76 - 4.22, m, 2 x $O\underline{CH_2}CH_3$; 4.75, brs, H4; 5.98, brs, H2.

Addition of Diene (139) to 3-Chlorojuglone (80)

To a solution of 3-chlorojuglone (80) (70 mg) in dichloromethane (3 cm^3) was added a solution of the diethyl diene (139) (150 mg) in dichloromethane (1 cm^3). After 2 h a further solution of the diene (100 mg) in dichloromethane (1 cm^3) was added and the reaction mixture was stirred overnight. The solvent was evaporated and the residue was dissolved in ethanol (15 cm^3), sodium acetate (80 mg) was added and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with water (50 cm^3), acidified and extracted with ethyl acetate (3 x 50 cm^3). The combined organic phase was washed with water (100 cm^3) dried and evaporated. The residue was chromatographed on silica containing 2% oxalic acid in toluene/ethyl acetate (9:1). The major yellow band, R_f 0.42, afforded *ethyl 3-ethoxycarbonyl-8-hydroxy-4,9-dihydro-4,9-dioxonaphtho[2,3-b]furan-2-yl acetate* (144) (33 mg, 26%) as yellow needles from ethyl acetate/petrol m.p. 187-189° (Found: C, 61.0; H, 4.4. $C_{19}H_{16}O_8$ requires C, 61.3; H, 4.3%). λ_{max} (log ε) 217 sh, 286, 412 nm (4.26, 3.77, 3.75). ν_{max} 2970, 1743, 1714, 1682, 1650, 1596 cm^{-1}. δ 1.27, 1.42, t, t, *J* 7Hz, *J* 7Hz, 2 x $CO_2CH_2\underline{CH_3}$; 4.16, s, CH_2; 4.21, q, q, *J* 7Hz, *J* 7Hz, 2 x $CO_2\underline{CH_2}CH_3$; 7.26, dd, *J* 2,8Hz,H7;

7.62, t, *J* 8Hz, H6; 7.76, dd, *J* 2, 8Hz, H5; 11.82, s, *peri*-OH. *m/z* 372 (M, 26%), 254 (48), 199 (22), 29 (100).

Addition of 1,1-Dimethoxyethene (88) to Chloro Quinone (132)

A solution of 1,1-dimethoxyethene (88) (60 mg) and the chloronaphthoquinone (132) (32 mg) in *N,N*-dimethylformamide (5 cm^3) was stirred at room temperature overnight. The reaction mixture was poured into water and extracted with ethyl acetate. The combined organic phase was washed with sat. sodium chloride, dried and evaporated. The residue was chromatographed on silica containing 2% oxalic acid in toluene/ethyl acetate (5:1). The yellow band, R_f 0.62, was recrystallized from ethyl acetate to yield *methyl 6,8-dimethoxy-1-hydroxy-3-methyl-9,10-anthraquinone-2-carboxylate* (146) (16 mg, 39%) as orange needles m.p. 254-255° (Found: C, 64.0; H, 4.5. $C_{19}H_{16}O_7$ requires C, 64.0; H, 4.5%). λ_{max} (log ε) 226, 273 sh, 283, 425, 437 sh, nm (4.10, 3.91, 3.99, 3.60, 3.59). ν_{max} 1720, 1680, 1632, 1595 cm^{-1}. δ 2.42, s, $ArCH_3$; 3.99 (6H), 4.02 (3H), s, s, 2 x $ArOCH_3$, CO_2CH_3; 6.78, d, *J* 3Hz, H7; 7.45, d, *J* 3Hz, H5; 7.58, s, H4; 13.45, s, *peri*-OH. *m/z* 356 (M, 34%), 325 (22), 324 (32), 296 (100).

Dealkylation of the Anthraquinone (146)

The foregoing anthraquinone (146) (14 mg) was added to molten anhydrous aluminium chloride (2.0 g) and sodium chloride (0.5 g) flushed with nitrogen at 160°. The purple melt was stirred for 3 min at 160° then cooled for 1 min before it was poured into a mixture of ice (100 cm^3) and conc. hydrochloric acid (10 cm^3). The aqueous solution was stirred at room temperature for 1 h, then extracted with ethyl acetate (3 x 50 cm^3). The combined organic layer was washed with water (50 cm^3) dried and evaporated. Chromatography of the residue on silica containing 2% oxalic acid in toluene/ethyl acetate (3:1) gave two yellow bands. The band

R_f 0.46, afforded *endocrocin methyl ester* (134) (7 mg, 54%) as orange needles from methanol m.p. 274-275° identical in every respect with that obtained previously. The band, R_f 0.24, yielded endocrocin (96) (4 mg, 32%) precipitated from ethyl acetate/petrol m.p. > 300°. The synthetic sample was identical to that obtained previously and indistinguishable from an authentic sample[117] in chromatographic behaviour.

Endocrocin (96)

A solution of endocrocin methyl ester (134) (3 mg) in aqueous sodium hydroxide (1 M, 3 cm^3) was refluxed for 1 h. The purple solution was acidified with aqueous hydrochloric acid, then extracted with ethyl acetate (2 x 25 cm^3). The combined organic layer was washed with water (2 x 25 cm^3) dried and evaporated. The residue was chromatographed on silica containing 2% oxalic acid in toluene/ethyl acetate (7:3) to yield endocrocin (96) as an orange solid (3 mg). This material precipitated from ethyl acetate/petrol m.p. > 300°. The synthetic sample was indistinguishable from material previously prepared.

1-Hydroxy-9,10-anthraquinone (147)[157]

m.p. 192-193° (lit.[157] 190°) δ 7.26 to 8.31, m, 7 x ArH; 12.62, s, *peri*-OH.

1-Hydroxy-5-methoxy-9,10-anthraquinone (151)[118]

m.p. 180-182° (lit.[118] 186°) δ 4.05, s, OCH_3; 7.20-8.00, m, 6 x ArH; 12.46, s, *peri*-OH.

1-Hydroxy-8-methoxy-9,10-anthraquinone (148)[118]

m.p. 204-205° (lit.[118] 197-199°) δ 4.08, s, OCH_3; 7.24-8.01, m, 6 x ArH; 12.94, s, *peri*-OH.

1,3-Dimethoxy-8-hydroxy-9,10-anthraquinone (152)[5]

m.p. 216-217° (lit.[5] 217.5-218°) δ 3.98, 4.02, s, s, 2 x OCH_3; 6.77, d, *J* 2Hz, H2; 7.26, dd, *J* 2, 8Hz, H7; 7.44, d, *J* 2Hz, H4; 7.57, t, *J* 8Hz, H6; 7.75, dd, *J* 2, 8Hz, H5; 13.13, s, *peri*-OH.

1,3-Dimethoxy-5-hydroxy-9,10-anthraquinone (153)[5]

m.p. 198-199.5° (lit.[5] 199-199.5°) δ 3.99, 4.01, s, s, 2 x OCH_3; 6.80, d, *J* 3Hz, H2; 7.21, dd, *J* 2, 8Hz, H6; 7.47, d, *J* 3Hz, H4; 7.64, t, *J* 8Hz, H7; 7.79, dd, *J* 2, 8Hz, H8; 12.40, s, *peri*-OH.

Synthesis of a Protected Acetyl Butadiene

Methyl 2-Acetyl-3-methyl-2-butenoate (113)

This compound was prepared by Knoevenagel condensation of methyl acetoacetate (114) and acetone using titanium tetrachloride and pyridine according to the method of Lenhert.[110] Repeated distillation afforded the methyl ester (113) (43%) as a colourless liquid b.p. 94-96°/16 mm (lit.[129] 98-100°/21 mm) δ 1.95, 2.11, s, s, $=C(CH_3)_2$; 2.29, s, $COCH_3$; 3.77, s, CO_2CH_3.

Ethyl 2-Acetyl-3-methyl-2-butenoate (160)

This compound was prepared as for its methyl analogue (113), as a colourless liquid (43%) b.p. 92-96°/9 mm (lit.[130] 94-96°/9 mm). δ 1.30, t, *J* 7Hz, $CO_2CH_2\underline{CH_3}$; 1.95, 2.10, s, s, $=C(CH_3)_2$; 2.29, s, $COCH_3$, 4.31, q, *J* 7Hz, $CO_2\underline{CH_2}CH_3$.

