NOVEL QUINONE SYNTHESES

A thesis submitted to

THE UNIVERSITY OF CAPE TOWN

in fulfilment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

by

GREGORY HAROLD PELTERET ROOS.
B.Sc. (Hons).

Department of Organic Chemistry,
University of Cape Town,
RONDEBOSCH,
Cape Town,
South Africa.

September, 1976.

CONTENTS

errata

In this thesis the spelling of napthalene and napthaquinone should be naphthalene and naphthaquinone.

SUMMARY

As indicated by the title, this dissertation deals with the investigation of the syntheses of a number of novel quinones. Chapter I deals with the syntheses of quinonoid derivatives of the compounds isobenzofuran and isoindole. These are the parent species of that series of heterocyclic compounds which contain a single heteroatom and are isoelectronic with naphthalene. They have been of considerable interest to workers in recent years, but have proved to be relatively unstable. We have therefore set out to prepare stable quinonoid derivatives of these.

In Chapter II we have sought to develop, via regiospecific Diels-Alder additions, simple syntheses of some synthetically useful napthaquinonoid systems. The formation of many of these, required in the past as intermediates for the syntheses of a number of naturally occurring quinones, has previously proved tedious. The study of these addition reactions has afforded a direct route for the synthesis of the natural quinone, droserone.

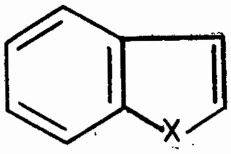
Finally, in Chapter III, some of the napthaquinones produced in Chapter II have been employed as intermediates in the syntheses of certain naturally occurring quinonoid species. These include α-caryopterone and model compounds for the proposed syntheses of the anti biotics, Juglomycins A and B.

CHAPTER I

Synthesis of Some Stable Derivatives of Isobenzofuran and Isoindole

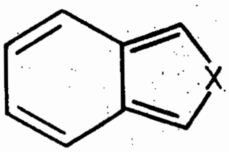
1.1 Introduction:

The series of π excessive heterocyclic compounds containing a single heteroatom and isoelectronic with napthalene falls into two distinct classes[1]. The first of these (1) represents the so called "normal" series[2]. These are well known stable compounds. However, the isoconjugate isomers (2), with the exception of isothianapthalene[3] (2c), are highly unstable although they are reported[4,5] as transient intermediates and may be isolated as their corresponding Diels-Alder adducts[5,6]. Recently, much interest has been shown in these isoconjugate species in the literature[7].



(1)

a. X = O benzofuran
b. X = NH indole
c. X = S benzothiophene

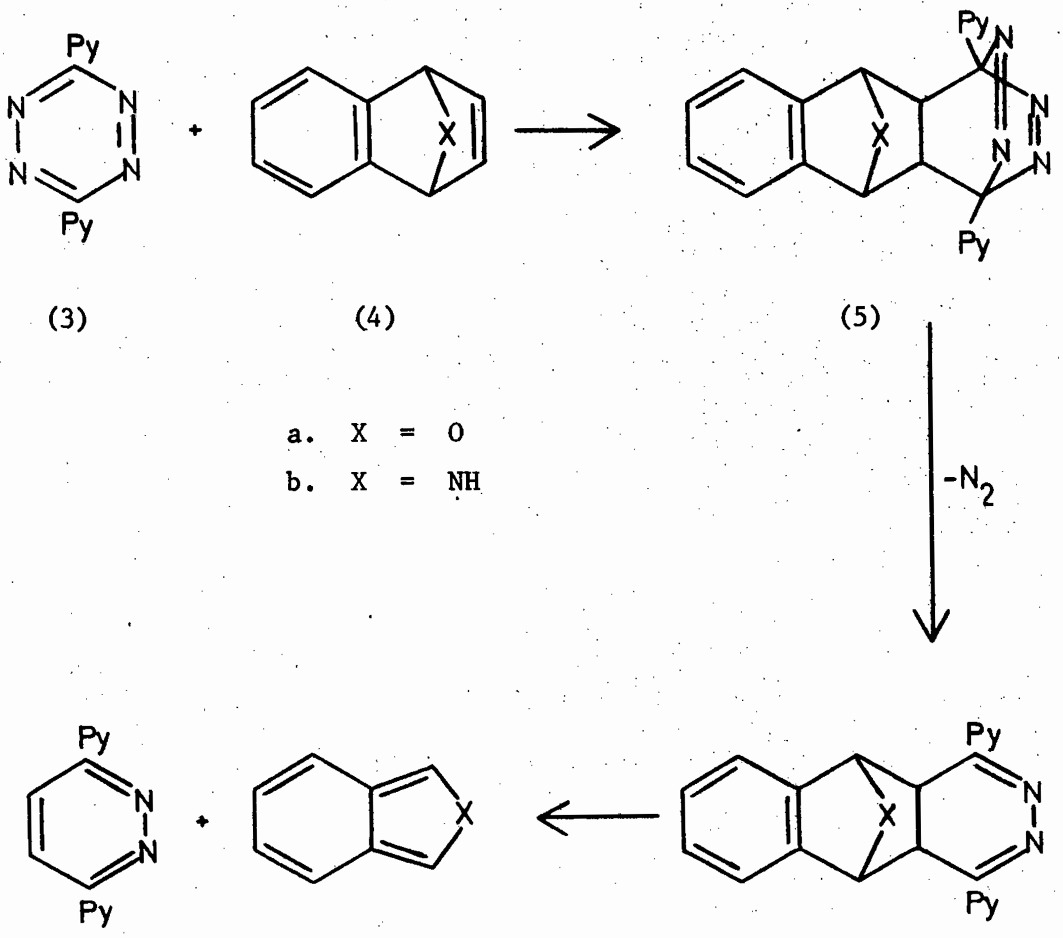


(2)

a. X = O isobenzofuran
b. X = NH isoindole
c. X = S isothianapthalene

The most convenient, as well as most recent reports on the syntheses of compounds of series (2) have been by Warrener and co-workers[4(c),6(a),6(b)]. These involve the use of the highly reactive diene 3,6 - di(2-pyridyl)-*s*-tetrazine[8] (3) in a reaction sequence as outlined in Scheme 1. Warrener had thus effectively removed the ethylene bridge of the endoxynapthalene(4a), the former becoming incorporated into the aromatic system of the pyridazine (7). The overall outcome of the conversion of compound (4) into (2) as shown in Scheme (1), represents a mild retro -$[\pi^4 s + \pi^2 s]$ Diels-Alder reaction. The method is based on a facile fragmentation, which depends for its success on the low activation energy attendant on cleavage of the tricyclo $[6.2.1.0^{2,7}]$ deca - 3,5,9 - triene system and aza-derivatives thereof[4(b),4(c),6(a),9]. Both compounds (2a) and (2b) have been successfully synthesized by the method shown in Scheme (1) and characterized by their Diels-Alder adduct derivatives.

Scheme (1)



(3) (4) (5)

a. X = O
b. X = NH

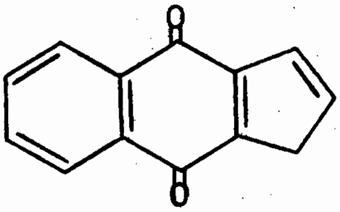
(7) (2) (6)

a. X = O
b. X = NH

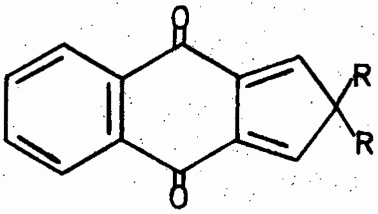
Py = 2-pyridyl

Furthermore, routes have been sought in this department to the quinone (8)[10], one of which involved the intermediacy of the species (9).

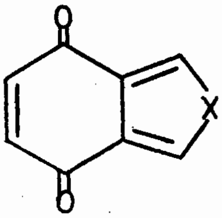
However, both (9) and its spiro derivative (10) proved too unstable to be isolated under the reaction conditions employed in their attempted syntheses. It might be expected that the three heterocyclic analogues (11), (12) and (13) would possess considerable stability relative to either the compounds of series (2) or structures (9) and (10) through resonance due to contributions from structures such as (14).



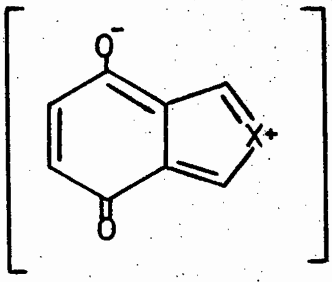
(8)



(9) R = H
(10) R⌒R = CH_2⌒CH_2

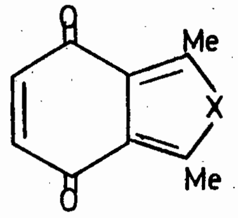


(11) X = O
(12) X = NH
(13) X = S



(14)

In view of the above, we have set about developing the as yet unreported syntheses of the parent species (11)+, (12) and (13). Since the completion and publication[11] of this work, the syntheses of stable derivatives (15) of species (11), (12) and (13) have been reported[12].



(15)

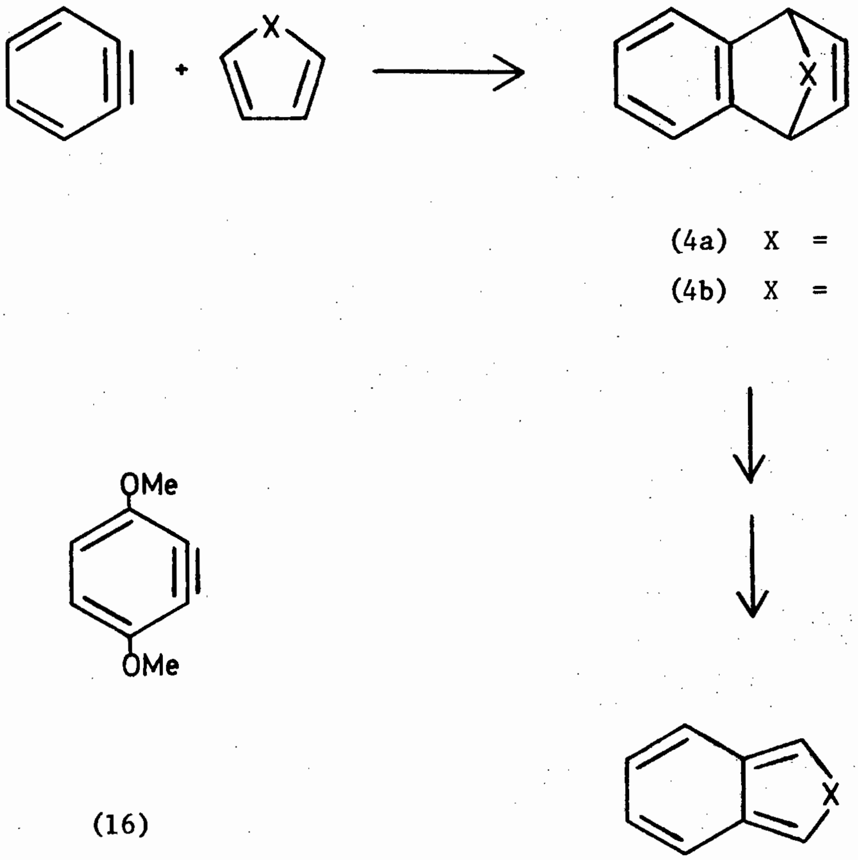
a. X = O
b. X = NMe
c. X = S

\+ The u.v., i.r., and p.m.r. data only for this compound have previously been reported[13].

1.2 Isobenzofuran - 4,7 - quinone (11):

For the proposed route, as outlined in Scheme (1), to be really attractive, it was necessary that simple methods for the generation of required starting materials of the type (4) should be developed. Of the number of possible methods that might be employed to accomplish this it was decided to select the highly efficient route that is presented by certain intermolecular benzyne Diels-Alder additions. Similar techniques had already been employed in the syntheses of (4a)[4(a),6(b)] and (4b)[6(a)] as shown by Scheme (2).

Scheme (2)

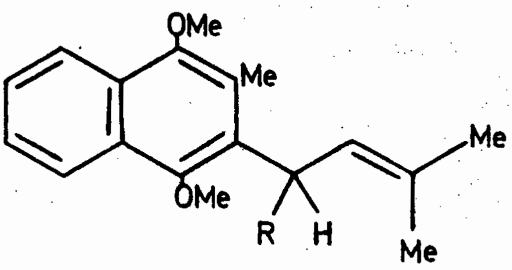


(4a) X = O

(4b) X = NH

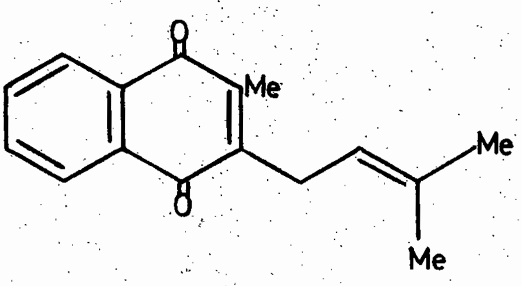
(16)

For our particular purposes we required a benzyne nucleus from which the quinone species could readily be derived. Thus we required the simplest and most efficient routes for the generation of 3,6 - dimethoxybenzyne (16). The conversion of aromatic 1,4 → dimethyl ethers into their corresponding quinones has been a subject of much research. Numerous methods have recently been reviewed by Musgrave[14]. Concentrated nitric acid appeared to be the most generally employed reagent in the oxidation of *para* - dimethoxy benzenes whereas, when applied to the 1,4 - dimethyl ethers of napthalene, nitration on the aromatic nucleus might occur instead of, or in addition to, demethylation. The use of inorganic oxidants such as Ce^{4+} and Cr^{3+} has also found widespread application although side reactions are known to prevail[15]. Silver (II) oxide has been shown to be particularly effective in the oxidation of various substituted toluenes to the corresponding aldehydes under mildly acidic conditions[15]. More recently a novel use for this reagent was reported by Snyder[16], who, when attempting to oxidise the dimethylether of menaquinol-1 (17) to the anticipated product (18), obtained instead menaquinone-1 (19) as the only product. This can only have arisen by oxidative demethylation of the dimethyl ether.



(17) R = H

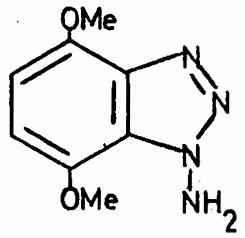
(18) R = OH



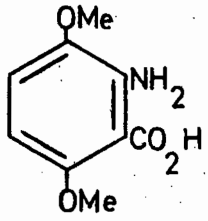
(19)

The scope of the use of silver (II) oxide as a general method for the oxidative cleavage of hydroquinone ethers has now been investigated[17]. The superiority of this reagent over conventional methods was demonstrated by the conversion of a number of substituted 1,4 - dimethoxynapthalenes into the corresponding 1,4 - napthaquinones in high yield. In addition, oxidative reactions of the side chains were shown to be minimal. This therefore presented an attractive route to the desired quinones by a relatively well established procedure.