Methyl (E) *and* (Z)*-2-(2'-Propenyl)-3-trimethylsilyloxy-2-butenoate (161)*

A solution of methyl 2-acetyl-3-methyl-2-butenoate (113) (8.0 g) triethylamine (7.6 g), chlorotrimethylsilane (8.15 g) and anhydrous zinc chloride (0.2 g) in benzene (50 cm^3) was stirred at 55° for 40 h under a nitrogen atmosphere. The suspension was filtered and the filter cake was washed with several small portions of ether. The combined filtrate

was evaporated and the residue was distilled to yield a 2:1 mixture of the (*E*) and (*Z*)-*dienes* (161) (6.0 g, 38%) as a colourless liquid b.p. 84-86°/6 mm (Found: C, 57.7; H, 8.8. $C_{11}H_{20}O_3Si$ requires C, 57.9; H, 8.8%). λ_{max} (log ε) 246 nm (3.68). ν_{max} 2954, 1723, 1611 cm^{-1}. δ 0.22, 0.25, s, s, (*E*)and(*Z*)$OSi(CH_3)_3$; 1.86, brs, 2'-CH_3; 1.95, s, (*E*)-CH_3; 2.26, s, (*Z*)-CH_3; 3.69, s, CO_2CH_3; 4.75, 4.81, 5.05, 5.11, m, m, m, m, (*E*)- and (*Z*)- $=CH_2$. *m/z* 228 (M, 13%), 213 (44), 123 (23), 96 (32), 89 (28), 73 (100).

Ethyl (E) *and* (Z)*-2-(2'-Propenyl)-3-trimethylsilyloxy-2-butenoate (162)*

This compound was prepared from ethyl 2-acetyl-3-methyl-2-butenoate (160) (4.75 g) according to the procedure described for the methyl analogue. Distillation bulb-to-bulb (100°/2 mm) of the residue after evaporation afforded an 8:1 (*E*):(*Z*) mixture of the *dienes* (162) (6.3 g, 92%) as a colourless liquid. (Found: C, 59.8; H, 9.1. $C_{12}H_{22}O_3Si$ requires C, 59.5; H, 9.2%). λ_{max} (log ε) 242 nm (3.73). ν_{max} 2840, 1722, 1614 cm^{-1}. δ 0.22, 0.25, s, s, (*E*) and (*Z*)-$OSi(CH_3)_3$; 1.27, t, *J* 8Hz, $CO_2CH_2\underline{CH_3}$; 1.86, m, 2'-CH_3; 1.94, s, (*E*)-CH_3; 2.24, s, (*Z*)-CH_3; 4.17, q, *J* 8Hz, $CO_2\underline{CH_2}CH_3$; 4.81, 5.09, m, m, $=CH_2$. *m/z* 242 (M, 9%), 213 (30), 96 (33), 73 (100).

Methyl 3-Chloro-5,7-dimethyl-1,4-naphthoquinone-6-carboxylate (163)

A solution of 2,6-dichlorobenzoquinone (62) (97 mg) and the diene (161) (275 mg) in dry toluene (10 cm^3) was heated at reflux under a nitrogen atmosphere for 16 h. The reaction mixture was evaporated and the residue slowly eluted down a column of silica using chloroform then ethyl acetate. The eluant was evaporated and the residue was chromatographed on silica using toluene/ethyl acetate (9:1). The yellow band, R_f 0.51, afforded the *product* (163) (131 mg, 86%) as pale yellow needles from ethyl acetate/petrol m.p. 133.5-134° (Found: C, 60.7;

H, 4.1; Cl, 12.4. $C_{14}H_{11}ClO_4$ requires C, 60.3; H, 4.0; Cl, 12.7%). λ_{max} (log ε) 255, 265 sh, 345 nm (4.11, 4.02, 3.38). ν_{max} 2956, 1738, 1681, 1660, 1605, 1583 cm^{-1}. δ 2.41, s, 7-CH_3; 2.66, s, 5-CH_3; 3.98, s, CO_2CH_3; 7.18, s, H2; 7.87, s, H8. *m/z* 280 (M[^{37}Cl], 36%), 278 (M[^{35}Cl], 100), 263 (26), 248 (25), 247 (52), 246 (56), 220 (25), 218 (69), 127 (21), 77 (20).

Methyl 1,3-Dimethyl-8-hydroxy-9,10-anthraquinone-2-carboxylate (164)

A solution of 2-chloro-8-hydroxy-1,4-naphthoquinone (80) (40 mg) and the diene (161) (163 mg) in dry toluene (6 cm^3) was boiled under a nitrogen atmosphere for 60 h. The solvent was evaporated and the residue was dissolved in methanol (20 cm^3) containing sodium acetate (60 mg). The reaction mixture was stirred at room temperature for 1 h, diluted with water (50 cm^3), acidified and extracted with ethyl acetate (3 x 50 cm^3). The combined organic phase was washed with water (50 cm^3), dried and evaporated. The residue was chromatographed on silica containing 2% oxalic acid in toluene/ethyl acetate (9:1). The single yellow band, R_f 0.53, afforded the *product* (164) (72 mg, 98%) as large orange-yellow needles from ethyl acetate/petrol m.p. 159-160° (Found: C, 70.0; H, 4.4. $C_{18}H_{14}O_5$ requires C, 69.7; H, 4.6%). λ_{max} (log ε) 254, 271 sh, 361 sh, 402 nm (4.58, 4.18, 3.64, 3.84). ν_{max} 2923, 1723, 1670, 1639, 1584 cm^{-1}. δ 2.44, s, 3-CH_3; 2.76, s, 1-CH_3; 4.00, s, CO_2CH_3; 7.30, dd, *J* 2, 8Hz, H7; 7.63, t, *J* 8Hz, H6; 7.79, dd, *J* 2, 8Hz, H5; 8.08, s, H4; 12.78, s, *peri*-OH. *m/z* 310 (M, 94%), 296 (20), 295 (100), 279 (25), 250 (66).

(Z)-1,3-Bistrimethylsilyloxy-1-methoxy-2-(2'-propenyl)-1,3-butadiene (165)

To a stirred solution of lithium diisopropylamide (3 mmole) in dry tetrahydrofuran (5 cm^3) at -78° under a nitrogen atmosphere was added a solution of the diene (161) (0.62 g) in dry tetrahydrofuran (1 cm^3).

The reaction mixture was stirred at -78° for 15 min. Chlorotrimethylsilane (0.33 g) was added slowly and the reaction was allowed to warm to 0° over 30 min. The solvent was removed *in vacuo* (5 mm) and the residue was dissolved in dry pentane (10 cm^3) and filtered. The filtrate was evaporated to yield the *triene* (165) (0.73 g, 97%) as a pale yellow oil (Found: $M^{+\cdot}$ 300.1578. $C_{14}H_{28}O_3Si_2$ requires $M^{+\cdot}$ 300.1577). The product was thermally labile but of greater than 95% purity as determined by ^1H n.m.r. spectroscopy. δ 0.19, 0.25, s, s, 2 x $OSi(CH_3)_3$; 1.88, brs, CH_3; 3.56, s, OCH_3; 3.63, 4.90, m, m, 2 x $=CH_2$. *m/z* 300 (M, 5%), 285 (100), 123 (60).

(Z)-1,3-Bistrimethylsilyloxy-1-ethoxy-2-(2'-propenyl)-1,3-butadiene (166)

This compound was prepared from the diene (162) (0.61 g) according to the procedure described for the methyl analogue (165) to yield the *triene* (166) (0.69 g, 88%) as a pale yellow oil. An analytical sample had b.p. 44-45°/< 0.001 mm with careful distillation. (Found: C, 57.8; H, 9.7. $C_{15}H_{30}O_3Si_2$ requires C, 57.3; H, 9.6%). λ_{max} (log ε) (cyclohexane) 244 nm (3.93). δ 0.18, 0.24, s, s, 2 x $OSi(CH_3)_3$; 1.22, t, *J* 7Hz, $OCH_2\underline{CH_3}$; 1.88, brs, CH_3; 3.85, q, *J* 7Hz, $O\underline{CH_2}CH_3$; 4.28, 4.86, m, m, 2 x $=CH_2$. *m/z* 314 (M, 5%), 286 (25), 285 (100), 195 (26), 147 (75), 123 (24), 75 (23).

2-(2'-Propenyl)-1,3,8-trihydroxy-9,10-anthraquinone (167)

A solution of the triene (165) (172 mg) and 2-chloro-8-hydroxy-1,4-naphthoquinone (80) (100 mg) in dichloromethane (11 cm^3) was stirred at room temperature under a nitrogen atmosphere overnight. The reaction mixture was cooled to -22° and treated with a solution of 1,5-diazabicyclo[5.4.0]undecene (88 mg) in dichloromethane (1 cm^3). The reaction mixture was warmed to room temperature and stirred for 1 h, acidified with aqueous hydrochloric acid and extracted with ethyl acetate (3 x 50 cm^3).

The combined organic phase was washed with water (100 cm^3), dried and evaporated. The residue was chromatographed on silica containing 2% oxalic acid in toluene/ethyl acetate (9:1). The major yellow band, R_f 0.38, afforded the *anthraquinone* (167) (19 mg, 13%) as orange needles from ethyl acetate/petrol m.p. 217-222° dec. (Found: C, 68.9; H, 3.8. $C_{17}H_{12}O_5$ requires C, 68.9; H, 4.1%). λ_{max} (log ε) 248, 284, 343 sh, 420 sh, 438, 449 nm (4.16, 4.30, 3.35, 3.91, 3.99, 3.96). ν_{max} 3385, 1668, 1616, 1579 cm^{-1}. δ 2.16, brs, CH_3; 5.21, 5.64, brs, brs, $=CH_2$; 6.47, brs, D_2O-exchangeable, 3-OH; 7.28, dd, *J* 1.5, 8Hz; 7.45, s, H4; 7.64, t, *J* 8Hz, H6; 7.82, dd, *J* 1.5, 8Hz, H5; 12.15, 12.65, s, s, 2 x-OH. *m/z* 296 (M, 76%), 295 (29), 281 (100), 264 (25), 249 (51), 43 (22).

3,8-Dihydroxy-1-ethoxy-2-(2'-propenyl)-9,10-anthraquinone (168)

A solution of the triene (166) (510 mg) and 2-chloro-8-hydroxy-1,4-naphthoquinone (80) (141 mg) in dry tetrahydrofuran (8 cm^3) was stirred at room temperature under a nitrogen atmosphere overnight. 1,5-Diazabicyclo[5.4.0]undecene (0.5 g) was added and the reaction mixture was stirred for 30 min, acidified with aqueous hydrochloric acid and extracted with ethyl acetate (3 x 50 cm^3). The combined organic phase was washed with water (100 cm^3), dried and evaporated. The residue was chromatographed on silica containing 2% oxalic acid in toluene/ethyl acetate (9:1). The major yellow band, R_f 0.50, was rechromatographed in chloroform to yield the only tractable band, R_f 0.35. This yellow band afforded the *anthraquinone* (168) (11 mg, 5%) as orange needles from dichloromethane/petrol m.p. 187.5-188° (Found: C, 70.5; H, 5.0. $C_{19}H_{16}O_5$ requires C, 70.4; H, 5.0%). λ_{max} (log ε) 218, 247 sh, 283, 397 sh, 413, 425 sh nm (4.46, 4.02, 4.41, 3.80, 3.83, 3.79). ν_{max} 3395, 2993, 1662, 1631, 1578, 1563 cm^{-1}. δ 1.49, t, *J* 7Hz, $OCH_2\underline{CH_3}$; 2.18, brs, 2'-CH_3; 4.07, q, *J* 7Hz, $O\underline{CH_2}CH_3$; 5.19, 5.64, brs, brs, C $=CH_2$; 6.40, brs, 3-OH;

7.28, dd, *J* 1.5, 8Hz, H7; 7.60, t, *J* 8Hz, H6; 7.70, s, H4; 7.77, dd, *J* 1.5, 8Hz, H5; 13.1, s, 8-OH. *m/z* 324 (M, 4%), 295 (16), 29 (100), 27 (47).

Ethyl (E)*-2-(2'-Propenyl)-4-trimethylsilyl-3-trimethylsilyloxy-2-butenoate (169)*

The triene (166) (0.82 g) was heated at 160° under reduced pressure (0.02 mm) for 30 min. After cooling to room temperature, the residue was distilled to yield the *rearranged diene* (169) (0.58 g, 71%) as a colourless liquid b.p. 49-50°/0.02 mm (Found: C, 57.2; H, 9.5. $C_{15}H_{30}O_3Si_2$ requires C, 57.3; H, 9.6%). λ_{max} (log ε) 244 nm (3.93). ν_{max} 2960, 1700, 1644, 1587 cm^{-1}. δ 0.06, s, 4-$Si(CH_3)_3$; 0.19, s, $OSi(CH_3)_3$; 1.24, t, *J* 7Hz, $CO_2CH_2\underline{CH_3}$; 1.84, brs, CH_3; 2.41, s, CH_2; 4.13, q, *J* 7Hz, $CO_2\underline{CH_2}CH_3$; 4.72, 5.03, m, m, $=CH_2$.

Addition of Cyanotrimethylsilane to Methyl Acetoacetate (114)

A stirred suspension of aluminium chloride (0.01 g) in methyl acetoacetate (159) (1.74 g) and cyanotrimethylsilane (1.68 g) was heated at 60° under a nitrogen atmosphere for 40 h. The crude reaction mixture consisted of a 1:1 mixture of methyl 3-cyano-3-trimethylsilyoxy-butanoate (170) [ν_{max} 2790, 1748 cm^{-1}. δ 0.25, s, $OSi(CH_3)_3$; 1.72, s, CH_3; 2.79, s, CH_2; 3.75, s, CO_2CH_3] and the enol ether (115). Distillation of the reaction mixture gave methyl (E) and (Z)-3-trimethylsilyloxy-2-butenoate (115) (1.61 g, 57%) as a colourless liquid b.p. 72-76°/6 mm (lit.[96] 65-67°/7 mm) whose ^1H n.m.r. spectrum was in agreement with those of an authentic sample.[97]

Formation of Cyclic Diene (172)

To a solution of dichlorodimethylsilane (3.20 g) in dichloromethane (10 cm^3) at -40° under a nitrogen atmosphere was added pentane-2,4-dione (0.51 g) dropwise. Triethylamine (2.53 g) was added dropwise

and the reaction mixture was stirred at room temperature for 1 h. The solvent was evaporated then the residue was diluted with ether and filtered. The filtrate was evaporated to yield the diene (172). The product was unstable and could not be further purified. Its purity was greater than 90% by ^{1}H n.m.r. spectroscopy. δ (60 MHz) 0.37, s, $Si(CH_3)_2$; 1.86, brs, CH_3; 3.93, 4.10, s, s, $=CH_2$; 5.11, brs, H4.

Reaction of the Acetoacetate (160) with Dichlorodimethylsilane

To a solution of lithium diisopropylamide (3 mmole) in dry tetrahydrofuran (5 cm^3) at -78° under a nitrogen atmosphere was added ethyl 2-acetyl-3-methyl-2-butenoate (160) (0.42 g). The reaction mixture was stirred at -78° for 30 min then dichlorodimethylsilane (0.38 g) was added dropwise and the solution was allowed to warm to 0° over 1 h. The reaction mixture was added dropwise to a stirred solution of lithium diisopropylamide (3 mmole) in dry tetrahydrofuran (5 cm^3) at -78° and stirred for a further 30 min then allowed to warm to 0° over 1 h. The solvent was evaporated *in vacuo* and the residue diluted with dry pentane and filtered. The filtrate was evaporated to the product (173) or oligomers thereof (0.55 g, 97%) a yellow viscous oil. δ (60 MHz) 0.26, brs, $Si(CH_3)_2$; 1.17, m, $OCH_2\underline{CH_3}$; 1.86, brs, CH_3; 4.14, m, $O\underline{CH_2}CH_3$; 4.51-5.17, m, m, m, 4 x vinyl-H.

2,2,6-Trimethyl-1,3-dioxol-5-en-4-one (174)

This compound was prepared according to the procedure of Carroll and Bader,[136] from diketene and acetone as a colourless liquid (174) b.p. 65-67°/2 mm (lit.[136] 65-67°/2 mm) λ_{max} (log ε) 237 nm (3.99). ν_{max} 1736, 1644 cm^{-1}. δ 1.69, s, 2 x 2-CH_3; 1.99, d, *J* 1Hz, 6-CH_3; 5.24, d, *J* 1Hz, H5. *m/z* 142 (M, 10%), 85 (40), 84 (24), 69 (27), 43 (100).

Formation of Cyclic Diene (175)

To a stirred solution of lithium diisopropylamide (6 mmole) at -78° under a nitrogen atmosphere was added 2,2,6-trimethyl-1,3-dioxol-5-en-4-one (174) (0.71 g) dropwise. The reaction mixture was stirred at -78° for 30 min, then chlorotrimethylsilane (0.66 g) was added dropwise and the reaction mixture was allowed to warm to 0° over 30 min. The solvent was evaporated *in vacuo* (5 mm) and the residue was diluted with dry pentane and filtered. The filtrate was evaporated to give the cyclic diene (175) (0.89 g, 95%) as a dark liquid. Its ^1H n.m.r. spectrum was consistent with greater than 90% purity. δ (60 MHz) 0.24, s, $OSi(CH_3)_3$; 1.52, s, 2 x CH_3, 3.93, 4.03, brs, brs, $=CH_2$; 4.60, s, H5.

4-Isopropylidene-5-isoxazalone (178)

This compound was prepared according to the method of Schiff[138] by condensation of ethyl acetoacetate oxime and acetone as colourless needles (178) (59%) from methanol m.p. 121-122° (lit.[138] 120-121°). λ_{max} (log ε) 222, 281 nm (3.37, 3.20). ν_{max} 1750, 1640 cm^{-1}. δ 2.37, s, 2 x CH_3; 2.56, s, CH_3. *m/z* 139 (M, 100%), 124 (33), 94 (21).

1,4-Enolization and Silylation of the Isoxazalone (178)

To a stirred solution of lithium diisopropylamide (6 mmole) in dry tetrahydrofuran (10 cm^3) under a nitrogen atmosphere at -78° was added a solution of the isoxazalone (178) (0.7 g) in dry tetrahydrofuran (10 cm^3). The reaction mixture was stirred at -78° for 15 min, then chlorotrimethylsilane (0.65 g) was added dropwise and the reaction mixture was allowed to warm to 0° over 30 min. The solvent was evaporated *in vacuo* then diluted with dry pentane and filtered under a nitrogen atmosphere. The filtrate was evaporated to leave the product (177) as a yellow viscous oil (0.83 g, 79%). The compound was unstable;

however, its ^{1}H n.m.r. spectrum indicated its purity was greater than 90%. δ (60 MHz) 0.33, s, $Si(CH_3)_3$; 1.97, s, 2 x vinyl-CH_3; 2.20, s, 3-CH_3; 4.90, m, $=CH_2$.