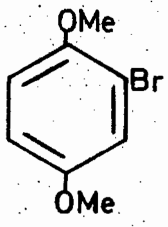
The previously reported routes to the benzyne (16) involved firstly the tedious synthesis of the precursor 1 - amino - 4,7 - dimethoxybenzotriazole (20)[18], which we found was difficult to prepare in amounts large enough for our needs. This was not very satisfactory because of the number of preparative steps (eight steps in all from gentisic acid) involved. However, this was partially offset by the ease of benzyne generation, subsequent addition, simple workup and the relatively good yields that were obtained. Secondly, species (16) may be generated from the precursor 2 - amino - 3,6 - dimethoxybenzoic acid (21)[19]. The preparation of this compound (21) again involves a fairly lengthly synthesis (five steps from gentisic acid). Finally, the reaction of 2,5 - dimethoxybromobenzene (22) with sodamide and sodium *t*-butoxide at low temperatures to generate (16), has been described[20].



(20)

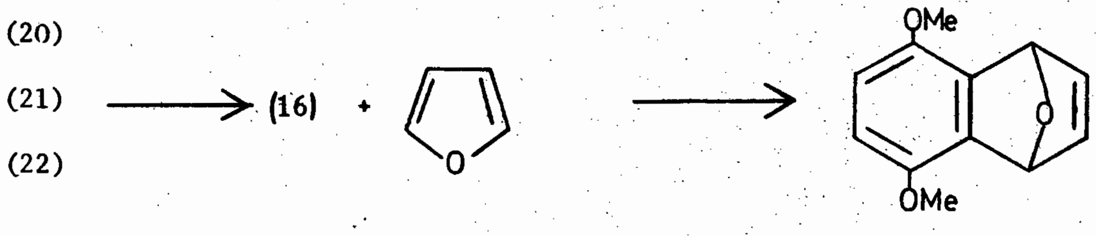


(21)



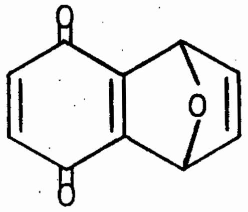
(22)

While we prepared and used both precursors (20) and (21) for the *in situ* generation of the benzyne (16), we found that it was most conviently obtained *in situ* by a modified route to that mentioned above, making use of the bromoether (22). Treatment of (22) with freshly powdered commercial sodamide in dry tetrahydrofuran under reflux conditions produced the desired results; although, whether subsequent Diels-Alder addition to a diene took place depended on the diene involved surviving the strongly basic reaction conditions. Thus we prepared adduct (23) from precursors (20), (21) and (22) - from the last by our own method just described - all of which routes provided the adduct (23)^{18} in about 70% yield. However, the ease of preparation of the bromoether (22) made this by far the most convenient precursor to this particular adduct.

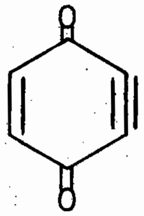


(23)

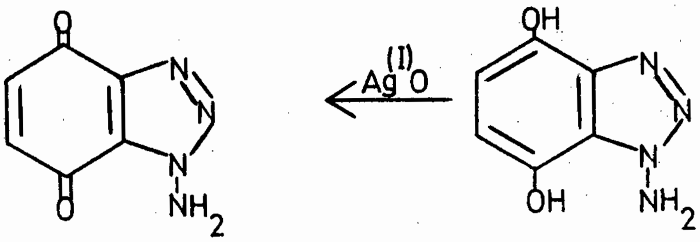
The conversion of this adduct (23) into the corresponding quinone (24) was readily achieved by the acid catalysed silver (II) oxide oxidation already described. An independent synthesis of the quinone (24) was performed directly, from the addition between benzyne quinone (25) and furan. The benzyne (25) is readily generated from 1-aminobenzotriazole-4,7-dione (26), which is obtained by silver (I) oxide oxidation of the demethylated derivative (27) of the triazole (20)^{18}.



(24)

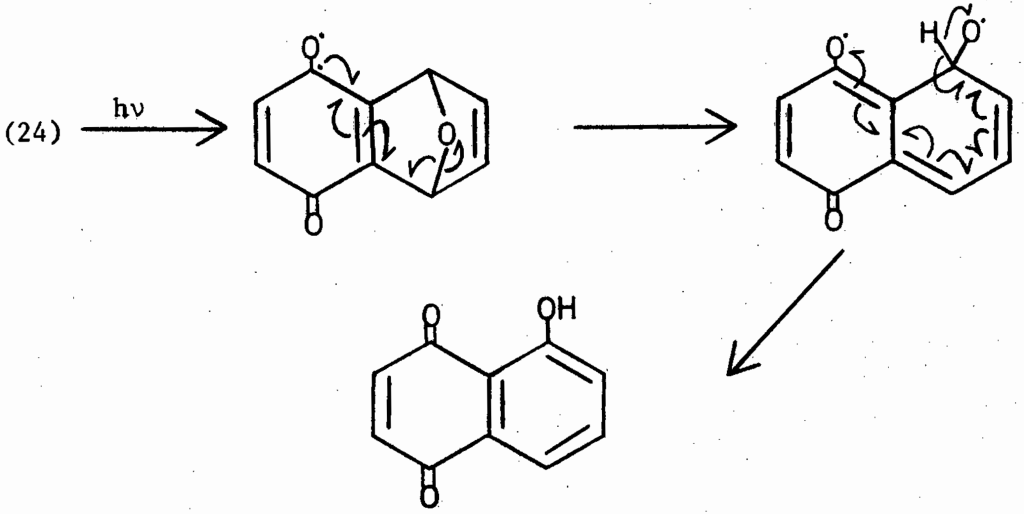


(25)



(26) (27)

During preparations of quinone (24), it was found that this compound was unstable in the presence of light. An investigation of the light-induced decomposition was carried out by irradiation of a solution of the quinone in sunlight and the simultaneous monitoring of a control experiment in the dark. This led to the almost quantitative formation of juglone (28) in the case of the irradiated sample, and no change in the control experiment. A possible route for juglone formation via a radical mechanism is outlined in Scheme (3).



(28)

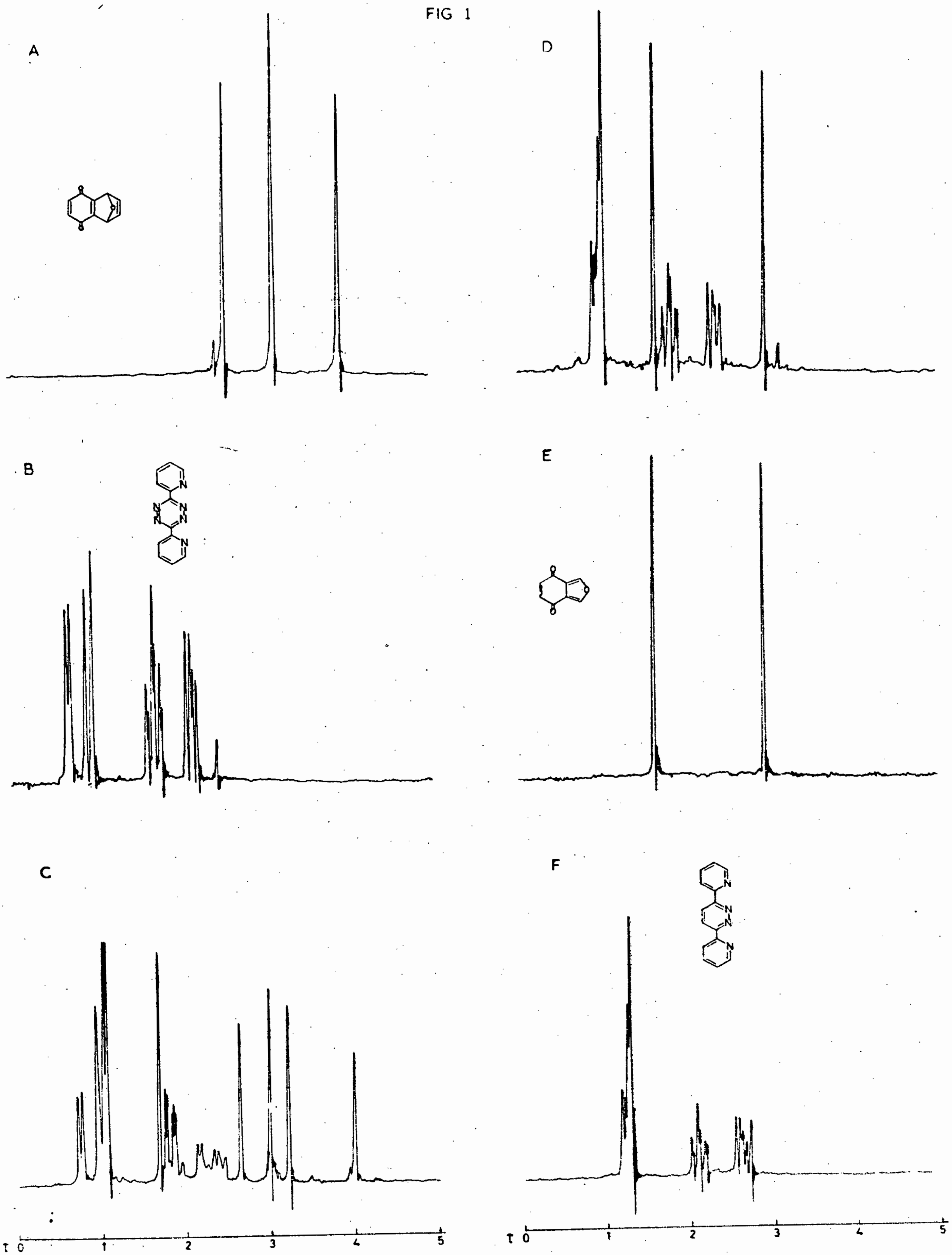
Scheme (3)

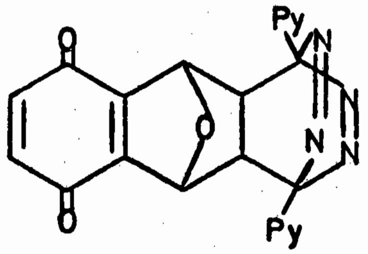
The remaining step in the synthesis used to obtain structure (11) involved the removal of the ethylene bridge from quinone (24), and as was anticipated, this proceeded readily on the addition of the *s* - tetrazine to the quinone (24), in a reaction sequence similar to that depicted in Scheme (1). The reaction with the *s* - tetrazine (3) was carried out at room temperature and afforded the required isobenzofuran - 4,7 - quinone (11) in good yield (70%). The addition and cycloreversion reactions occurring were monitored by H^1n.m.r. spectroscopy in a separate experiment. These results are as shown by Fig. (1).

Discussion Fig. (1)

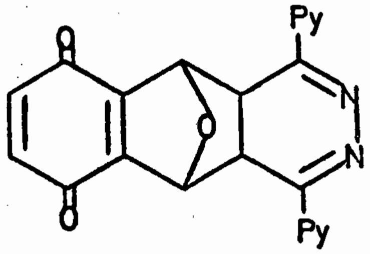
Spectra A - F were recorded in $CDCl_3$, at ambient temperature. A and B represent the respective starting materials, quinone (24) and *s* - tetrazine. E and F show the final products of reaction after workup of the reaction mixture at the completion of the cycloreversion. Spectrum C was recorded at reaction time t=5 min and shows the rapid consumption of quinone (24) and *s* - tetrazine and the generation of the final products isobenzofuran - 4,7 - quinone (11) and pyridazine (7); however, no indication of the presence of either intermediate adduct (5a) or (6a) is seen. Finally, D represents the reaction mixture at the completion of reaction. (t=10 min .)

FIG 1



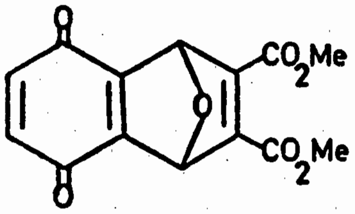


(5a)

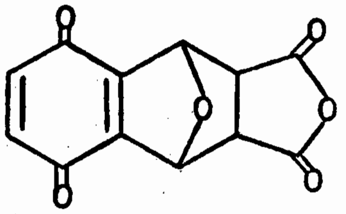


(6a)

To obtain information as to the reactivity (and stability) of the product (11), attempts to incorporate it in further Diels-Alder type additions as a diene were carried out with reactive dienophiles such as the electron deficient dimethyl acetylene dicarboxylate, maleic anhydride, and benzyne (16), and with the electron rich 2,3 - dihydropyran. These reactions were similar to those carried out by Warrener$^{6(a),6(b)}$ with *N* - methylmaleimide and isobenzofuran or isoindole for purpose of characterising these two compounds. The anticipated products from the first two dienophiles mentioned would be respectively (29) and (30). However, under the reaction conditions employed, both at room temperature and under reflux, only starting materials could be detected. This fact is in accordance with our original proposal of the added stability of this system afforded by the extended conjugation possible as shown by structure (14). Addition of dienes to the enedione moiety of compound (11) to give the alternative adducts was not investigated.

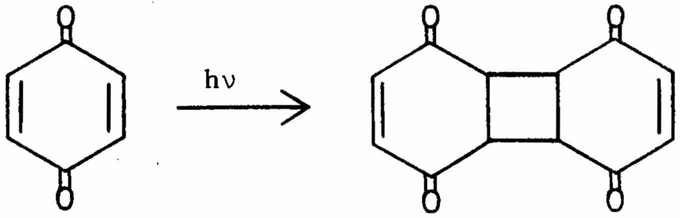


(29)

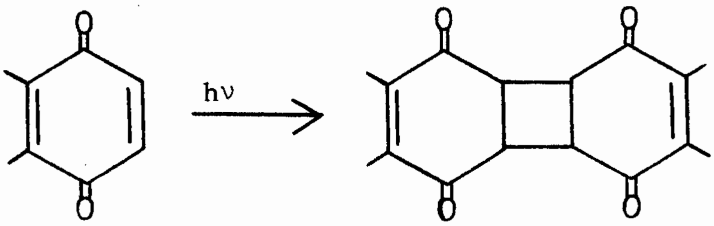


(30)

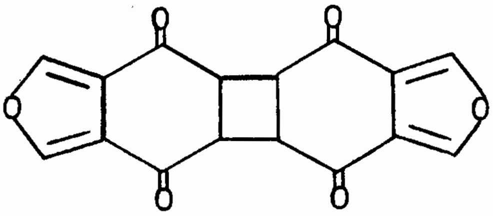
The photochemistry of 1,4 - benzoquinones has been extensively investigated. 1,4 - Benzoquinone (31) is itself reported[21] to give the *anti* - cyclobutane dimer (32), while 2,3 - dimethyl - 1,4 - benzoquinone (33) affords the *syn* dimer (34)[22]. The photochemistry of the furanquinone (11) was investigated to see whether a cyclobutane dimer (35) might be formed by analogy. Irradiation[+] led, however, to the formation of an intractable gum from which no single product could be isolated.



(31) (32)



(33) (34)

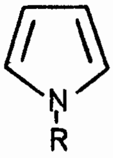


(35)

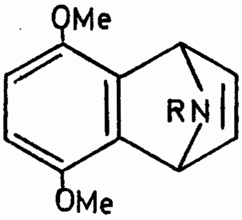
[+] A 500 W photoreactor with pyrex filter was employed.