Methyl 3-Methyl-2-(2'-propyl)-3-butenoate (182)

Methyl 3-methyl-2-butenoate (117) (2.85 g) was added slowly to a stirred solution of lithium diisopropylamide (30 mmole) in dry tetrahydrofuran (50 cm^3) under nitrogen at -78°. Hexamethylphosphoramide (10 cm^3) was added after 15 min and the resulting yellow solution was stirred for 10 min at -78°. 2-Bromopropane (3.68 g) was added dropwise and the reaction mixture was stirred at -78° for 30 min. The reaction mixture was warmed to room temperature and diluted with aqueous sat. ammonium chloride (50 cm^3). The ether extract (3 x 50 cm^3) was washed with aqueous hydrochloric acid (2 x 50 cm^3, 1.6 M) and water (50 cm^3) then dried and evaporated. The residue was distilled bulb-to-bulb to yield the *product* (182) (2.78 g, 71%) as a colourless liquid. An analytical sample had b.p. 52-54°/10 mm. (Found: C, 69.1; H, 10.6. $C_9H_{16}O_2$ requires C, 69.2; H, 10.3%). ν_{max} 2960, 1739, 1643 cm^{-1}. δ 0.85, 0.91, d, d, *J* 8Hz, $CH(\underline{CH_3})_2$; 1.75, t, *J* 1Hz, 3-CH_3; 1.87 - 2.31, m, H2'; 2.68, d, *J* 11Hz, H2; 3.67, s, CO_2CH_3; 4.90, q, *J* 1Hz, $=CH_2$.

Methyl 3-Bromomethyl-2-(2'-propyl)-3-butenoate (184)

A suspension of *N*-bromosuccinimide (1.58 g) and the foregoing ester (182) (0.97 g) in carbon tetrachloride (10 cm^3) was irradiated for 5 h with a tungsten lamp (40 w). The reaction mixture was filtered and the filtrate evaporated. Bulb-to-bulb distillation of the residue gave the *γ-bromo ester* (184) (1.3 g, 89%) as a colourless liquid. An analytical sample had b.p. 72-74°/0.8 mm (Found: C, 46.0; H, 6.3. $C_9H_{15}BrO_2$ requires C, 46.0; H, 6.4%). ν_{max} 2967, 1739 cm^{-1}. δ 0.93, 0.97, d, d, *J* 7Hz, $CH(\underline{CH_3})_2$; 1.9 - 2.4, m, $\underline{CH}(CH_3)_2$; 2.96, d, *J* 8Hz, H2;

3.69, s, CO_2CH_3; 4.01, brs, CH_2Br; 5.31, 5.44, brs, brs, $C=CH_2$. *m/z* 155 (M-Br, 100%), 95 (29).

Methyl 2-Hydroxy-3-methyl-2-(2'-propyl)butanoate (186)

2-Bromopropane (11.5 g) in dry ether (20 cm^3) was added slowly to a suspension of magnesium (2.3 g) in ether (50 cm^3) under a nitrogen atmosphere. The reaction mixture was heated until all the magnesium had been consumed. The ethereal solution was added dropwise to a solution of dimethyl oxalate (5.0 g) in ether (100 cm^3) under nitrogen at 0^o. The resulting reaction mixture was stirred at 0^o for 1 h then at room temperature for 3 h. Aqueous sat. ammonium chloride (500 cm^3) and ether (200 cm^3) were then added. The separated organic phase was washed with water (2 x 100 cm^3), dried and evaporated. Bulb-to-bulb distillation gave the crude *alcohol* (186) (3.0 g, 40%). An analytical sample had b.p. $68-70^o$/10 mm (Found: $M^{+\cdot}$ 174.1250. $C_9H_{18}O_3$ requires $M^{+\cdot}$ 174.1259). ν_{max} 3530, 2962, 1730 cm^{-1}. δ 0.90, d, *J* 7Hz, 2 x $CH(\underline{CH_3})_2$; 2.08, septet, *J* 7Hz, 2 x $\underline{CH}(CH_3)_2$; 3.23, brs, D_2O-exchangeable, OH; 3.79, s, CO_2CH_3. *m/z* 174 (M, 1%), 131 (100), 115 (100), 103 (33), 99 (62), 85 (29), 73 (100), 71 (100).

Methyl 3-Methyl-2-(2'-Methyl-1',3'-dioxalan-2'-yl)-2-butenoate (187)

A solution of the methyl ester (113) (5.4 g), trimethyl orthoformate (18.4 g), ethylene glycol (10.7 g) and *p*-toluenesulphonic acid (0.05 g) in benzene (30 cm^3) was stirred at room temperature for 4 days. The reaction mixture was diluted with ether (150 cm^3) and washed with water (100 cm^3), aqueous sat. sodium bicarbonate (2 x 100 cm^3) and finally with water (100 cm^3). The organic phase was dried and evaporated. The residue was distilled bulb-to-bulb to yield the *acetal* (187) (5.4 g, 77%). An analytical sample had b.p. $65-66^o$/1.5 mm (Found: C, 60.2; H, 7.9. $C_{10}H_{16}O_4$ requires C, 60.0; H, 8.1%). ν_{max} 2960, 1730,

1664 cm^{-1}. δ 1.66, 1.70, 1.89, s, s, s, 3 x CH_3; 3.74, s, CO_2CH_3; 3.90, brs, 2 x CH_2. *m/z* (10 eV) 185 (M-15, 28%), 87 (100), 43 (20).

Formation of Ethylene Acetal (188)

The ethyl ester (160) (4.3 g) was reacted with ethylene glycol as for the methyl ester (113). Distillation afforded the *acetal* (188) (3.2 g, 58%) b.p. 96-98°/6 mm (Found: C, 61.2; H, 8.2. $C_{11}H_{18}O_4$ requires C, 61.6; H, 8.5%). ν_{max} 2990, 1743, 1658 cm^{-1}. δ 1.30, t, *J* 7Hz, $CO_2CH_2\underline{CH_3}$; 1.67, 1.71, 1.88, s, s, s, 3 x CH_3; 3.91, brs, 2 x CH_2; 4.22, q, *J* 7Hz, $CO_2\underline{CH_2}CH_3$.

Formation of Neopentylene Acetal (189)

A solution of methyl acetoacetate (113) (8.9 g), 2, 2-dimethylpropane-1,3-diol (8.62 g) and *p*-toluenesulphonic acid (0.2 g) in benzene (50 cm^3) was refluxed for 2 h with azeotropic removal of water. The reaction mixture was diluted with ether (150 cm^3) and washed successively with aqueous sodium hydroxide (2 x 100 cm^3, 5%) and water (100 cm^3), then dried and evaporated. The residue was distilled to afford the *acetal* (189) (10.7 g, 77%) as a colourless liquid b.p. 72-73°/1.5 mm. (Found: C, 59.7; H, 9.4. $C_{10}H_{18}O_4$ requires C, 59.4; H, 9.0%). ν_{max} 2957, 2870, 1744 cm^{-1}. δ 0.97, brs, $C(CH_3)_2$; 1.54, s, CH_3; 2.80, s, CH_2; 3.45, s, CO_2CH_3; 3.70, s, 2 x O-CH_2. *m/z* 203 (M+1, 17%), 187 (22), 129 (93), 117 (56), 69 (48), 56 (36), 43 (100).

Enolization of Acetal (189)

To a solution of lithium diisopropylamide (6 mmole) in dry tetrahydrofuran (10 cm^3) at -78° under a nitrogen atmosphere was added a solution of the acetal (189) (1.01 g) in dry tetrahydrofuran (5 cm^3). After stirring at -78° for 30 min, chlorotrimethylsilane (0.65 g) was added dropwise and the reaction mixture was allowed to warm to 0° over 30 min. The solvent was evaporated and the residue was distilled bulb-

to-bulb to yield the *product* (195) (0.56, 41%) as a colourless liquid. An analytical sample had b.p. 68-70°/0.2 mm. (Found: C, 57.2; H, 9.3. $C_{13}H_{26}O_4Si$ requires C, 56.9; H, 9.6%). λ_{max} (log ε) 235 nm (4.05). ν_{max} 2958, 1720, 1636 cm^{-1}. δ 0.07, s, $OSi(CH_3)_3$; 0.90, s, 2 x 2'-CH_3; 2.29, brs, 4-CH_3; 3.34, 3.48, s, s, 2 x CH_2; 3.67, s, CO_2CH_3; 5.03, brs, H2. *m/z* (12 eV) 274 (M, 25), 158 (100).

Methyl 3-Methyl-2-(2',5',5'-trimethyl-1',3'-dioxan-2'-yl)-2-butenoate (190)

A solution of methyl 2-acetyl-3-methyl-2-butenoate (113) (11.9 g) (11.9 g) and 2,2-dimethylpropane-1,3-diol(11.9 g) in benzene (120 cm^3) containing *p*-toluenesulphonic acid (0.12 g) was refluxed with azeotropic removal of water for 24 h. The reaction mixture was then diluted with ether (250 cm^3). The organic phase was washed with aqueous sodium hydroxide (2 x 100 cm^3, 2 M) and with water (2 x 100 cm^3), then dried and evaporated. Distillation of the residue afforded the *acetal* (190) (13.7 g, 77%) as a colourless liquid b.p. 90-92°/2 mm. (Found: C, 64.7; H, 9.0. $C_{13}H_{22}O_4$ requires C, 64.4; H, 9.2%). ν_{max} 2950, 1730, 1650 cm^{-1}. δ 0.72, 1.17, s, s, 2 x 5'-CH_3; 1.62, 1.76, 1.87, s, s, s, 2'-CH_3, 3-CH_3, 4-CH_3; 3.23, 3.69, m, m, 2 x CH_2; 3.74, s, CO_2CH_3. *m/z* (12 eV) 227 (M-15, 47), 129 (100).

Formation of Acetal Diene (201)

To a solution of lithium diisopropylamide (3 mmole) in dry tetrahydrofuran (5 cm^3) at -78° under a nitrogen atmosphere was added slowly a solution of the acetal (190) (0.6 g) in dry tetrahydrofuran (1 cm^3). The reaction mixture was stirred for 10 min then chlorotrimethylsilane (0.33 g) was added slowly. The reaction mixture was warmed to 0° over 30 min and the solvent was removed *in vacuo* (5 mm). Dry pentane (15 cm^3) was added, the suspension was quickly filtered and the filter cake was washed with dry pentane (5 cm^3). The filtrate was

evaporated to yield the *diene* (201) (0.66 g, 84%) as a pale yellow oil. The ^{1}H n.m.r. spectrum of freshly prepared material was consistent with greater than 80% purity, the compound decomposes on standing at room temperature and was used without further purification. (Found: $M^{+\cdot}$ 314.1908. $C_{16}H_{30}O_4Si$ requires $M^{+\cdot}$ 314.1909). δ 0.21, s, $OSi(CH_3)_3$; 0.68, 1.17, s, s, $C(CH_3)_2$; 1.60, s, 2'-CH_3; 1.93, brs, 3-CH_3; 3.20-3.74, m, 2 x CH_2; 3.55, s, OCH_3; 4.90, 5.08, m, m, $=CH_2$. *m/z* 314 (M, 9%), 227 (29), 159 (32), 129 (100), 123 (26).

Methyl 3-Methyl-2-(2'-methyl-1',3'-dioxan-2'-yl)-2-butenoate (191)

A solution of the methyl ester (161) (11.9 g), propane-1,3-diol (11.6 g) and *p*-toluenesulphonic acid (0.2 g) in benzene (100 cm^3) was refluxed with azeotropic removal of water for 90 h. Ether (250 cm^3) was added and the organic phase was washed with sat. sodium bicarbonate (2 x 100 cm^3) and sat. sodium chloride (100 cm^3), then dried and evaporated. The residue was distilled to yield the *acetal* (191) (9.7 g, 60%) as a colourless liquid b.p. 100-102°/4 mm. (Found: C, 61.8; H, 8.7. $C_{11}H_{18}O_4$ requires C, 61.7; H, 8.5%). ν_{max} 2945, 1726, 1649 cm^{-1}. δ 1.57, s, 2'-CH_3; 1.77, 1.87, s, s, $=C(CH_3)_2$; 1.79-2.28, m, 5'-CH_2; 3.65 - 4.13, m, 4'-CH_2, 6'-CH_2; 3.75, s, CO_2CH_3. *m/z* (10 eV) 214 (M, 0.5%), 199 (78), 101 (100), 100 (50).

Formation of Acetal Diene (202)

This compound was prepared from (191) (0.53 g) accordiing to the procedure described for the neopentylene analogue (201) to yield the *diene* (202) (0.70 g, 98%) as a pale yellow oil. Its ^{1}H n.m.r. spectrum was consistent with > 85% purity and the material was used without further purification. (Found: $M^{+\cdot}$ 286.1594. $C_{14}H_{26}O_4Si$ requires $M^{+\cdot}$ 286.1600). δ 0.21, s, $OSi(CH_3)_3$; 1.56, s, 2'-CH_3, 1.79-2.06, m, 5'-CH_2; 1.94, brs, 3-CH_3; 3.56, s, OCH_3; 3.59-4.20, m,

4'-CH_2, 6'-CH_2.

Synthesis of 2-Acetylemodin and Related Quinones

Addition of Diene (201) to 2-Chloro-8-hydroxy-1,4-naphthoquinone (80)

A solution of 2-chloro-8-hydroxy-1,4-naphthoquinone (80) (60 mg) and diene (201) (181 mg) in dry tetrahydrofuran (3 cm^3) was stirred at room temperature under a nitrogen atmosphere for 3 h. A further portion of the diene (201) (100 mg) was then added and the reaction mixture was stirred overnight. The solvent was evaporated and the residue was dissolved in methanol (10 cm^3) and treated with aqueous hydrochloric acid (6.4 M, 5 cm^3). The reaction mixture was stirred at room temperature for 2 h then diluted with water (50 cm^3) and extracted with ethyl acetate (3 x 50 cm^3). The combined organic phase was washed with water (100 cm^3), dried and evaporated. The residue was chromatographed on silica containing 2% oxalic acid in toluene/ethyl acetate (3:1). The band, R_f 0.74, gave unreacted 2-chloro-8-hydroxy-1,4-naphthoquinone (80) (38 mg). The more polar band, R_f 0.24, afforded *1,8-dihydroxy-2-[1'-(2",2"-dimethyl-3"-hydroxypropyloxy)ethenyl]-3-methyl-9,10-anthraquinone* (205) (23 mg, 57%) as orange plates from methanol m.p. 211.5-215° dec. (Found: C, 69.3; H, 5.9. $C_{22}H_{22}O_6$ requires C, 69.1; H, 5.8%). λ_{max} (log ε) 215, 247, 277, 411 sh, 437, 449 sh nm (4.43, 4.12, 4.36, 3.97, 4.04, 4.01). ν_{max} 3480, 2950, 1671, 1624, 1592 cm^{-1}. δ 1.05, s, $C(CH_3)_2$; 1.90, brt, *J* 5Hz, 3"-OH; 2.08, s, $ArCH_3$; 3.55, brd, *J* 5Hz, 2 x H3"; 3.99, s, 2 x H1"; 4.98, 5.45, m, m, $=CH_2$; 7.28, dd, *J* 1.5, 8Hz, H7; 7.41, s, H4; 7.64, t, *J* 8Hz, H6; 7.83, dd, *J* 1.5, 8Hz, H5; 12.17, 12.37, s, s, 2 x *peri*-OH. *m/z* 382 (M, 68%), 309 (28), 296 (41), 295 (100), 281 (64).

1,8-Dihydroxy-2-[1'-(2",2"-dimethyl-3"-acetoxypropyloxy)ethenyl]-3-methyl-9,10-anthraquinone (206)

To a solution of the foregoing enol ether (205) (15 mg) in acetic acid (15 cm^3) was added hydrobromic acid in acetic acid (30 drops, 48%). The reaction mixture was stirred at room temperature for 4 h, diluted with ethyl acetate (50 cm^3). The organic phase was washed with water (3 x 50 cm^3), dried and evaporated. The residue was chromatographed on silica containing 2% oxalic acid in toluene/ethyl acetate (9:1). The yellow band, R_f 0.54, afforded the *acetate* (206) (12 mg, 72%) as yellow-orange prisms from petrol m.p. 134-137° (Found: C, 67.6; H, 5.5. $C_{24}H_{24}O_7$ requires C, 67.9; H, 5.7%). λ_{max} (log ε) 240 sh, 274, 314 sh, 420 sh, 437, 446 sh nm (4.33, 4.45, 3.53, 4.03, 4.10, 4.07). ν_{max} 2982, 1740, 1669, 1620, 1595, 1509 cm^{-1}. δ 1.07, s, $C(CH_3)_2$; 2.06, 6H, s, $ArCH_3$, $OCOCH_3$; 3.93, 3.98, s, s, 2 x H1", 2 x H3"; 4.95, 5.43, brs, brs, $=CH_2$; 7.29, dd, *J* 1.5, 8Hz, H7; 7.41, s, H4; 7.64, t, *J* 8Hz, H6; 7.83, dd, *J* 1.5, 8Hz, H5; 12.17, 12.37, s, s, 2 x OH. *m/z* 424 (M, 36%), 296 (23), 295 (32), 69 (34), 43 (100).