1.3 Isoindole - 4,7 - quinone (12):

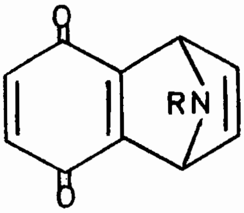
The primary problem that had to be overcome if the synthesis of quinone (12) was to follow a route similar to that devised for compound (11), was the non-participation of pyrrole in Diels-Alder type reactions as a diene due to its greater aromatic character relative to furan. Warrener, in his synthesis of isoindole (2b), had overcome this by the use of N- ethoxycarbonylpyrrole (36) in place of pyrrole. By substitution of the pyrrole nucleus in this manner with an electron withdrawing group, its diene-like nature was enhanced and it was able to participate in the required formation of adduct (4b). Subsequent removal of the ethoxycarbonyl grouping prior to elimination of the ethylene bridge had been possible with aqueous sodium hydroxide treatment.



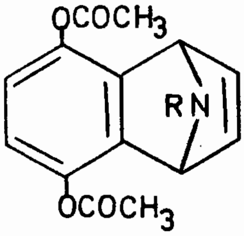
(36)



(37)



(38)

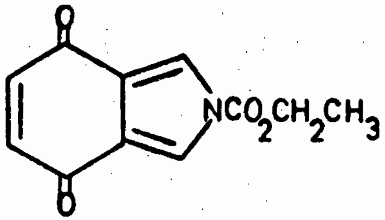


(39)

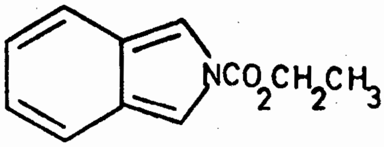
$R = CO_2CH_2CH_3$

In our case this was found to be equally true and the generation of the appropriate benzyne (16) from either precursor (20) or (21)+ in the presence of the pyrrole (36) led in good yield (70 - 80%) to the required adduct (37). Conversion of the adduct (37) to the corresponding quinone (38) by silver (II) oxide oxidation proceeded readily, but during attempts to characterise it fully, the quinone was found to be relatively unstable++. However, reductive acetylation with zinc dust, pyridine and acetic anhydride by the method of Sargent[23], afforded the diacetate (39) as a stable derivative for purposes of characterisation.

Freshly prepared samples of quinone (38) were therefore immediately subjected to treatment with the *s* - tetrazine (3) in an attempt to obtain product (40), which is the analogue of species (41) prepared by Warrener[6(a)]. Replacement of the ester function by hydrogen at this stage would have afforded the required quinone (12).



(40)

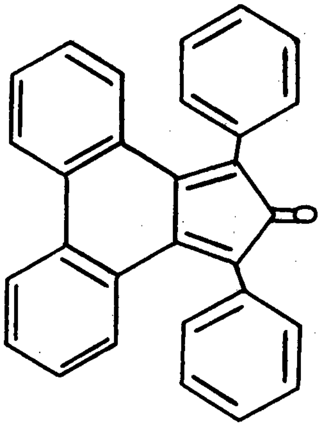


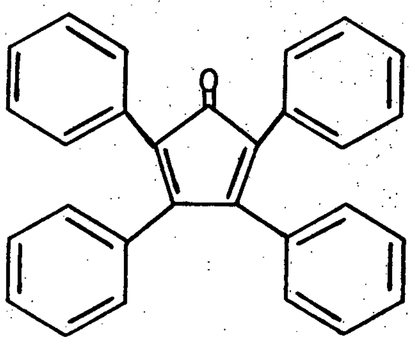
(41)

\+ It was found that the precursor (22) could not be used in this case, for the reason mentioned earlier (p 9), and discussed later in Section 1.5

++ This led to a dark brown intractable residue, the nature of which was not investigated.

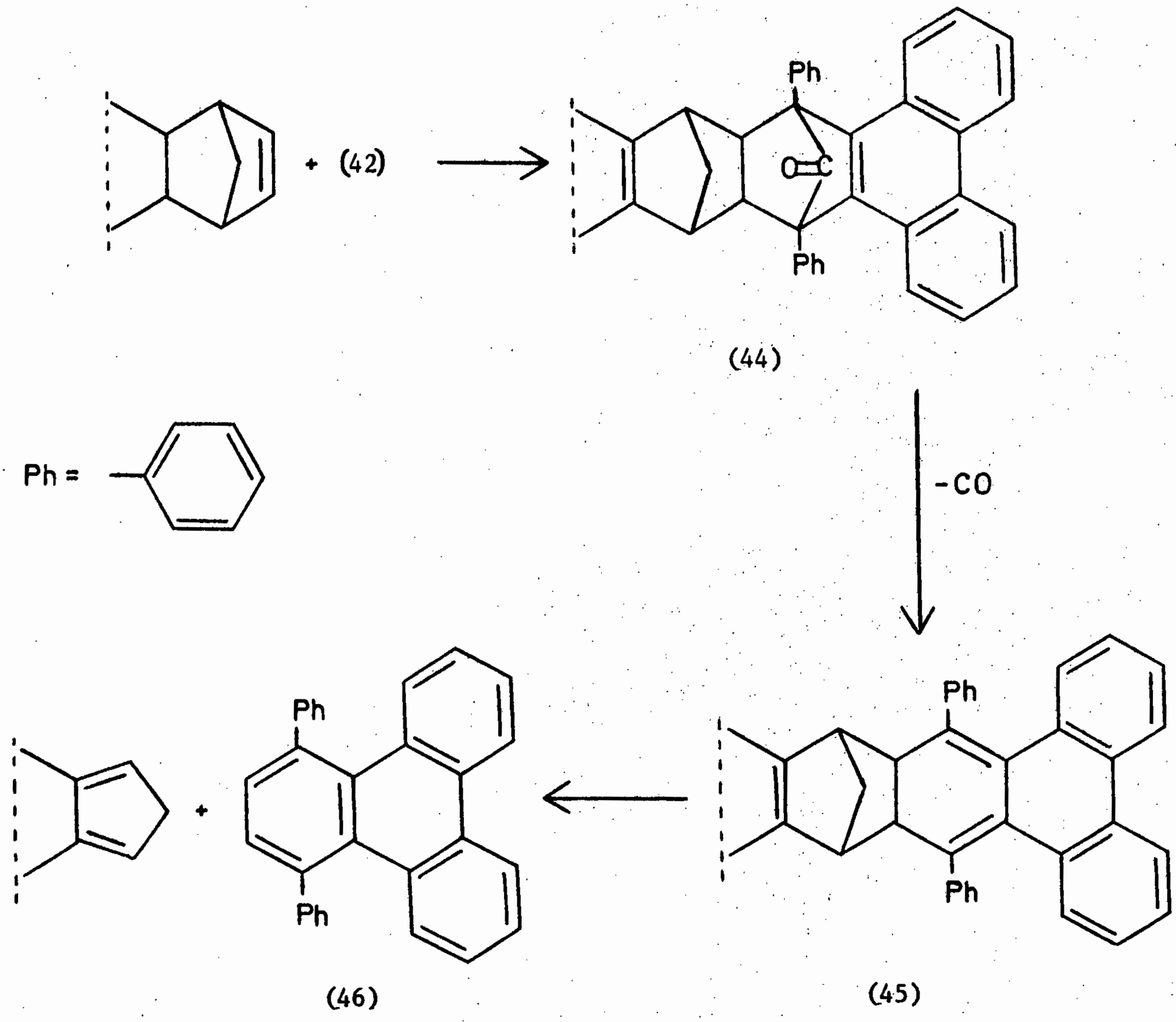
Contrary to expectations, no reaction could be induced, even under the more vigorous conditions of reflux. This was surprising, and perhaps finds its reason in the deactivation to a certain extent of the isolated double bond of quinone (38) by the presence of the electron withdrawing ester function. It can be argued that the reason for this unreactivity is not one of steric nature since, at the completion of this work, it was found that reaction with the more bulky phencyclone molecule (42) did occur. Phencyclone is another species used for similar purposes as *s* - tetrazine, as outlined by Scheme (4).


(42)


(43)

The reason for phencyclone, or other similar molecules such as tetraphenylcyclopentadiene (43), not being used initially in preference to *s* - tetrazine, is the relatively high activation energies which must be overcome in the cycloreversion of the adducts (44, 45) so formed. The decomposition of these adducts to the products (see Scheme 4) normally requires high temperatures and, since the stability of our final products (11), (12) and (13) was unknown, it was decided to perform these bridge removals under as mild a set of reaction conditions as possible.

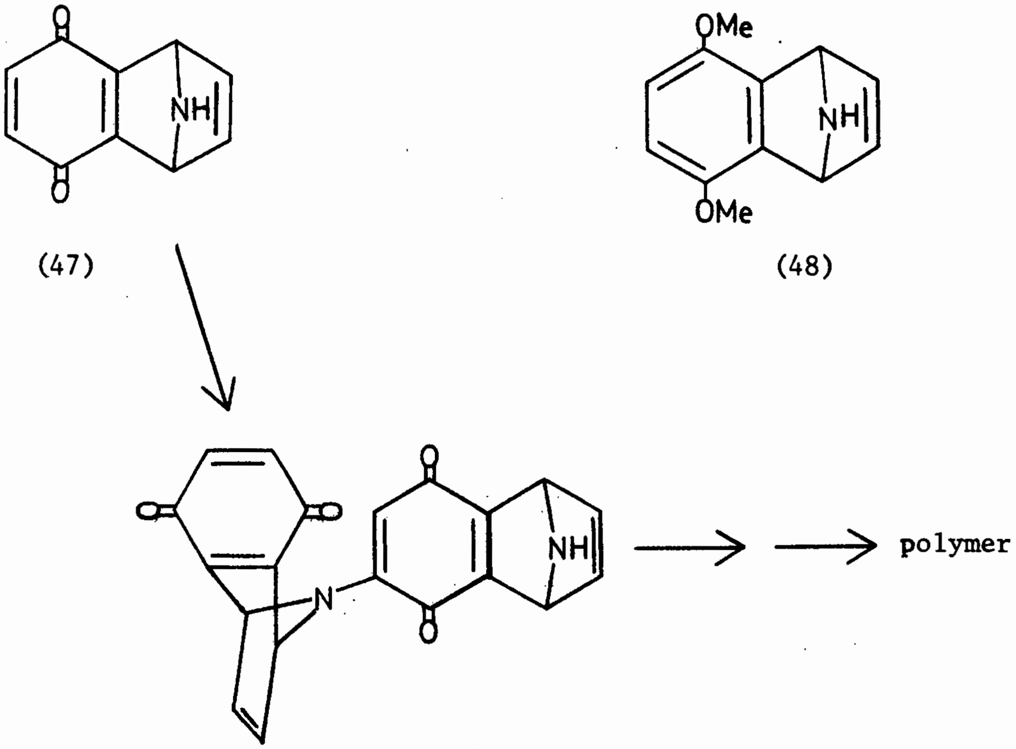
Scheme (4)



However, an alternate route to the required compound (12) was established without itsbeing necessary to investigate the pyrolytic decomposition of the adduct of type (44).

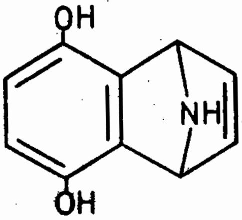
It was then proposed that the removal of the ester grouping from the quinone (38) to give the amine (47) would facilitate the removal of the ethylene bridge by enhancing the reactivity of the heterocyclic ring double bond. This removal of the ethoxycarbonyl function was attempted by hydrolysis with aqueous base as had been done by Warrener in his analogous synthesis mentioned earlier. This, however, led only to extensive decomposition to form a dark resinous tar from which no product or starting material could be recovered. This may have been due to the possibility of reaction between the quinone (47) and itself via the amine function if the >NH were generated. Nucleophilic additions of amines to quinone systems have long been known[24]. In our case, this could have led to a polymeric residue by a sequence, as depicted by Scheme (5).

Scheme (5)

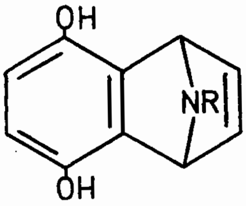


Since the quinone (47) either underwent reaction according to Scheme (5) or was unstable under the basic conditions employed in the ester removal, it was thought that this latter reaction might proceed more favourably on the adduct (37) to yield the amine (48), which might then be oxidised under acidic conditions to the required quinone (47). Subsequent reaction of the adduct with aqueous base under reflux for 3 hours provided compound (48) in good yield (85%) and this proved a relatively stable species, although it slowly darkened during extended periods in the light. However, all attempts to oxidise compound (48) with silver (II) oxide resulted in the formation of a brown tar, as was the case on attempting to remove the ester function from quinone (38). Similar results were obtained with other oxidative demethylating reagents and this route to compound (12) was therefore abandoned. Because the failure of quinone (47) to form might have been due to either the inherent instability of the species or to the severity of the oxidative techniques employed, the following two proposals were formulated and tested.

Firstly, the preparation of the adduct (49) was attempted, which might be expected to form readily by reduction of quinone (38) with sodium dithionite, which has been shown to be a good mild reagent for the reduction of quinones to the corresponding quinols[25]. Removal of the ester at this stage would afford amine (50), which might now be oxidized to the required quinone (47) by decidedly milder reagents such as silver (I) oxide or silver carbonate. The quinone (38), alternatively prepared by reaction of benzyne quinone (25) and pyrrole (36), the former generated from triazole (27) in the presence of lead tetraacetate, however resisted all attempts at reduction to the quinol with dithionite; spontaneous aerial oxidation during workup of the ethereal solution repeatedly afforded the quinone after initial reduction had occurred, as indicated by the loss of yellow colour.

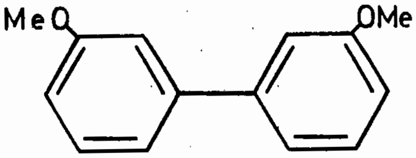


(50)

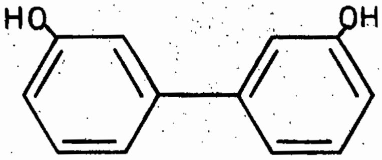


(49) R = $CO_2CH_2CH_3$

As an alternative test that the particular oxidative demethylation method was perhaps the cause of failure to afford the quinone, boron tribromide was tried. Much success has been reported with this reagent for the demethylation of aromatic ethers. McOmie [26(a). 26(b)] has shown the value of the reagent over others, in that reactions are usually carried out at room temperature or well below. Amongst other preparations, the conversion of compound (51) into the biphenol (52) has demonstrated the usefulness of the reagent. This reaction with adduct (48) could possibly yield the amine (50) directly in a way similar to that used by Rees[18] and repeated by us in the preparation of the triazole (27) from the corresponding dimethyl ether (20). However, this met with no success, yielding only a dark oil from which no single product could be obtained.

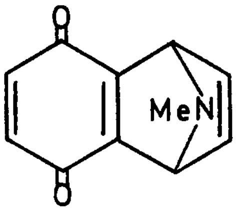


(51)

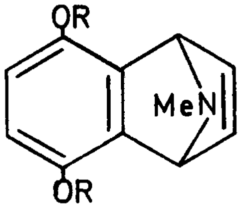


(52)

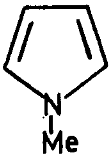
Secondly, in the event that silver (II) oxide had given rise to the quinonoid secondary amine (47), and that the inability to isolate this compound was due to its nucleophilic polymerisation as speculated earlier, it was decided to modify the secondary amine function to a tertiary analogue (53). This would preclude any such polymerisation from taking place. Furthermore, the preparation of compound (53) would provide an analogue of the quinone (38), in which it was earlier shown that reaction with *s* - tetrazine (3) was probably precluded by factors of an electronic nature. The replacement of the electron withdrawing ester function by methyl, in going from (38) to (53), might well alter the resulting reactivity of the quinone in the reaction with *s* - tetrazine to remove the ethylene bridge. A number of routes to this quinone were subsequently investigated.