Addition of Diene (201) to 2,6-Dichloro-1,4-benzoquinone (62)

A solution of 2,6-dichloro-1,4-benzoquinone (62) (66 mg) and diene (201) (140 mg) in dry tetrahydrofuran (3 cm^3) was stirred at room temperature for 1 h. A further portion of diene (201) (100 mg) was added and the solution was stirred overnight. The reaction mixture was diluted with methanol (10 cm^3) and aqueous hydrochloric acid (3.2 M, 5 cm^3) and stirred at room temperature for 30 min. It was then diluted with water (50 cm^3) and extracted with ethyl acetate (3 x 50 cm^3). The combined organic phase was washed with water (100 cm^3), dried and evaporated. The residue was chromatographed on silica containing 2% oxalic acid in toluene/ethyl acetate (3:1). The yellow band, R_f 0.68,

afforded *2-chloro-7-[1'-(2",2"-dimethyl-3"-hydroxypropyloxy)ethenyl]-8-hydroxy-6-methyl-1,4-naphthoquinone* (207) (20 mg, 15%) as orange plates from ethyl acetate/petrol m.p. 205-209° dec. (Found: C, 61.8; H, 5.9. $C_{18}H_{19}ClO_5$ requires C, 61.6; H, 5.5%). λ_{max} (log ε) 225, 265 sh, 272, 288 sh, 321 sh, 436 nm (4.59, 4.18, 4.21, 4.02, 3.47, 3.63). ν_{max} 3500, 2920, 1663, 1632, 1590, 1560 cm^{-1}. δ 1.04, s, $C(CH_3)_2$; 2.05, s, $ArCH_3$; 3.53, 3.88, s, s, 2 x CH_2; 4.96, 5.44, m, m, $=CH_2$; 7.13, s, H3; 7.23, s, H5; 11.97, s, *peri*-OH. *m/z* 352 [M(^{37}Cl, 34%], 350 [M(^{35}Cl), 100], 266 (24).

Addition of Sodium Methoxide to the Naphthoquinone (207)

To a stirred solution of the naphthoquinone (207) (9 mg) in methanol (15 cm^3) under a nitrogen atmosphere was added a solution of sodium methoxide (10 mg) in methanol (0.04 cm^3). The reaction mixture was stirred for 45 min, then acidified with aqueous hydrochloric acid. The ethyl acetate extract (2 x 25 cm^3) was washed with water (50 cm^3), dried and evaporated. The residue was chromatographed on silica containing 2% oxalic acid in toluene/ethyl acetate (3:1). The more polar band, R_f 0.22, afforded *7-[1'-(2",2"-dimethyl-3"-hydroxypropoxy)ethenyl]-8-hydroxy-2-methoxy-6-methyl-1,4-naphthoquinone* (208) (7 mg, 79%) as orange plates from benzene/petrol m.p. 148-151° (Found: $M^{+\cdot}$ 346.1418. $C_{19}H_{22}O_6$ requires $M^{+\cdot}$ 346.1416). λ_{max} (log ε) 219, 264 sh, 268, 309, 420 nm (4.51, 4.22, 4.24, 4.13, 3.71). ν_{max} 3540, 2934, 1640, 1602, 1560 cm^{-1}. δ 1.03, s, $C(CH_3)_2$; 2.05, s, $ArCH_3$; 3.52, 3.94, s, s, 2 x CH_2; 3.91, s, OCH_3; 4.96, 5.42, m, m, $=CH_2$; 6.08, s, H3; 7.22, s, H5; 12.07, s, *peri*-OH. *m/z* 347 (24%), 346 (M, 100), 260 (61), 259 (97), 245 (71), 175 (25), 69 (28), 45 (41), 41 (63), 31 (48), 29 (32).

The less polar band, R_f 0.32, afforded the *isomer* (209) (1 mg, 9%) (Found: $M^{+\cdot}$ 346.1414. $C_{19}H_{22}O_6$ requires $M^{+\cdot}$ 346.1416) λ_{max} (log ε)

220, 254, 308, 420 nm (4.07, 3.73, 3.47, 3.40). ν_{max} 3510, 2919, 1675, 1623 cm^{-1}. δ 1.04, s, $C(CH_3)_2$; 2.06, s, $ArCH_3$; 3.53, 3.93, s, s, 2 x CH_2; 3.91, s, OCH_3; 4.95, 5.43, m, m, $=CH_2$; 6.04, s, H3; 7.24, s, H8; 12.49, s, *peri*-OH. *m/z* (10 eV) 346 (M, 100%), 289 (52), 282 (22), 279 (55), 268 (24), 264 (40), 254 (24), 250 (21), 246 (21), 242 (22), 236 (23).

Addition of Diene (202) to 2-Chloro-8-hydroxy-1,4-naphthoquinone (80)

A solution of 2-chloro-8-hydroxy-1,4-naphthoquinone (80) (100 mg) and the butadiene (202) (165 mg) in dichloromethane (2 cm^3) was stirred at room temperature under a nitrogen atmosphere for 3 h. A further portion of the butadiene (202) (100 mg) was added and the reaction mixture was stirred overnight and then evaporated. The residue was dissolved in methanol (30 cm^3) and aqueous hydrochloric acid (6.4 M, 10 cm^3) and heated to reflux for 2 h. The ethyl acetate extract (3 x 50 cm^3) was washed with water (50 cm^3), dried and evaporated. Chromatography of the residue on silica containing 2% oxalic acid in toluene/ethyl acetate (9:1) gave recovered 3-chlorojuglone (32 mg). The yellow band, R_f 0.62, afforded *2-acetyl-1,8-dihydroxy-3-methyl-9,10-anthraquinone* (203) (27 mg, 28%) as orange plates from ethyl acetate/petrol m.p. 200.5-202° (Found: C, 68.7; H, 3.8. $C_{17}H_{12}O_5$ requires C, 68.9; H, 4.1%). λ_{max} (log ε) (ethanol + 1% formic acid) 257, 278 sh, 289, 414 sh, 432, 446 sh nm (4.32, 4.01, 4.00, 3.93, 3.99, 3.92). ν_{max} 1703, 1673, 1620, 1594, 1570 cm^{-1}. δ 2.41, s, $ArCH_3$; 2.62, s, $COCH_3$; 7.32, dd, *J* 1.5, 8Hz, H7; 7.62-7.90, m, 3 x ArH; 11.99, 12.36, 2 x *peri*-OH. *m/z* 296 (M, 49%), 281 (100).

Addition of Diene (202) to Acetoxynaphthoquinone (123)

A solution of the diene (202) (200 mg) and the quinone (123) (50 mg) in dichloromethane (1 cm^3) was stirred at room temperature under

a nitrogen atmosphere for 2 h. A further amount of diene (202) (200 mg) was added and stirring was continued for a further 4 h. The reaction mixture was diluted with dichloromethane (5 cm^3), cooled to 0^o, and treated with 1,5-diazabicyclo[5.4.0]undecene (3 drops). After 30 min it was acidified with acetic acid and extracted with ethyl acetate (2 x 75 cm^3). The combined organic phase was washed with water (2 x 100 cm^3), dried and evaporated. The residue was chromatographed on silica containing 2% oxalic acid in toluene/ethyl acetate (3:1). The more mobile band, R_f 0.82, afforded *6-acetoxy-2-acetyl-1,8-dihydroxy-3-methyl-9,10-anthraquinone* (210) (16 mg, 24%) as orange needles from ethyl acetate/petrol m.p. 187-189° (Found: C, 64.5; H, 4.1. $C_{19}H_{14}O_7$ requires C, 64.4; H, 4.0%). λ_{max} (log ε) 219, 259, 285 sh, 417 sh, 431, 443 sh nm (4.42, 4.07, 3.78, 3.70, 3.75, 3.70). ν_{max} 2918, 1777, 1691, 1675, 1621, 1590 cm^{-1}. δ 2.36, s, $OCOCH_3$; 2.40, s, $ArCH_3$; 2.62, $COCH_3$; 7.09, d, *J* 2Hz, H7; 7.57, d, *J* 2Hz, H5; 7.69, s, H4; 12.06, 12.31, s, s, 2 x *peri*-OH. *m/z* 354 (M, 31%), 312 (34), 297 (100), 43 (70).

The less mobile band, R_f 0.44, afforded the *enol ether* (211) (22 mg, 29%) as yellow needles from ethyl acetate/petrol m.p. 136.5-140° dec. (Found: C, 64.3; H, 447. $C_{22}H_{20}O_8$ requires C, 64.1; H, 4.9%). λ_{max} (log ε) [ethanol + 1% formic acid] 253, 280, 306 sh, 437, 450 sh nm (4.09, 4.22, 3.82, 3.92, 3.89). ν_{max} 3400, 2920, 1768, 1670, 1625, 1597 cm^{-1}. δ 1.93-2.27, m, 2''-CH_2; 2.06, s, $ArCH_3$; 2.36, s, $OCOCH_3$; 3.88, m, 3''-CH_2; 4.35, t, *J* 6Hz, 1''-CH_2; 5.00, 5.44, m, m, =CH_2; 7.05, d, *J* 2Hz, H7; 7.45, s, H4; 7.55, d, *J* 2Hz, H5; 12.23, 12.33, s, s, 2 x *peri*-OH. *m/z* 412 (M, 43%), 370 (21), 337 (21), 312 (22), 311 (100), 101 (77), 43 (95).