(53)



(54) R = Me
(56) R = H



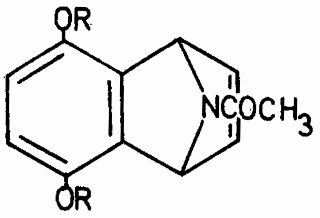
(55)

As might be expected, the corresponding adduct (54) did not form when 3,6 - dimethoxybenzyne (16) was generated in the presence of

N - methylpyrrole (55). This follows, as the methyl substituted pyrrole might be expected to be more aromatic and display even lower diene character that pyrrole itself, due to the electron releasing nature of the substituent. An alternative preparation involved the attempted methylation of the amine (48). The first attempt at achieving this with a sodium hydride - dimethylsulphoxide - methyl iodide methylating mixture has previously been shown by other workers[27] to be highly successful in polysaccharide hydroxyl methylation. This, however, yielded only a brown oil in which none of the desired product (54) could be detected. A second attempt made use of the methylating conditions that had successfully been employed by Sarett et al[28] in the synthesis of cortisone. This involves the use of potassium *t* - butoxide as the base for generation of a nucleophilic species for attack on, and subsequent methylation by, methyl iodide. This proved as fruitless as the previous method, yielding again an oily intractable residue. The third route to the tertiary amine (54) was one involving the reduction with lithium aluminium hydride in diethyl ether of the adduct (37). This proved to be highly successful in affording the required product in good yield (69%) as a stable white crystalline material.

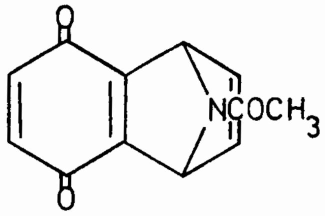
The tertiary amine (54) was then subjected to the oxidative demethylation reaction conditions of silver (II) oxide, but this failed to yield the quinone (53). Instead, an intractable gum was obtained from which not even the starting material could be isolated. The alternative oxidative demethylation technique, mentioned earlier, involving boron tribromide to give rise to either compound (56), or (53) if spontaneous oxidation occurred, was tried but found to yield a gum as well. As a further possible route to the quinone (53), the lithium aluminium hydride reduction conditions, that had earlier proved successful with the adduct (37), were applied to the quinone (38) and its diacetate derivative (39). This was particularly attractive since it precluded the necessity of performing the fairly vigorous demethylation reaction. Here again the expected product might be of the form (56) or (53), depending on the oxidation potential of the quinone. However, these reactions proved unsuccessful and only dark oils remained after workup.

At this stage, because of the above difficulties with the N - methyl species, one further substituent on the bridge nitrogen was tried. It was found that compound (48) could easily be acetylated at the bridge with a pyridine-acetic anhydride mixture to yield the N - acetyl species (57). Treatment of this with silver (II) oxide now readily gave the corresponding quinone (58) in 80% yield. This quinone proved to be relatively unstable and was characterised as its diacetate (59), derived as for the earlier compound (39). The ^{1}H n.m.r. spectra of the N - acetyl derivatives (57), (58) and (59) were of interest since they showed a lack of symmetry not exhibited by all the other N - bridged species reported here. This was shown by the bridgehead protons of the former showing different chemical shifts, owing to the restricted rotation about the amide N - C bond due to partial N = C double bond character as depicted by the resonance contributor (60). These signals were found to coalesce at elevated temperatures (cf: 45°C). This phenomenon finds precedence in the case of N,N - dimethylformamide, where similar differences in the methyl proton shift are seen[29]. Here the coalescence temperature is 110° C.

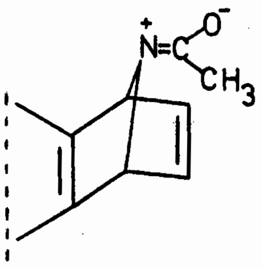


(57) R = Me

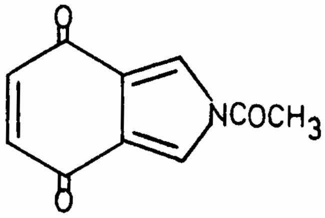
(59) R = Ac



(58)



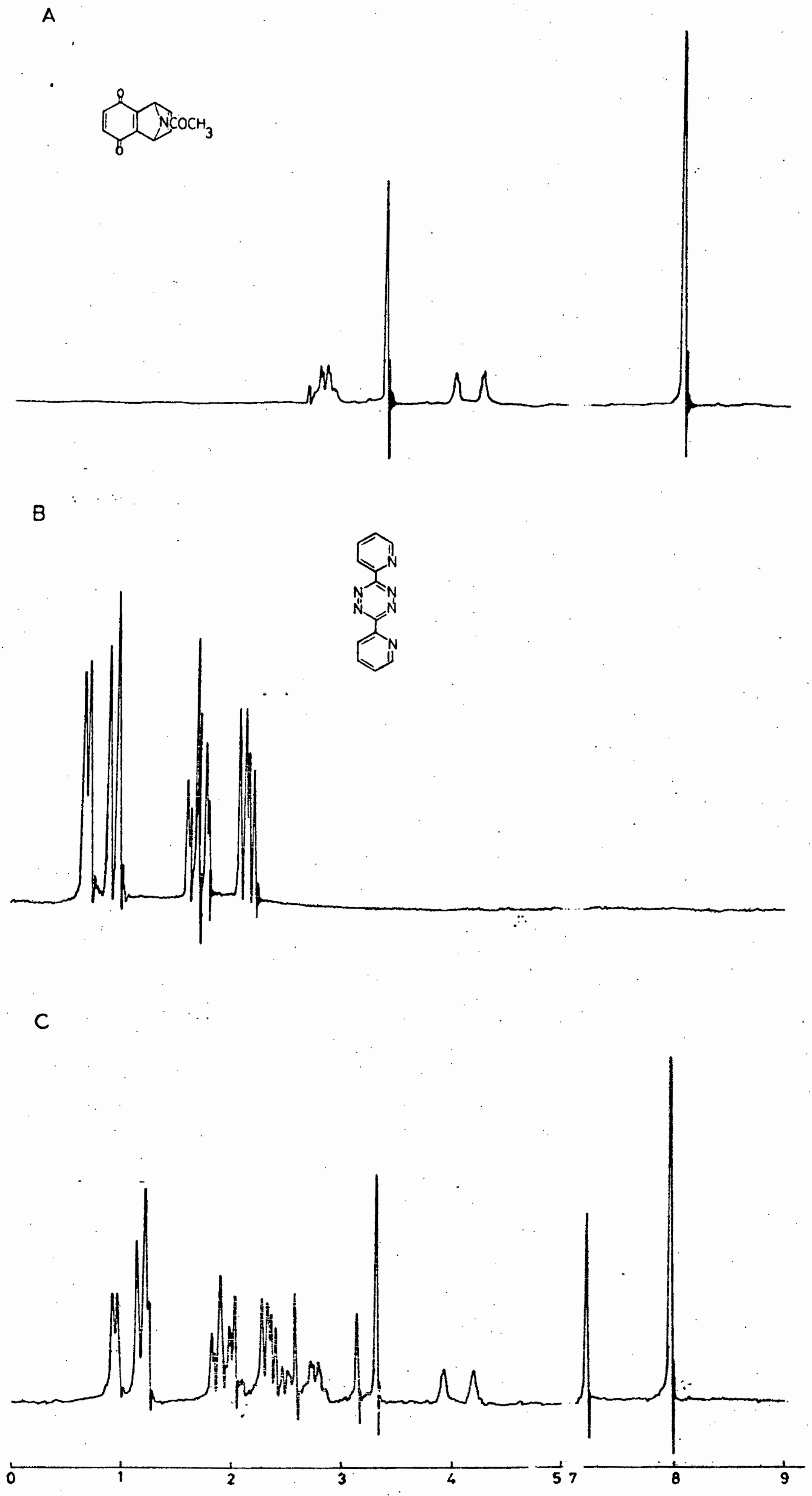
(60)

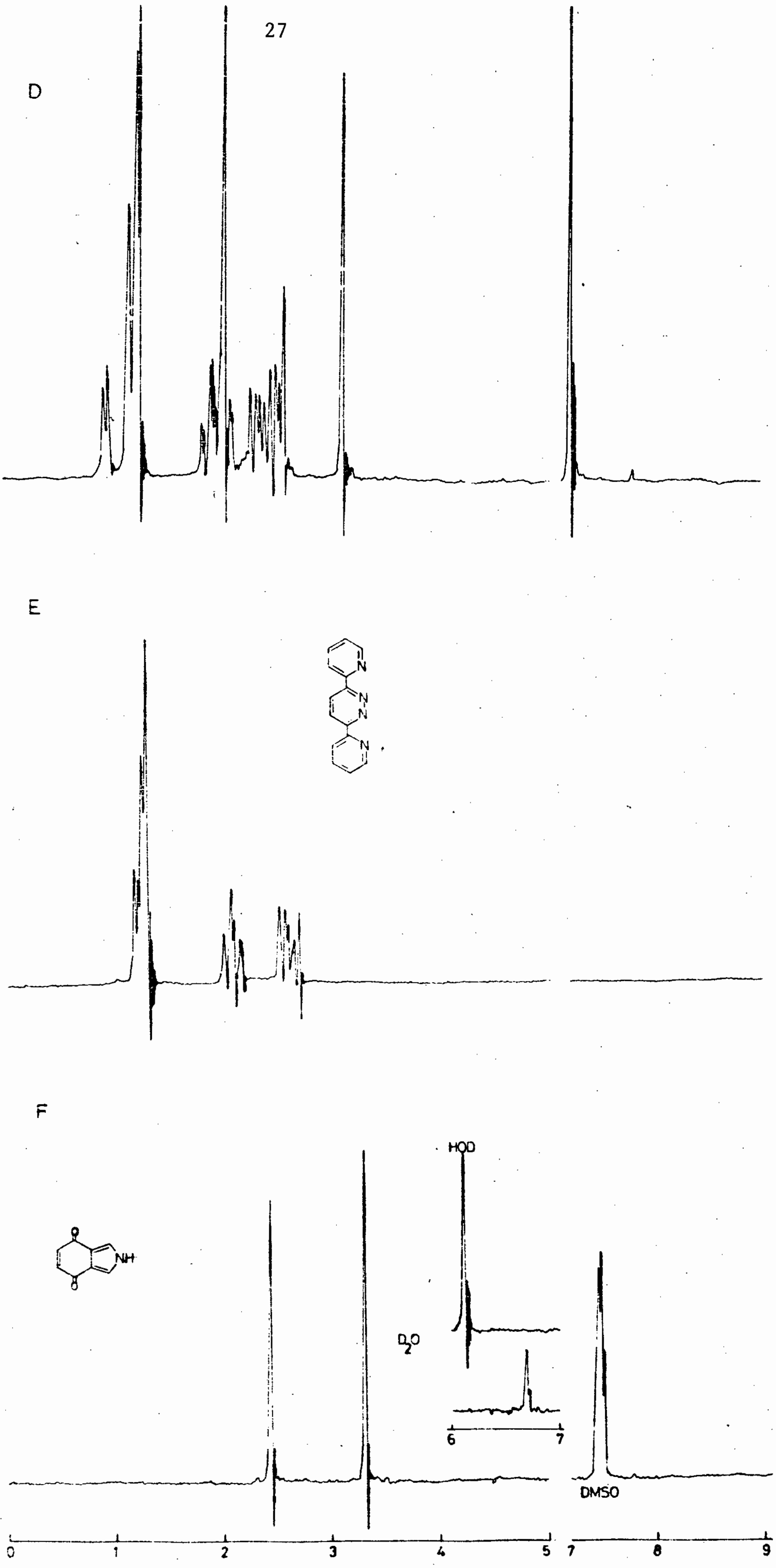


(61)

The reaction of a freshly prepared sample of quinone (58) with *s* - tetrazine (3) was carried out in chloroform - *d* in the n.m.r. spectrometer and found to proceed readily with rapid evolution of nitrogen to yield the required product (61) and the pyridazine by-product (7). The reaction was monitored throughout its duration by proton n.m.r. spectroscopy and the results are as shown in Fig. (2). Workup by column chromotography of the reaction mixture, however, did not afford the N - acetyl compound (61), but instead the desired

FIG 2



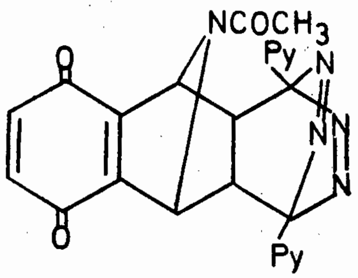

D
E
N
N
N
N
F
NH
HOD
D2O
6
7
DMSO
τ
0
1
2
3
4
5
7
8
9

isoindole - 4,7, - quinone (12). This involved the deacetylation of species (61) on the silica gel column (eluants: ethyl acetate/petroleum ether, 60/40). This reaction was repeated a number of times, with totally reproducible results. On each occasion the N - acetyl was converted to N-H during chromotography. ^1H n.m.r. samples of the reaction mixture were allowed to stand for up to 24 hours at room temperature or were heated to $50^oC (\pm 3^o)$ for short periods, to see if deacetylation could be effected prior to chromotography. All these efforts were of no avail and the reaction products appeared as before.

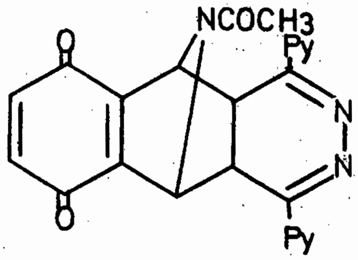
Discussion Fig. (2)

All spectra were recorded at ambient temperature, A-E in $CDCl_3$ and F in d_6 DMSO.
A and B represent the respective starting materials, quinone (58) and *s* - tetrazine (3). E shows the product, pyridazine (7), derived from the latter reagent, whilst F depicts isoindole - 4,7 - quinone (12) isolated from the reaction mixture after chromotography and the deacetylation which accompanies it. Spectrum C was recorded at reaction time t = 8 mins. and shows an intermediate stage in the conversion of reagents into products. Finally, D represents the reaction mixture at the completion of reaction and clearly shows that the quinone product is the N - acetyl modification (61) and not compound (12). That the acetyl signal in D is as above and not possibly due to acetic acid was shown by recording the spectrum of the latter

in the same solvent. Again, as was the case in the parallel reaction to prepare the isobenzofuran (11) (viz. Fig (1)), no evidence for the presence of adducts of type (5) or (6) (viz. (5b) and (6b)) is seen.



(5b)

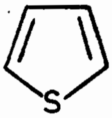


(6b)

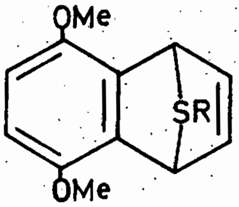
The quinone (12) is a high melting (180-181°C) relatively stable species, although discolouration occurred during lengthy exposure to the light. Characterisation of the compound fully confirms its structure, the H^1 n.m.r. spectrum [in d_6 - acetone because of greater insolubility over that of precursor (61)] clearly showed the absence of the acetyl $-CH_3$ and presence of a D_2O exchangeable N -H proton. High resolution mass spectral analysis yielded M^+ (at $^m/_e$: 147.03212) corresponding to the formula for the structure (12) (theoretical $^m/_e$: 147.03202). No chemical investigation of the isoindole - 4,7 - quinone nucleus has to date been undertaken.