On one occasion a yellow band, R_f 0.27, of *3-acetoxy-1,8-dihydroxy-6-(3'-hydroxypropoxy)-9,10-anthraquinone* (212) (14%) was

obtained as orange needles from methanol m.p. 158.5-160° (Found: C, 61.0; H, 4.2. $C_{19}H_{16}O_8$ requires C, 61.3; H, 4.3%). λ_{max} (log ε) 222, 249, 263, 287, 417 sh, 436, 448 sh nm (4.65, 4.40, 4.37, 4.41, 4.07, 4.19, 4.16). ν_{max} 3415, 1774, 1676, 1630, 1604, 1560 cm^{-1}. δ 2.10, m, *J* 6Hz, 2'-CH_2; 2.35, s, $OCOCH_3$; 3.89, m, 3'-CH_2; 4.26, t, *J* 6Hz, 1'-CH_2; 6.70, d, *J* 2Hz, H7; 7.04, d, *J* 2Hz, H2; 7.37, d, *J* 2Hz, H5; 7.53, d, *J* 2Hz, H4; 12.19, 12.26, s, s, 2 x *peri*-OH. *m/z* 372 (M, 23%), 330 (64), 272 (47), 101 (98), 43 (100), 31 (31).

2-Acetylemodin (97)

A solution of the acetate (210) (5 mg) in aqueous sodium hydroxide (5%, 5 cm^3) was warmed on a steam bath for 15 min then allowed to cool at room temperature and acidified with aqueous hydrochloric acid. The ethyl acetate extract (3 x 25 cm^3) was washed with water (50 cm^3), dried and evaporated. The residue was chromatographed on silica containing 2% oxalic acid in toluene/ethyl acetate (3:1) to afford 2-acetylemodin (97) (5 mg, 100%) as orange microplates after sublimation (235°, 0.001 mm) m.m.p. 296-297° (lit.[71] 295-296°). It was identical in ultraviolet and infrared spectra and chromatographic behaviour with an authentic sample.[71] Interestingly, a sample of this product recrystallized from ethyl acetate/petrol showed a dimorphic difference in infrared absorption from that of sublimed material (ν_{max} 3416, 1698, 1662, 1612, 1578, 1543 cm^{-1}). Re-subliming this recrystallized material regenerated the original spectrum.

3-Chloro-4-hydroxy-5-methoxybenzaldehyde (216)

This compound was prepared from vanillin by the known method[148] as colourless plates (62%) from acetic acid m.p. 164-165° (lit.[148] 163°). λ_{max} (log ε) 213, 232, 264 sh, 288, 298 sh, 306 sh, 330 sh, 357 nm (4.33, 4.30, 3.82, 4.03, 4.00, 3.97, 3.70, 3.67).

ν_{max} 3295, 1680, 1590 cm^{-1}. δ 3.99, s, CH_3; 6.46, brs, OH; 7.33, d, *J* 2Hz, H2; 7.50, d, *J* 2Hz, H6; 9.79, s, CHO. *m/z* 186 (M, 100%), 185 (95).

2-Chloro-6-methoxy-1,4-benzoquinone (214)

This was prepared from the foregoing benzaldehyde (216) by the method of Asp and Lindberg[147] as orange needles from methanol (73%) m.p. 155-157° (lit.[147] 156.5-157°). λ_{max} (log ε) 275, 375 nm (3.44, 2.25). ν_{max} 3060, 1694, 1638, 1582 cm^{-1}. δ 3.86, s, OCH_3; 5.96, d, *J* 2Hz, H5; 6.93, d, *J* 2Hz, H3. *m/z* 172 (M, 55%), 142 (72), 69 (100).

2-Chloro-1,4-dihydroxy-5-methoxybenzene (217)

This was prepared by the modified method of Miller and Stewart.[13] A solution of 2-methoxy-1,4-benzoquinone (790 mg), tetraethylammonium chloride (300 mg) and chlorotrimethylsilane (1.87 g) in dry acetonitrile (10 cm^3) was stirred under a nitrogen atmosphere for 2 h. Water (30 cm^3) was added and the reaction mixture was extracted with ether (3 x 50 cm^3). The combined organic phase was washed sequentially with water (2 x 50 cm^3) and sat. sodium chloride (50 cm^3), then it was dried and evaporated. The solid was recrystallized from chloroform/petrol to yield the quinol (217) (580 mg, 73%) as pale needles m.p. 126-128° (lit.[147] 128-129°). λ_{max} (log ε) 220 sh, 298 nm (4.27, 3.97). ν_{max} 3300, 1620, 1520 cm^{-1}. δ 3.85, s, OCH_3; 5.19, 5.28, s, s, 2 x OH; 6.58, s, H6; 6.87, s, H3. *m/z* 174 (M, 88%), 159 (100).

2-Chloro-5-methoxy-1,4-benzoquinone (215)

The foregoing quinol (217) (508 mg) in ether (20 cm^3) containing a suspension of sodium sulphate (2.0 g) and silver (I) oxide (2.2 g) was stirred at room temperature for 2 h. The solution was filtered through Supercel, and washed with ethyl acetate then the filtrate was evaporated. The resulting solid was recrystallized from methanol to give the quinone (215) (385 mg, 77%) as orange plates m.p. 172-173°

(lit.[147] 169-170°). λ_{max} (log ε) 273, 373 nm (3.67, 2.22). ν_{max} 3050, 1678, 1652, 1620, 1587 cm^{-1}. δ 3.87, s, OCH_3; 6.08, s, H6; 6.95, s, H3. *m/z* 172 (M, 21%), 144 (39), 69 (100).

Addition of Diene (4) to 2-Chloro-6-methoxy-1,4-benzoquinone (214)

(i) A solution of (*E*)-1-methoxy-3-trimethylsilyloxy-1,3-butadiene (4) (80 mg) and 2-chloro-6-methoxy-1,4-benzoquinone (214) (60 mg) in dry benzene (10 cm^3) was heated to reflux under a nitrogen atmosphere for 1.5 h. The solvent was evaporated leaving a pale white crystalline residue. The residue was recrystallized from dichloromethane/light petrol to yield *8aβ-chloro-2,8α-dimethoxy-6-trimethylsilyloxy-1,4,4aβ,5β,8,8aβ-hexahydro-1,4-naphthalenedione* (218) (95 mg, 79%) as colourless prisms m.p. 135-140° dec. λ_{max} (log ε) (cyclohexane) 204, 269 nm (4.40, 3.86). δ 0.26, s, $OSi(CH_3)_3$; 2.32, brdd, *J* 7, 18Hz, H5β; 3.10, brd, *J* 18Hz, H5α; 3.10, s, 8α-OCH_3; 3.38, d, *J* 7Hz, H4aβ; 3.80, s, 2-OCH_3; 4.08, d, *J* 5Hz, H8β; 5.05, brd, *J* 5Hz, H7; 6.10, s, H3. The product was unstable, and satisfactory conbustion analysis could not be obtained.

(ii) A solution of (*E*)- 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (4) (50 mg) and 2-chloro-6-methoxy-1,4-benzoquinone (214) (40 mg) in dry benzene (10 cm^3) was heated to reflux under a nitrogen atmosphere for 1 h. The solvent was evaporated and the crude adduct (218) was dissolved in methanol (10 cm^3) and treated with aqueous hydrochloric acid (3.2 M, 5 cm^3). The reaction mixture was stirred at room temperature for 2 h then diluted with water (50 cm^3) and extracted with ethyl acetate (3 x 50 cm^3). The combined organic phase was washed with water (50 cm^3), dried and evaporated. The residue was chromatographed on silica containing 2% oxalic acid in toluene/ethyl acetate (3:1) to yield 6-hydroxy-2-methoxy-1,4-naphthoquinone (219) (40 mg, 84%) as

golden plates from methanol m.p. > 275° dec. (lit.[149] 285-295°). λ_{max} (log ε) 217 sh, 270, 292, 334, 389 nm (3.77, 3.94, 3.90, 3.19, 2.86). ν_{max} 3338, 1667, 1650, 1612, 1589, 1572 cm^{-1}. δ [$(CD_3)_2CO$] 3.91, s, OCH_3; 6.20, s, H3; 7.19, dd, *J* 3, 9Hz, H7; 7.41, d, *J* 3Hz, H5; 7.97, d, *J* 9Hz, H8. *m/z* 204 (M, 85%), 189 (35), 175 (40), 146 (26), 118 (40), 105 (100), 92 (22), 69 (27), 63 (46).

Addition of Diene (4) to 2-Chloro-5-methoxy-1,4-benzoquinone (215)

A solution of (*E*)-1-methoxy-3-trimethylsilyloxy-1,3-butadiene (4) (60 mg) and 2-chloro-5-methoxy-1,4-benzoquinone (215) (50 mg) in dry benzene (10 cm^3) was refluxed under a nitrogen atmosphere for 7 h. The solvent was evaporated and the residue was treated with methanol (20 cm^3) and aqueous hydrochloric acid (6.4 M, 10 cm^3). The reaction mixture was stirred at room temperature for 20 min, then diluted with water (50 cm^3) and extracted with ethyl acetate (2 x 50 cm^3). The combined organic phase was washed with water (3 x 25 cm^3), dried and evaporated. The residue was chromatographed on silica containing 2% oxalic acid in toluene/ethyl acetate (3:1). The yellow band, R_f 0.29, afforded *7-hydroxy-2-methoxy-1,4-naphthoquinone* (220) (55 mg, 93%) as yellow needles from methanol m.p. 235-245° dec. (Found: C, 64.4; H, 3.9. $C_{11}H_8O_4$ requires C, 64.6; H, 4.0%). λ_{max} (log ε) 216 sh, 264, 289, 335, 401 nm (4.16, 4.36, 4.11, 3.41, 3.19). ν_{max} 3360, 1683, 1647, 1618, 1580 cm^{-1}. δ [$(CD_3)_2SO$] 3.81, s, OCH_3; 6.21, s, H3; 7.14, dd, *J* 2, 8Hz, H6; 7.29, d, *J* 2, 8Hz, H8; 7.82, d, *J* 8Hz, H5; 10.85, brs, OH. *m/z* 204 (M, 100%).

Addition of Diene (202) to 2,6-Dichlorobenzoquinone (62)

A solution of the diene (202) (194 mg) and 2,6-dichlorobenzoquinone (62) (100 mg) in dichloromethane (2 cm^3) was stirred at room temperature under a nitrogen atmosphere for 2 h. A further

portion of the diene (202) (100 mg) was added and the reaction mixture was stirred for 4 h. The solvent was evaporated and the residue was dissolved in methanol (20 cm^3) and treated with aqueous hydrochloric acid (6.4 M, 10 cm^3). The reaction mixture was heated at reflux for 2h then diluted with water (50 cm^3) and extracted with ethyl acetate (2 x 50 cm^3). The combined organic phase was washed with water (50 cm^3), dried and evaporated. The residue was chromatographed on silica containing 2% oxalic acid in toluene/ethyl acetate (19:1). The yellow band, R_f 0.55, afforded *7-acetyl-2-chloro-8-hydroxy-6-methyl-1,4-naphthoquinone* (221) (42 mg, 28%) as orange needles from ethyl acetate/petrol m.p. 167-170° dec. (Found: C, 58.7; H, 3.1. $C_{13}H_9ClO_4$ requires C, 59.0; H, 3.4%). λ_{max} (log ε) 215, 228 sh, 245 sh, 283, 413 nm (4.31, 4.23, 4.06, 3.99, 3.54). ν_{max} 1703, 1665, 1635, 1591 cm^{-1}. δ 2.38, s, $ArCH_3$; 2.59, s, $COCH_3$; 7.19, s, H3; 7.49, s, H5; 11.94, s, *peri*-OH. *m/z* 266 (M[^{37}Cl], 20%), 264 (M[^{35}Cl], 57), 251 (35), 249 (100), 43 (31).

Reaction of Sodium Methoxide with Chloro Quinone (221)

To a solution of the crude chloro quinone (221) (15 mg) in dry methanol (15 cm^3) under a nitrogen atmosphere was added a solution of sodium methoxide (11 mg) in methanol (0.05 cm^3). The reaction was stirred at room temperature for 45 min then acidified with aqueous hydrochloric acid and extracted with ethyl acetate (2 x 50 cm^3). The combined extract was washed with water (50 cm^3), dried and evaporated. The crude product was dissolved in dichloromethane (10 cm^3) and cooled to -78° under a nitrogen atmosphere. Boron trichloride (~ 200 mg) was added and the reaction mixture was allowed to warm to 0°, stirred for 1 h, then acidified with aqueous hydrochloric acid. This was to demethylate any contaminant methyl ether that might have been retained after the aromati-

zation process leading to (121).[76,158] The dichloromethane extract (2 x 50 cm^3) was washed with water (50 cm^3) dried and evaporated. The residue was chromatographed on silica containing 2% oxalic acid in toluene/ethyl acetate (3:1). The yellow band, R_f 0.48, afforded 7-acetyl-8-hydroxy-2-methoxy-6-methyl-1,4-naphthoquinone (99)[76] (13 mg, 88%) as yellow needles from methanol m.p. 201-202°. λ_{max} (log ε) 211, 226 sh, 243 sh, 280, 411 nm (4.24, 4.19, 4.03, 4.05, 3.56). ν_{max} 1696, 1650, 1608 cm^{-1}. δ 2.37, s, $ArCH_3$; 2.59, s, $COCH_3$; 3.92, s, OCH_3; 6.14, s, H3; 7.48, s, H5; 12.03, s, *peri*-OH. *m/z* 260 (M, 85%), 245 (100), 181 (33). Its spectral data were significantly different from those reported for orientalone.[73]

The only physical data quoted for this compound in Jung's preliminary communication[76] are two resonances in its ^1H n.m.r. spectrum; δ (solvent unspecified) 6.1, 1H, s; 7.89, 1H, s. The latter value significantly disagrees with that quoted above for H5 and it cannot be accepted until more explicit comparison becomes available. It is noted that for stypendrone (98) and for several of its 2(3)-substituted derivates (99), (100), (221) and (222) the benzenoid proton H5 invariably resonated within the range δ 7.46-7.57.

The minor yellow band, R_f 0.59, afforded compound (100) assigned here as orientalone (1 mg, 7%). This material was chromatographically indistinguishable from that described in a subsequent paragraph. (p.160).

Addition of Diene (202) to 2,5-Dichlorobenzoquinone (60)

A solution of the diene (202) (242 mg) and 2,5-dichlorobenzoquinone (60) (100 mg) in dichloromethane (2 cm^3) was stirred at room temperature for 4 h. The solvent was evaporated and the residue was dissolved in methanol (20 cm^3) and aqueous hydrochloric acid (6.4 M,

10 cm^3). The reaction mixture was refluxed for 1 h then extracted with ethyl acetate (2 x 50 cm^3). The combined organic phase was washed with water (50 cm^3), dried and evaporated. The residue was chromatographed on silica containing 2% oxalic acid in toluene/ethyl acetate (19:1). The orange band, R_f 0.60, afforded *6-acetyl-2-chloro-5-hydroxy-7-methyl-1,4-naphthoquinone* (222) (27 mg, 18%) as orange needles from ethyl acetate/petrol m.p. 153-155° (Found: C, 59.3; H, 3.3. $C_{13}H_9ClO_4$ requires C, 59.0; H, 3.4%). λ_{max} (log ε) 209, 248 sh, 277, 417 nm (4.30, 3.94, 3.92, 3.42). ν_{max} 1699, 1679, 1628, 1586 cm^{-1}. δ 2.38, s, $ArCH_3$; 2.59, s, $COCH_3$; 7.20, s, H3; 7.57, s, H8, 12.08, s, *peri*-OH. *m/z* 266 [M(^{37}Cl), 18%], 264 [M(^{35}Cl), 56], 251 (31), 249 (100), 43 (34).

Reaction of Sodium Methoxide with the Chloro Quinone (222)

The crude chloro quinone (222) (27 mg) was treated sequentially with sodium methoxide and boron trichloride as for its isomer (221). Chromatography afforded *orientalone* (100) (18 mg, 68%) as orange plates from ethyl acetate/petrol m.p. 194-195° (lit.[73] for natural orientalone 195-196°) (Found: C, 64.4; H, 4.6. $C_{14}H_{12}O_5$ requires C, 64.6; H, 4.7%). λ_{max} (log ε) 224 sh, 246 sh, 279, 412 nm (4.30, 4.06, 4.04, 3.62). ν_{max} 1703, 1681, 1630, 1594 cm^{-1}. δ 2.35, s, $ArCH_3$; 2.59, 2, $COCH_3$; 3.93, s, OCH_3; 6.11, s, H3; 7.52, H8; 12.51, s, *peri*-OH. *m/z* 260 (M, 93), 245 (100), 231 (21), 217 (28), 43 (26).

These spectroscopic data closely resemble those reported in considerable detail for natural orientalone.[73] In particular the respective infrared and ^{1}H n.m.r. data were in acceptable agreement. The only significant discrepancies were (a) that the quoted electronic absorption of natural material did not include the maximum at 279 nm, though such an absorption is commonly observed for other methoxylated

juglones,[159] and (b) that the quoted mass spectrum of natural material included a prominent ion *m/z* 230 in place of the ion *m/z* 231 recorded above.

The minor band afforded 7-acetyl-8-hydroxy-2-methoxy-6-methyl-1,4-naphthoquinone (99) (1 mg, 4%). This material was chromatographically indistinguishable from that described in an earlier paragraph. (p.159).

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