1.4 Isothianapthalene - 4,7 - quinone (13):

As indicated earlier, isothianapthalene (2c) has been shown to be the most stable molecule of the three isoconjugate species (2). However, the problem that exists here is to involve the thiophene nucleus (62), or some suitable derivative thereof, in a Diels-Alder addition under conditions that might yield an adduct of type (4), *viz*: (63). Attempts to accomplish this with thiophene by reaction with benzyne (16) under a variety of conditions failed to produce any adduct formation. Calculations of the stabilisation energy of thiophene by comparison of the experimental and calculated heats of combustion^{30}, along with the fact that the electronegativities of the heteroatoms are in the order oxygen > nitrogen > sulphur, allow the prediction of thiophene being more aromatic than either furan or pyrrole. Hence structure (63) would require the nature of the -R function to be such that it lowered the aromatic character of thiophene and permitted its participation in Diels-Alder additions as a diene.

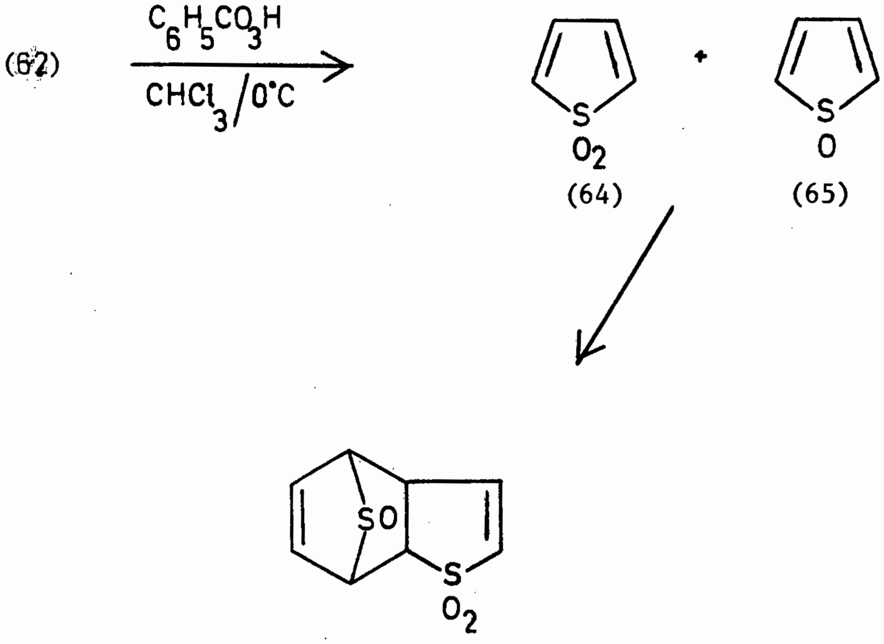


(62)



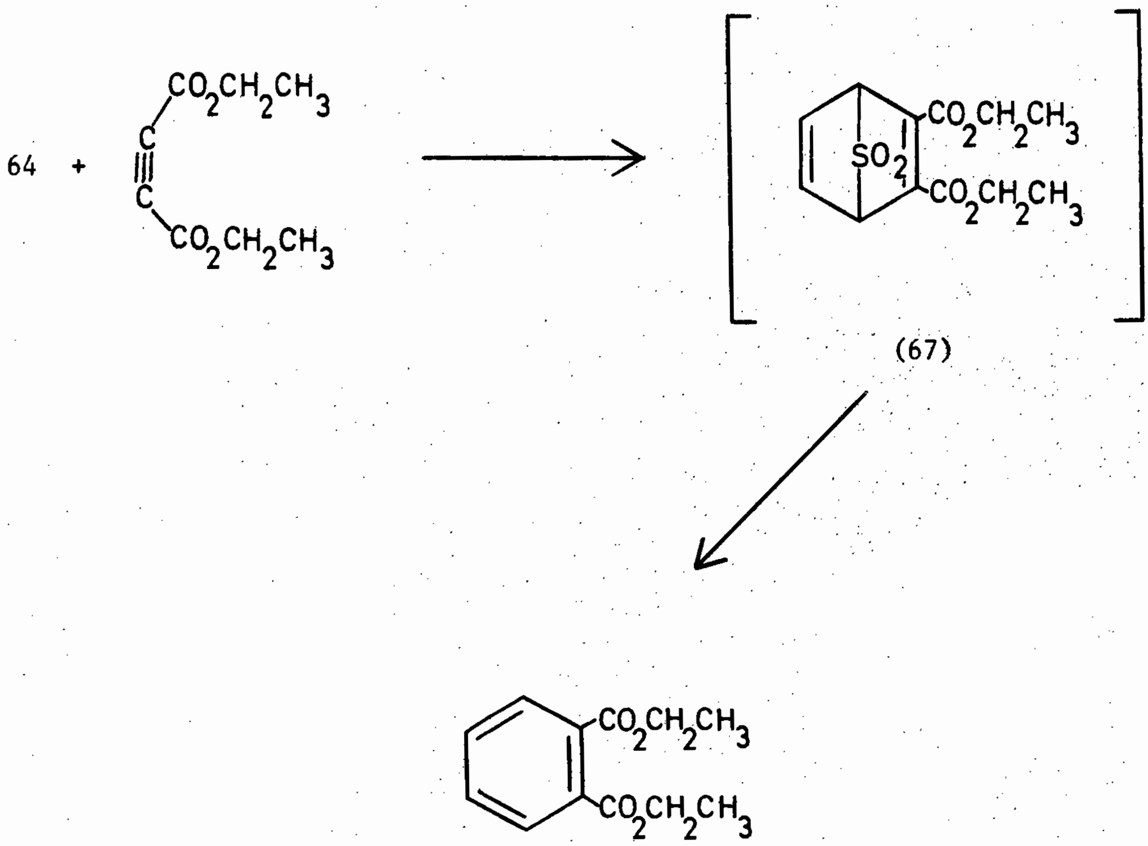
(63)

Attempts to oxidize thiophene have been shown to lead to compound (66), which is presumed to result via a Diels-Alder reaction of the intermediate thiophene sulphoxide (65) to thiophene sulphone (64)[30, 31]. Thiophene - 1,1 - dioxide (64) can be synthesized in six steps from butadiene sulphone[32(a)] and has been found to be stable only in dilute solution. It is extremely reactive and may function as a diene or dienophile in a Diels-Alder reaction, and a number of addition reactions in either capacity have been reported[32(b), 32(c)]. However, these involving species (64) as a diene, which was our requirement, gave products arising from cheletropic elimination of sulphur dioxide from the intermediate adduct, *viz*: (67) → (68). Thiophene - 1 - oxide (65) can also be obtained in dilute solution, but is even less stable, and dimerizes spontaneously by a similar diene type reaction[33].



(66)

As mentioned in the introduction, compound (15c), a stable derivative of the required product (13), has been reported since completion of this work. The formation of this derivative does not involve reaction schemes such as devised by us in the preceeding sections for the preparation of species (11) and (12). Also, further work is required to establish whether the parent compound (13) that we sought may be derived either by a similar method to that used in the synthesis of (15c) or directly from this derivative.

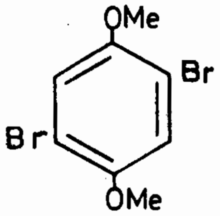


(67)

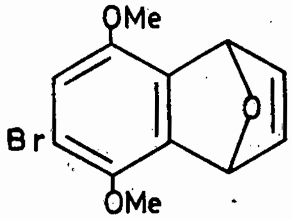
(68)

1.5 Attempted syntheses of some Related Diadducts:

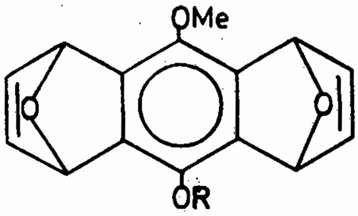
During investigations into the routes for the generation of the benzyne species (16), the synthesis of the precursor (22) by the method of Haberman[34] was used. This bromination of 1,4 - dimethoxybenzene yields not only the liquid mono-brominated species (22), but also 1,4 - dibromo - 2,5 - dimethoxybenzene (69) as a white crystalline solid. When this was treated under the benzyne generating conditions in the presence of furan, as were applied to the mono-bromo species, it was found that compound (70) was isolated in good yields (63%). Furthermore, if the reaction were repeated on this bromoadduct, the diadduct (71) was obtained as a pale off-white solid. That this was present as a mixture of the *syn* - and *anti* - isomers (72) and (73), was suggested by t.l.c. in methylene chloride, which showed two distinct spots with very close R_f values. No separation of the two isomers was attempted and the mixture was characterised by ^{1}H n.m.r. spectroscopy and elemental analysis. Of more interest to us was whether the diadduct could be converted to the corresponding quinone (74) from which the difuran (75) might be derived.



(69)

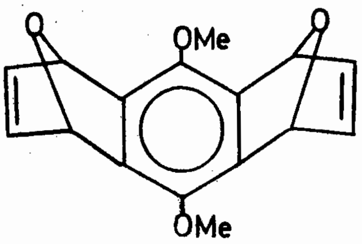


(70)

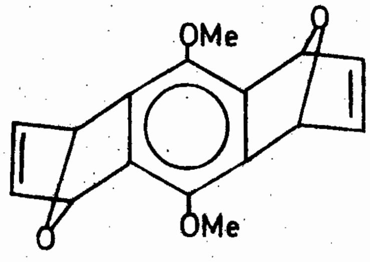


(71) R = Me

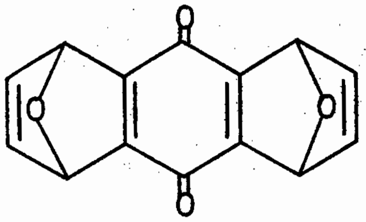
(76) R = H



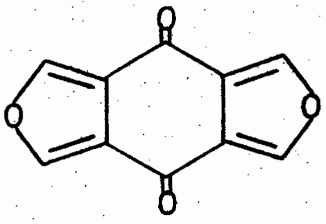
(72)



(73)



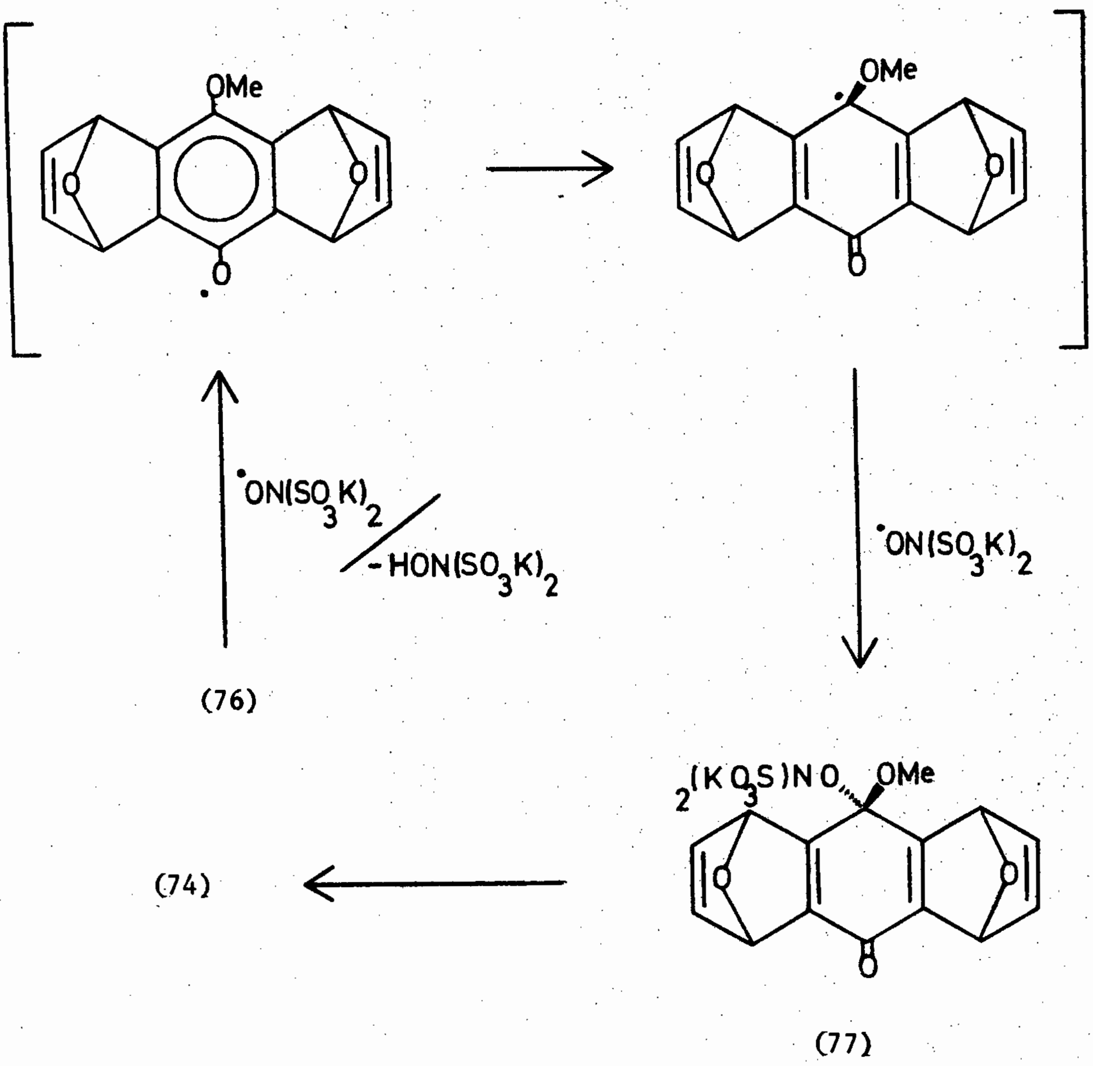
(74)



(75)

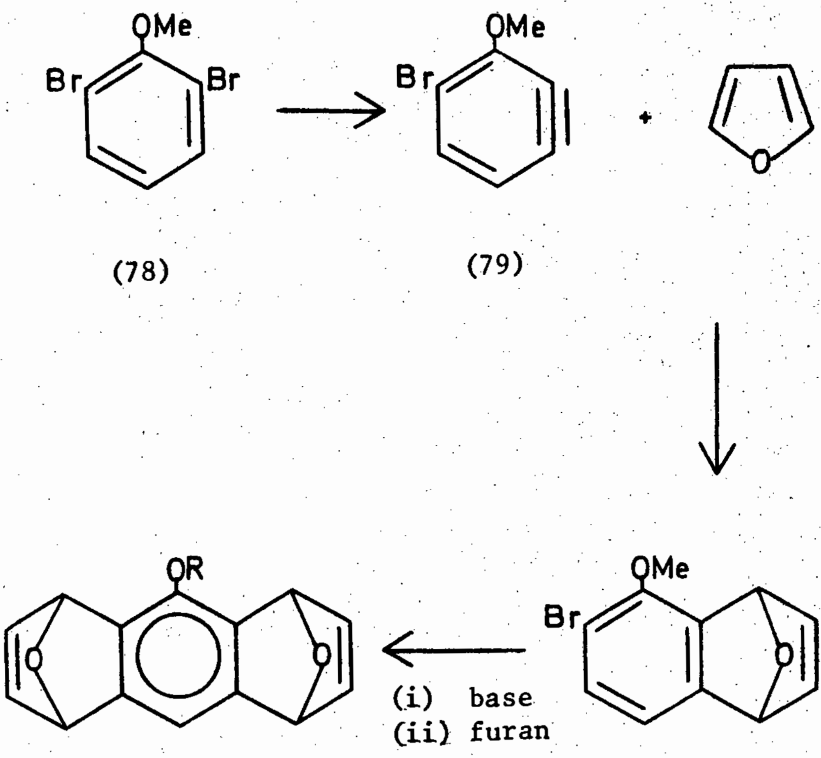
All attempts to oxidatively demethylate the diether (71) with silver (II) oxide led only to dark oils containing no trace of quinone species. An alternative procedure for oxidation first involved the preparation of the monodemethylated species (76) using the Feutrill and Mirrington[35] reagent for the demethylation of aromatic methyl ethers. This involves the use of the powerful nucleophilic mixture of sodium thioethoxide in N,N - dimethylformamide. Treatment of this species (76) with potassium nitrosodisulphonate (Fremy's salt) could then be expected to yield the required quinone (74). The scope of phenol oxidations by this method to yield corresponding quinones has been reviewed[36] and shown to be a highly attractive route. In our case, however, this did not lead to the formation of (74); a possible steric reason for this failure can be proposed, viz: Scheme (6). In the route outlined, the intermediate (77) might be considered to be a highly crowded molecule and steric hindrance to formation of this species could explain the failure of the oxidative procedure.

Scheme (6)



As an alternative route to quinone (74), we attempted to synthesize the diadduct (81). The presence of only one -OMe might allow the formation of the desired quinone on treatment of the intermediate phenol (82) with Fremy's salt; the possibility of a crowded state in the oxidation procedure would be reduced. The preparation of diadduct (81) was attempted by the route shown in Scheme (7). However, when the dibromoanisole[37] was treated under the conditions used earlier to generate benzynes from the dibromo species (69), only starting materials were returned. A possible explanation of this is that the sodamide anion, NH_2^-, is not sufficiently basic to abstract a proton from the aromatic nucleus (78).

Scheme (7)



(78)

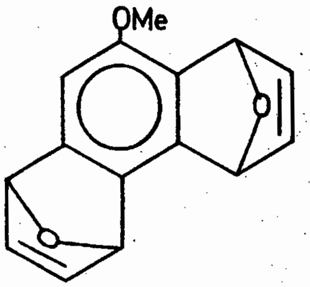
(79)

(80)

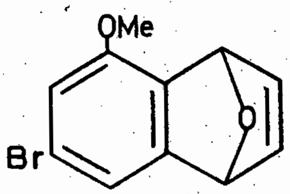
(81) R = OMe

(82) R = H

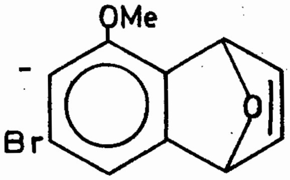
This is understandable, since reaction of base with either the bromodiether (22) or the dibromodiether (69) would presumably initially afford an anion in which the negative charge is situated ortho to a methoxyl group; in the case of the dibromoanisole (78), the initially formed anion could not be similarly stabilised. Use of the base butyl lithium as an alternative was rejected because of the reports of the reaction of this base with tetrahydrofuran[38], and use of the lithio derivative of 2,2,6,6 - tetramethylpiperidine was not attempted because of a recent report that this base reacts with furan[39]. However, a possibility not yet attempted is to react 3,5 - dibromoanisole with sodamide; diadduct (81) would be expected to be formed to the exclusion of alternative adducts such as (83), since the anion derived by base on the intermediate mono adduct (84) would no doubt be (85) rather than (86).



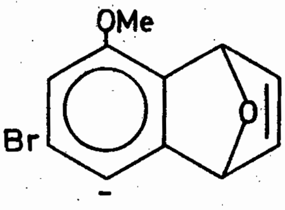
(83)



(84)

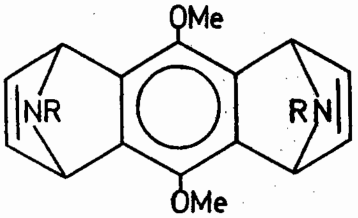


(85)

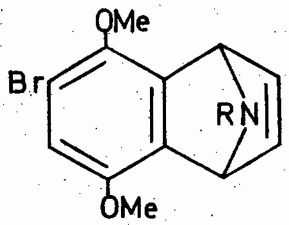


(86)

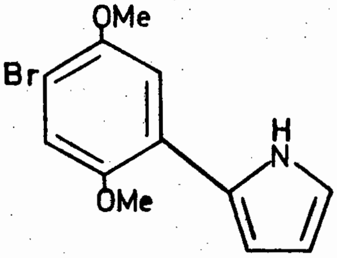
Since double treatment of the bromobenzene (69) with sodamide and furan had afforded the diadduct (71), the possibility of preparing the analogous nitrogen species (87) by similar reaction was considered. This was attempted merely by substituting N-ethoxycarbonypyrrole (36) for furan in a parallel reaction. Instead of isolating the intermediate monoadduct (88), the only product (65%) that formed had the structure (89). This must have resulted from a nucleophilic displacement of the pyrrole anion by amide at the carbonyl carbon of N - ethoxycarbonylpyrrole, followed by addition of this pyrrole to the benzyne derived from the dibromide (69). That this was the case was shown by the fact that, on repeating the reaction with pyrrole in place of N - ethoxycarbonyl derivative (36), that same product was isolated in similar yield. Furthermore, that the pyrrole group in compound (89) was para to the bromine substituent was suggested by the H^1 n.m.r. spectrum. This showed signals for two benzenoid protons as separate singlets, a low-field N-H absorption, and three signals consistent with 2 - substitution on the pyrrole nucleus.



(87)



(88)



(89)

R = $CO_2CH_2CH_3$

EXPERIMENTAL

Unless otherwise stated, the following conditions apply to all experimental sections in this thesis.

Infrared spectra were measured either as nujol mulls or solutions in solvents as shown, on a Perkin Elmer 237 spectrometer, while Ultraviolet spectra were measured in chloroform on a Beckman D.B. spectrophotometer. Nuclear magnetic resonance (^{1}H n.m.r.) spectra were recorded in [^{2}H] chloroform with tetramethylsilane as internal reference on a 100 MHz Varian XL 100 spectrometer. Light petroleum refers to the fraction having b.p. between 60 and 80 and sodamide refers to B.D.H. material. All melting points are quoted uncorrected as determined on a Fisher-Johns m.p. apparatus. Thin layer chromatography (t.l.c.) was carried out on Merck aluminium foil plates of Kieselgel 60 F 254, while preparative layer chromatography (p.l.c.) was performed on Merck glass plates of the same Kieselgel. Column chromatography was carried out with Merck Kieselgel 60 (70 - 230 mesh) in dry columns, unless wet columns are indicated, in which cases Merck Kieselgel 60 (30 - 70 mesh) was used; when alumina dry columns are referred to, these were prepared with Merck neutral active aluminium oxide.

3,6-Di-(2-pyridyl)-*s*-tetrazine: (3)

The *s*-tetrazine was prepared in 60% yield as red-violet plates (from benzene) m.p. 229° according to the method of Geldard[8] who reported m.p. 229-230°.

2-Amino-3,6-dimethoxybenzoic acid: (21)

This was prepared from 2,5-dimethoxy-6-nitrobenzamide[18] by the method of Heaney[19].

1-Amino-4,7-dimethoxybenzotriazole: (20) and 1-Amino-4,7-dihydroxybenzotriazole: (27)

These were prepared from gentisic acid via the method of Rees and West[18].

2,5-Dimethoxybromobenzene: (22) and 2,5-Dimethoxy-1,4-dibromobenzene: (69)

These were prepared from 1,4-dimethoxybenzene via the method of Haberman[34].

1,4-Dihydro-5,8-dimethoxy-1,4-epoxynapthalene: (23)

(a) From 1-Amino-4,7-dimethoxybenzotriazole (20):

A suspension of 1-amino-4,7-dimethoxybenzotriazole (0.5g) in furan (32.25ml) (freshly distilled from calcium hydride) was added portionwise to a stirred suspension of lead tetraacetate (1.7g) in furan (6.5ml) at room temperature. The mixture was stirred until nitrogen evolution ceased. The slurry was then filtered and the residue washed with methylene chloride (3 x 5ml). The combined filtrate and washings were evaporated to dryness under reduced pressure and the residue applied to a short column (14x2.5 cm) in a minimum of light petroleum/methylene chloride (10:1). Elution with benzene/methylene chloride (20:1) afforded the adduct as white prisms, m.p. 86-87°C. (lit[18] 86-87°) from light petroleum (40-60°) (0.340g, 68%).

(b) From 2,5-Dimethoxybromobenzene (22):

Sodamide (14.6g) was rapidly ground under dry tetrahydrofuran (120 ml) and transferred to a round bottom flask. Dry furan (100 ml) in tetrahydrofuran was added at room temperature. The mixture was warmed to 50°C and 2,5-dimethoxybromobenzene (21g) was added dropwise in tetrahydrofuran (40 ml). The solution was stirred at this temperature for 56 hrs under nitrogen, then cooled, filtered and partitioned between water and ethyl acetate. The organic layer was dried and evaporated and the residue chromatographed over a silica gel wet column with 10% ethyl acetate/light petroleum, to afford the adduct (15g, 77%), which gave prisms, m.p. 86-87° from light petroleum

(c) From 2-Amino-3,6-dimethoxybenzoic acid (21):

Solutions of the acid (21) (0.5g) in methylene chloride (20 ml) and pentyl nitrite (0.6 ml) in acetonitrile (20 ml) were added dropwise concurrently over 0.5 h to a mixture of furan (10 ml) in acetonitrile (40 ml) at 60°C. After addition was completed, the mixture was heated for a further 40 min. The solvents were then evaporated and the residue chromatographed over silica gel with methylene chloride/benzene (1:1) to yield the adduct (0.4g, 77%) which gave prisms m.p.86°C from light petroleum.

1,4-Dihydro-1,4-epoxy-5,8-napthaquinone: (24)

(a) From adduct (23):

The dimethyl ether (23) (0.79g), silver (II)oxide (1.63g), and dioxan (dried over sodium hydride; 20 ml) were mixed, and oxidation was initiated by addition of 6N-nitric acid (3.2 ml). As soon as all the silver oxide had been consumed, the reaction was stopped by addition of chloroform (30 ml) and water (8 ml). The chloroform layer was washed with water, dried, and evaporated and the residue sublimed at 75° and 0.5 mm Hg to give the quinone (0.19g, 33%) as yellow needles, m.p. 117-118°. (Found: C, 68.7; H, 3.5 $C_{10}H_6O_3$ requires C, 68.9; H, 3.5%), λ_{max} 255 and 396 nm ($\log_{\varepsilon}$ 4.24 and 2.82), ν_{max} ($CHCl_3$) 1665 and 1581 cm^{-1}, τ 2.88 (2H, s, CH=CH), 3.45 (2H, s, quinone H), and 4.22 (2H, s, bridgehead H).

(b) From 1- aminobenzotriazole-4,7-dione: (26)

1-Amino-4,7-dihydroxybenzotriazole (0.50g) as a suspension in dry tetrahydrofuran (20 ml) had silver (I) oxide (1.0g) and anhydrous sodium sulphate (0.50g) added and the mixture stirred for 1.5 h. The solution was then filtered and evaporated. To the brown residue, was added furan (10 ml) and lead tetra-acetate (2.0g) in methylene chloride (20 ml). This mixture was stirred until nitrogen evolution ceased. Filtration and evaporation of the solvent yielded a brown residue. Sublimation at 85°C and 1 mm Hg yielded a yellow product (0.21g, 40%) identical with that from procedure (a)

Isobenzofuran-4,7-quinone: (11)

The quinone (24) (0.100g) and 3,6-di-(2-pyridyl)-*s*-tetrazine (0.138g) were dissolved in chloroform (25 ml). Nitrogen bubbled off and the solution was stirred until the red colour disappeared. The solution was evaporated and the residue sublimed at 70° and 0.8 mm Hg to give the furan (0.060g, 70%) as fine needles, m.p. 140-142°. (Found: C, 64.6; H, 3.0; M^+, 148.1580. $C_8H_4O_3$ requires C, 64.8; H, 2.7%; M, 148.1604), λ_{max} 240 and 340 nm ($\log_\varepsilon$ 4.10 and 3.43), ν_{max} 1642 and 1585 cm^{-1}, τ 1.91 (2H, s, 1-and 3-H) and 3.16 (2H, s, 5-and 6-H).

Irradiation of the Quinone: (24) Formation of Juglone: (28)

The quinone (25mg) in dry benzene (3 ml) was kept in a Pyrex container in sunlight for 15 h, during which time the initially pale yellow solution became dark orange. Evaporation and sublimation afforded juglone (20 mg), identical with an authentic sample (m.p., i.r., n.m.r.). A similar solution of quinone kept in the dark remained unchanged during the same period.

N-ethoxycarbonylpyrrole: (36)

This was prepared from pyrrole by the method of Ciamician[40], to yield the product (b.p. 179-180° lit 180°) in 70% yield as a clear liquid. τ 2.4 (2H, m, pyrrole 2- and 5-H), 3.48 (2H, m, pyrrole 3- and 4-H), 5.4 (2H, q, OCH_2), 8.52 (3H, t, CH_3).

Ethyl 1,4-Dihydro-5,8-dimethoxy-1,4-iminonapthalene-9-carboxylate: (37)

(a) From 1-amino-4,7-dimethoxybenzotriazole (20):

To the triazole (0.946g) and N-ethoxycarbonylpyrrole (0.800g) in dry methylene chloride (25 ml) was added in small portions a suspension of lead tetraacetate (3.0g) in methylene chloride (50 ml). The solution was stirred until nitrogen evolution ceased and then filtered;

the precipitate was washed with methylene chloride and the organic solvent evaporated. The residue was chromatographed over silica gel (wet column, 10% chloroform/benzene). The clear oil (1.16g, 86%) was sufficiently pure for further reaction. Preparative t.l.c. (5% ethyl acetate/benzene) gave the adduct as needles, m.p. 53-53.5°C (Found: C, 65.2; H, 6.1; N, 5.1. $C_{15}H_{17}NO_4$ requires C, 65.45; H, 6.25; N, 5.1%), λ_{max} 235 and 299 nm ($\log_\varepsilon$ 3.67 and 3.46), ν_{max} 1709 and 1619 cm^{-1}, τ 2.99 br (2H, s, CH=CH), 3.46 (2H, s, ArH), 4.22 br (2H, s, bridgehead H), 5.92 (2H, q, OCH_2), 6.20 (6H, s, $2xOCH_3$) and 8.80 (3H, t, CH_3).

(b) From 2-Amino-3,6-dimethoxybenzoic acid (21):

To a solution of N-ethoxycarbonylpyrrole (0.85g) in acetonitrile (40ml), the acid (1.0g) in methylene chloride (25ml) and pentyl nitrite (1.2g) in acetonitrile (20ml) were added dropwise during 30 min. The solution was heated under reflux for 2 h, and then evaporated. The residue was chromatographed as in (a) to yield identical material (1g, 72%).

1,4-Dihydro-5,8-dimethoxy-1,4-iminonapthalene: (48)

The foregoing carbamate (37) (2.9g) in aqueous sodium hydroxide (10%, 40ml) was heated under reflux for 3 h. The solution was cooled and extracted with methylene chloride. The organic layer was dried and evaporated. The residue was sublimed at 70° and 0.5 mm Hg to yield white needles (1.83g, 85%), m.p. 80-81°. (Found: C, 71.1; H, 6.7; N, 6.6. $C_{12}H_{13}NO_2$ requires C, 70.9; H, 6.4; N, 6.9%), λ_{max} 240 and 302 nm ($\log_\varepsilon$3.46 and 3.55), ν_{max}3262 cm^{-1}, τ 2.98 br (2H, s, CH=CH), 3.54 (2H, s, ArH), 4.87 br (2H, s, bridgehead H), 6.21 (6H, s, 2xOCH_3), and 7.01 (1H, s, D_2O exchangeable, NH).

N-methylpyrrole: (55)

This was prepared as a colourless liquid (b.p. 114-115° lit. 115°) in 80% yield from pyrrole by the method of Heaney$^{7(a)}$.

1,4-Dihydro-5,8-dimethoxy-9-methyl-1,4-iminonapthalene: (54)

The carbamate (37) (1.20g) in dry diethyl ether (10 ml) was added dropwise to a suspension of lithium aluminium hydride (0.3g) in diethyl ether (5 ml). The mixture was stirred under reflux for 1 h. A saturated ammonium chloride solution was added, and the ethereal solution was filtered, dried and evaporated. The residue was sublimed at 65° and 0.5 mm Hg to give white needles, m.p. 84-86° (0.70g, 69%). (Found: C, 72.0; H, 7.1; N, 6.6. $C_{13}H_{15}NO_2$ requires C, 71.95; H, 6.9; N, 6.45%). λ_{max} 240 and 301 nm ($\log_{\varepsilon}$ 3.35 and 3,45), τ 3.00 br (2H, s, CH=CH), 3.43 (2H, s, ArH), 5.23 br (2H, s, bridgehead H), 6.21 (6H, s, 2xOCH_3), and 7.84 br (3H, s, NCH_3).

9-Ethoxycarbonyl-1,4-dihydro-1,4-imino-5,8-napthaquinone: (38)

(a) From the carbamate (37):

The carbamate (85 mg) and silver (II) oxide (500 mg) in dry dioxan (10 ml) were treated with 6N - nitric acid (1.2 ml) for 5 min. Chloroform (16 ml) and water (4 ml) were added and the organic layer was separated, washed with water, dried and evaporated. The resulting oil was chromatographed over silica gel with chloroform as eluant to afford semi-crystalline unstable quinone. ν_{max} 1718 and 1655 cm^{-1}, τ 2.88 (2H, s, CH=CH), 3.40 (2H, s, quinone H), 4.29 br (2H, s, bridgehead H), 5.89 (2H, q, OCH_2), and 8.77 (3H, t, CH_3).

(b) From 1-Amino-4,7-dihydroxybenzotriazole (27):

To a stirred solution of the triazole (0.327g) and N-ethoxycarbonylpyrrole (0.310g) in dry methylene chloride (40 ml) was added a suspension of lead tetraacetate (3.0g) in methylene chloride (20 ml). The mixture was stirred until nitrogen evolution ceased, filtered and the residue washed with methylene chloride. The filtrate was reduced and the residue chromatographed over silica gel with chloroform to afford a product identical with that in (a).

Ethyl 5,8-Diacetoxy-1,4-dihydro-1,4-iminonapthalene-9-carboxylate: (39)

The foregoing quinone (0.50g) was mixed with zinc dust (0.43g) in acetic anhydride (5 ml) and pyridine (1.7 ml). The mixture was heated on a steam bath and further additions of similar quantities of zinc were made after 10 and 15 min. The mixture was heated under reflux for 15 min, poured onto ice and extracted with ethyl acetate (5x15 ml). The extract was washed with saturated brine, dried and evaporated. The residue was chromatographed over silica with 10% ethyl acetate/benzene as eluant. The white crystalline product was recrystallised from methylene chloride/light petroleum; m.p. 107.5-108.5° (0.20g, 30%) (Found: C, 61.6; H, 4.8; N, 4.5. $C_{17}H_{17}NO_6$ requires C, 61.6; H, 5.15; N, 4.25%), ν_{max} 1755 and 1710 cm^{-1}, τ 2.92 br (2H, s, CH=CH), 3.29 (2H, s, ArH), 4.46 br (2H, s, bridgehead H), 5.92 (2H, q, $\underline{CH_2}CH_3$), 7.67 (6H, s, Ac) and 8.80 (3H, t, $CH_2\underline{CH_3}$).

9-Acetyl-1,4-dihydro-5,8-dimethoxy-1,4-iminonapthalene : (57)

The amine (48) (0.80g) in pyridine (3 ml) and acetic anhydride (8 ml) was heated on a steam bath for 30 min. The solution was thrown into a large excess of water and extracted with chloroform. The organic layer was dried and evaporated. The residue (0.95g, 98%) was recrystallised from ethyl acetate/light petroleum to give white needles, m.p. 115.5-116.5°. (Found: C, 68.4; H, 6.25; N, 5.9 $C_{14}H_{15}NO_3$ requires C, 68.6; H, 6.1; N, 5.7%) λ_{max} 259 and 306 nm ($\log_{\varepsilon}$ 3.33 and 3.54), ν_{max} 1717, 1631 and 1602 cm^{-1}, τ 2.98 (2H, m, CH=CH), 3.47 (2H, s, ArH), 3.91 and 4.26 (1H each, m, bridgehead H), 6.22 (6H, s, OCH_3) and 8.06 (3H, s, Ac).

9-Acetyl-1,4-dihydro-1,4-imino-5,8-napthaquinone: (58)

The foregoing diether (70 mg) and silver (II) oxide (0.145g) in dry dioxan (3 ml) were treated with 6N-nitric acid (0.25 ml). When the silver oxide was consumed, chloroform (16 ml) and water (4 ml) were added. The chloroform layer was washed with water, dried and evaporated. The residue (57 mg) was purified by preparative t.l.c. (5% ethanol/chloroform) to give a yellow oil (50 mg, 82%), τ 2.80 (2H, m, CH=CH), 3.37 (2H, s, quinone H), 4.00 and 4.25 (1H, each, m, bridgehead H) and 8.03 (3H, s, Ac).

5,8-Diacetoxy-9-acetyl-1,4-dihydro-1,4-iminonapthalene: (59)

The foregoing quinone (58) was reductively acetylated as described for the quinone (38). The reaction residue was sublimed at 75° and 0.2 mm Hg to give white crystals, m.p. 155-156°. (Found: C, 63.4; H, 5.1; N, 4.7 $C_{16}H_{15}NO_5$ requires C, 63.8; H, 5.1; N, 4.6%), ν_{max} ($CHCl_3$) 1760 and 1645 cm^{-1}, τ 2.90 (2H, m, CH=CH), 3.30 (2H, s, ArH), 4.16 br and 4.52 br (1H each, s, bridgehead H), 7.64 and 7.66 (3H each, s, OAc) and 8.03 (3H, s, NAc).

Isoindole-4,7-quinone: (12)

A solution of the quinone (58) (41 mg) and 3,6-di-(2-pyridyl)-*s*-tetrazine (45 mg) in [^{2}H]- chloroform (0.5 ml) was monitored by ^{1}H n.m.r. spectroscopy. Nitrogen evolution took place and pressure in the n.m.r. tube was periodically released. Signals due to starting materials had disappeared after 1.5 h. The solution was evaporated and the product purified by preparative t.l.c. (eluant benzene). The yellow band was collected and sublimed at 110° and 0.5 mm Hg to yield the product (20 mg, 71%), m.p. 180-181° (decomp). (Found: C, 65.4; H, 3.4; N, 9.3 M^+, 147.03212. $C_8H_5NO_2$ requires C, 65.3; H, 3.4; N, 9.5%; M, 147.03202), ν_{max} 3250, 1647 and 1582 cm^{-1}, $\tau[(CD_3)_2CO]$ 2.50 (2H, s, 1- and 3- H), 3.34 (2H, s, 5- amd 6- H) and 7.18 br (1H, s, NH, D_2O exchangeable).

6-Bromo-1,4-dihydro-5,8-dimethoxy-1,4-epoxynapthalene: (70)

Sodamide (5g) which had been rapidly ground under dry tetrahydrofuran (60 ml) was treated with furan (30 ml) in tetrahydrofuran (30 ml). 1,4-Dibromo-2,5-dimethoxybenzene (2.07g) was added dropwise in tetrahydrofuran (30 ml) and the solution was stirred at 65°C under nitrogen for 24 h. The solution was filtered and partitioned between water and ethyl acetate. The organic layer was dried and evaporated. The residue was recrystallised from methylene chloride/light petroleum to give the bromo-adduct (1.24g, 63%). A sample was sublimed at 75° and 0.6 mm Hg to yield white needles, m.p. 105°. (Found: C, 51.0; H, 3.8 $C_{12}H_{11}BrO_3$ requires C, 50.9; H, 3.9%), ν_{max} 1610 cm^{-1}, τ 3.03 br (2H, s, CH=CH), 3.32 (1H, s, 7- H), 4.19 br (1H, s, bridgehead H), 4.27 br (1H, s, bridgehead H), 6.21 (3H, s, OCH_3) and 6.26 (3H, s, OCH_3).

1,4,5,8-Tetrahydro-9,10-dimethoxy-1,4:5,8-diepoxyanthracene: (71)

Sodamide (11g) was rapidly ground as before under dimethoxyethane (dried over sodium hydride; 60 ml) and dry furan (50 ml) in dimethoxyethane (80 ml) was added. The bromo-adduct (70) (3.5g) in dimethoxyethane (40 ml) was added dropwise and the solution stirred under nitrogen under reflux for 60 h. The volume of the solution was held constant by additions of furan. The solution was filtered and evaporated to half its volume, then partitioned between ethyl acetate and water. The organic layer was dried and evaporated to yield the diadduct (1.88g, 57%), as needles, m.p. 203-223° (from ethanol) (mixture of *syn*- and *anti*- isomers shown by t.l.c. with methylene chloride as solvent). (Found: C, 70.8; H, 5.5 $C_{16}H_{14}O_4$ requires C, 71.1; H, 5.2%). τ 2.96 br (4H, s, CH=CH), 4.16 br (4H, s, bridgehead H) and 6.16 (6H, s, $2xOCH_3$).

1,4,5,8-Tetrahydro-9-hydroxy-10-methoxy-1,4:5,8-diepoxyanthracene: (76)

Ethanethiol (0.325g; 0.39 ml) in dry dimethylformamide (5 ml) and sodamide (0.16g of an 80% dispersion) were stirred under nitrogen for 5 min. The dimethyl ether (73) (0.512g) was added in dry dimethylformamide (5 ml) and the solution stirred under reflux for 4 h. Water (10 ml) was then added and the mixture extracted with diethyl ether (3x30ml). The organic layer was extracted with 5% aqueous sodium hydroxide (30ml). This was acidified with dilute hydrchloric acid and re-extracted with diethyl ether. The organic layer was dried and reduced to afford the demethylated species (0.213g, 44%) as pale yellow needles. τ 2.57 (1H, s, OH), 3.02 (4H, s, 2xCH=CH), 4.20 (4H, s, bridgehead H), 6.25 (3H, s, OCH_3).

2-Bromo-1,4-dimethoxy-5-(pyrrol-2-yl)benzene: (89)

(a) From N-ethoxycarbonylpyrrole (36):

1,4-Dibromo-2,5-dimethoxybenzene (1.6g) in dry tetrahydrofuran (40 ml) was added dropwise to a stirred mixture of finely ground sodamide (5g) and N-ethoxycarbonylpyrrole (3g) in more tetrahydrofuran (100 ml) at 65°C under nitrogen. After 20 h, the solution was filtered and partitioned between ethyl acetate and water. The organic layer was dried and evaporated and the brown residue chromatographed (eluant 15% ethyl acetate/light petroleum) to give white rosettes, m.p. 119° (from methylene chloride/light petroleum) (1g, 65%). (Found: C, 50.8; H, 4.15; N, 5.0 $C_{12}H_{12}BrNO_2$ requires C, 51.0; H, 4.25; N, 5.0%) ν_{max} 3440 cm^{-1}, τ 0.23 br (1H, s, NH; D_2O exchangeable), 2.84 and 2.88 (1H each, s, 3- and 6- H), 3.13 (1H, m, pyrrole5- H), 3.40 (1H, m, pyrrole3- H), 3.70 (1H, m, pyrrole4- H) and 6.12 (6H, s, $2xOCH_3$).

(b) From pyrrole:

Pyrrole was substituted for N-ethoxycarbonylpyrrole in procedure (a). Product (89), identical (m.p.; mixed m.p.; and n.m.r.) with that from (a), was obtained in similar yield.

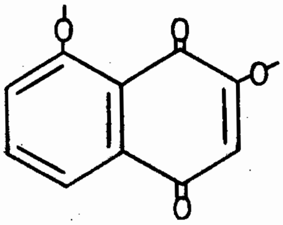
CHAPTER II

Regiospecific Addition of Methoxycyclohexa-1,3-dienes to Substituted 1,4-Benzoquinones

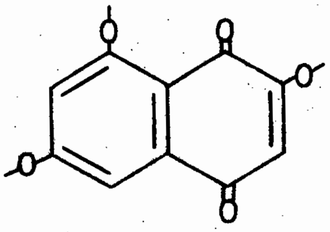
2.1 Introduction:

Quinones have in recent years become recognised as a major group of natural pigments. The number of natural quinones has multiplied rapidly and continues to increase. This fact is reflected in the increased activity in the literature with regard to their chemistry and syntheses. Of the five or six general classes of natural quinones, the napthaquinone nucleus and its varied derivatives provide many systems of chemical and synthetic interest. The occurrence of napthaquinones in nature is sporadic and ranges through the higher plant families and fungal sources to echinoderms. The occurrence, structure, chemistry, and certain syntheses of these have recently been reviewed[41]. This chapter deals with the investigation of some routes towards the syntheses of certain substituted napthaquinone nuclei which might be employed in the syntheses of some of the naturally occurring species.

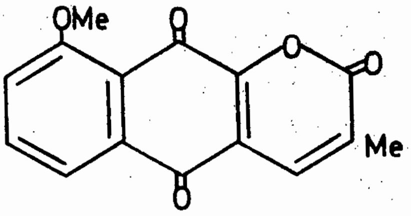
Several natural napthaquinones, with oxygenation patterns as represented by structures (90) and (91), are found. Over and above the simple derivatives which fall into these series, there is also an increasing group with an oxygen heterocycle fused to the quinonoid or benzenoid ring. The literature shows that the methods employed to arrive at nuclei of the type (90) and (91) can be tedious. Thomson, in synthesising compound (92)[42], required the quinone (93) which he had earlier prepared by his novel syntheses of substituted 2-hydroxynapthaquinones from the corresponding substituted α- or β- tetralones[43], e.g. (94) and (95). However, if the necessary tetralone is not readily available, the synthesis of (93) becomes lengthy. Similarly, Coombe[44] found that in the synthesis of the compound (96), the 5-methoxyderivative of a pigment obtained from Cyclindrocarpon, he required the napthaquinone (97), which had been prepared in 12 steps by Davies *et al*[45].



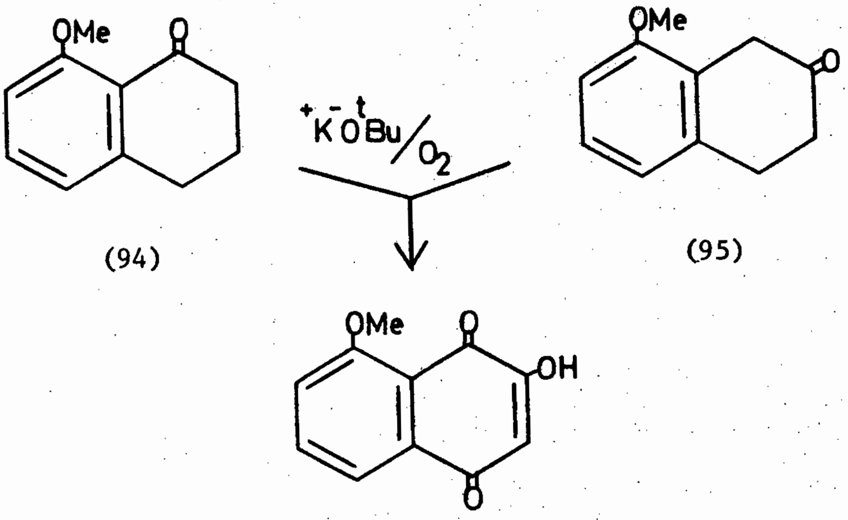
(90)



(91)



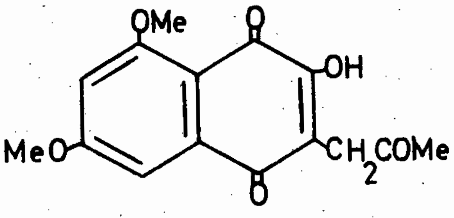
(92)



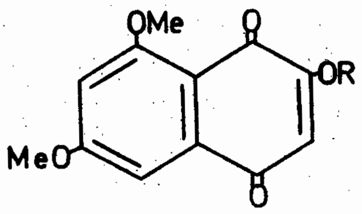
(94)

(95)

(93)



(96)



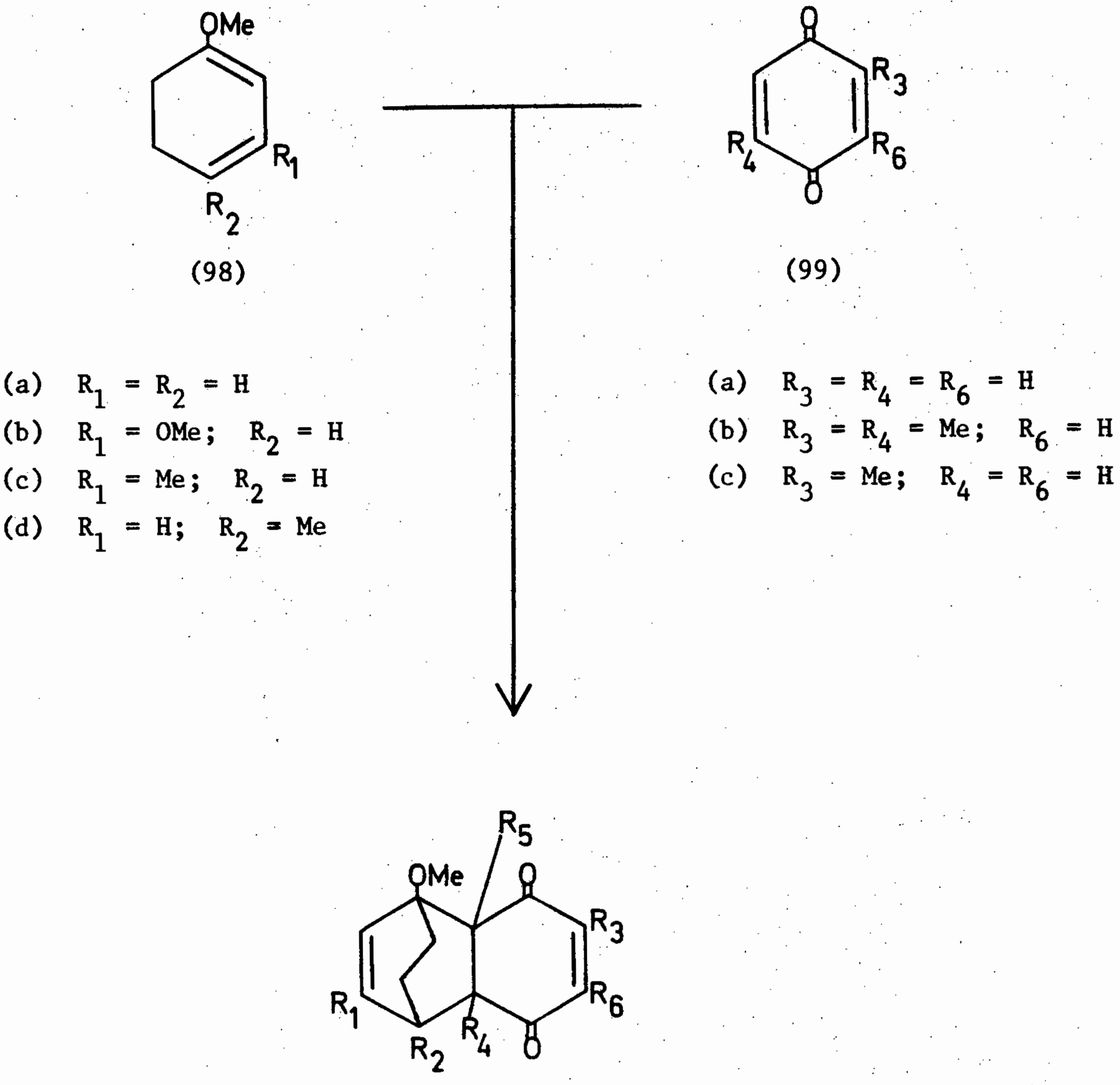
(97) (a) R = H
(b) R = Me

The initial aim of this work was to develop simple syntheses of nuclei of the types (90) and (91) by investigation of routes which involve the overall benzannelation of appropriately substituted 1,4-benzoquinones. It was then hoped to make use of these as synthetic intermediates in the preparation of some naturally occurring napthaquinones which incorporate the basic structures (90) and (91).

2.2 Syntheses of some 2,8-Oxygenated Napthaquinones:

In his work on the reactions of cyclohexadienes, Birch[46] has reported the formation of Diels-Alder adducts between 1-methoxycyclohexa-1,3-dienes and benzoquinones, and the subsequent conversion of some of these into the corresponding napthaquinones (Scheme 8).

Scheme (8)



(98)

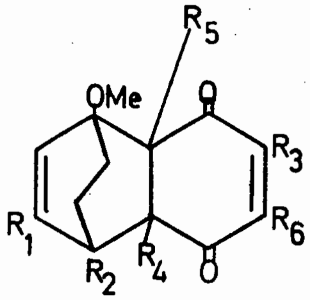
(a) $R_1 = R_2 = H$
(b) $R_1 = OMe; \quad R_2 = H$
(c) $R_1 = Me; \quad R_2 = H$
(d) $R_1 = H; \quad R_2 = Me$

(99)

(a) $R_3 = R_4 = R_6 = H$
(b) $R_3 = R_4 = Me; \quad R_6 = H$
(c) $R_3 = Me; \quad R_4 = R_6 = H$

(100) to (104) ..... see page 56

Scheme (8) contd.



(98) (a) + (99) (a) $\longrightarrow$ (100) $R_1 = R_2 = R_3 = R_4 = R_5 = R_6 = H$

(98) (b) + (99) (a) $\longrightarrow$ (101) $R_1 = OMe; R_2 = R_3 = R_4 = R_5 = R_6 = H$

(98) (d) + (99) (a) $\longrightarrow$ (102) $R_2 = Me; R_1 = R_3 = R_4 = R_5 = R_6 = H$

(98) (a) + (99) (b) $\longrightarrow$ (103) (a) $R_1 = R_2 = R_5 = R_6 = H; R_3 = R_4 = Me$

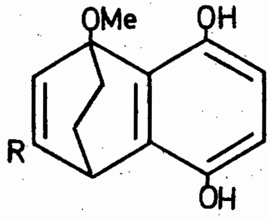
(b) $R_1 = R_2 = R_3 = R_4 = H; R_5 = R_6 = Me$

(98) (d) + (99) (c) $\longrightarrow$ (104) $R_2 = R_3 = Me; R_1 = R_4 = R_5 = R_6 = H$

(100) $\longrightarrow$ (105)

(101) $\longrightarrow$ (106)

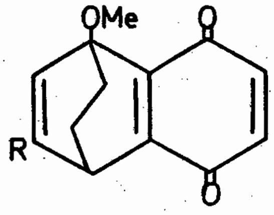
$\longrightarrow$



(105) R = H

(106) R = OMe

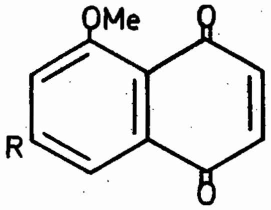
$\downarrow$



(107) R = H

(108) R = OMe

$\longleftarrow$

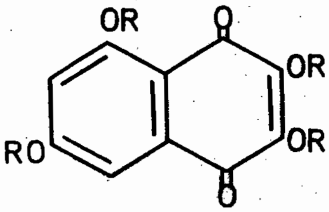


(109) R = H

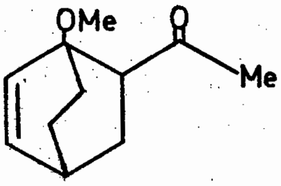
(110) R = OMe

The conversion of the adducts (100) and (101) into the hydroquinones (105) and (106) was readily accomplished with N - aqueous ammonia, and their subsequent oxidation to the quinones (107) and (108) with silver (I) oxide. The final formation of the napthaquinones (109) and (110), by the removal of the ethylene bridge, was achieved in good yields by pyrolysis. It was already known that ready thermal elimination of a bridge containing two carbon atoms across the 1,4- positions of a cyclohexa-2,5-diene, to generate an aromatic nucleus, would occur. These facile eliminations find their prototype in the reaction of dimethyl acetylenedicarboxylate with cyclohexa-1,3-dienes to yield, finally, an olefin corresponding to the released bridge, together with dimethyl phthalate[47].

The above procedure, in the cases where the nature of the reagents is such that only one adduct is specifically formed, and hence good yields of particular substituted napthaquinone nuclei are obtained, is one of great synthetic application. This is exemplified by the synthesis of the tetramethyl ether (111) of the napthaquinonoid phenol spinochrome - B (112)[48], the principal pigment of spines and tests of a number of echinoderms[49].



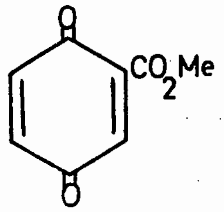
(111) R = Me
(112) R = H



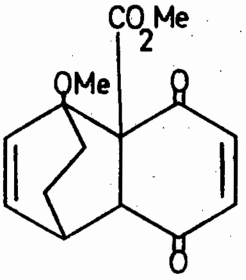
(113)

A drawback of the general method is the frequent production of mixtures of adducts when the quinone used in the Diels-Alder addition contains substituents which do not have the same spatial relationships with both carbonyl groups. The 1-methoxy group of the cyclohexa-1,3-diene results in completely specific orientation of addition using α, β - unsaturated ketones as addenda[49], e.g. 1-methoxycyclohexa-1,3-diene and but-3-ene-2-one give only the adduct (113) in high yield. Hence, if one of the α, β - unsaturated carbonyl systems of a quinone can be appropriately activated, or the other deactivated, similar specific addition could be expected.

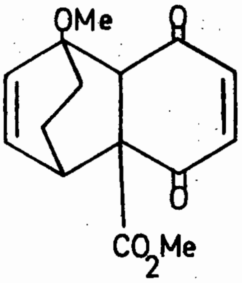
Birch and Powell[48] have demonstrated this directive effect in adduct formation with the reaction of quinone (114) with diene (98a). Here, one α, β - unsaturated carbonyl system is made more electron deficient by the carbomethoxy substituent, and gave rise to adduct (115) in good yield and no trace of the alternative structure (116). Although potentially solving the orientation problem, this process was not attractive unless efficient methods were found for the removal or suitable replacement of the ester substituent. Alternatively[48], the use of the hydrogen-bonding from a *peri* -hydroxyl group of an hydroxynapthaquinone has been shown to provide effective polarisation which imparts specific orientation to the addition. Hence juglone (117), when reacted with the diene (98a), gave solely the adduct (118), quantitatively. It might then be expected that the quinone (119) would react in a similar manner. Other workers[50] have also investigated the factors controlling the relative orientation in adducts between various other unsymmetrical dienes and unsymmetrically substituted *para* -benzoquinones.



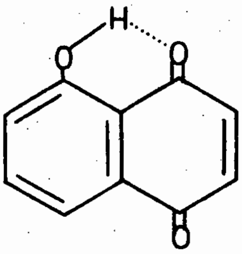
(114)



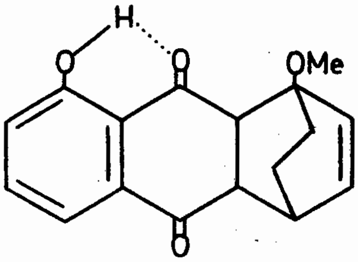
(115)



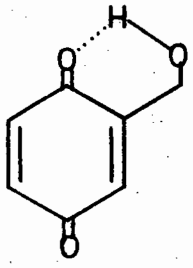
(116)



(117)

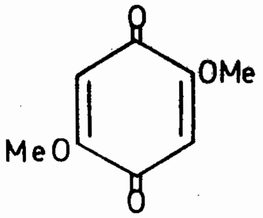


(118)

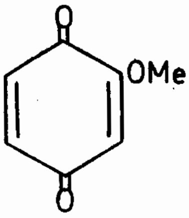


(119)

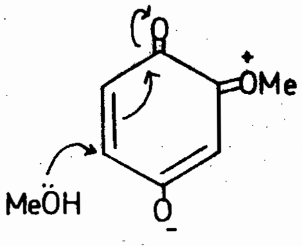
Nucleophilic attack on 1,4-benzoquinone (99a) leads in general to 2,5-disubstituted-1,4-benzoquinones[51]. For example, the action of methanol on benzoquinone, in the presence of zinc chloride, gives 2,5-dimethoxy-1,4-benzoquinone (120)[52]. This suggests that the methoxyl substituent in the intermediate 2-methoxybenzoquinone (121) directs the second methanol molecule to attack at a position *para* to it on the quinone nucleus. This is understandable in terms of the charged contributor (122), since attack at position 6 is not favoured by conjugation effects, whereas attack at position 5 is.



(120)

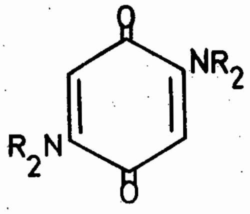


(121)

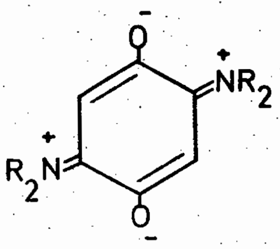


(122)

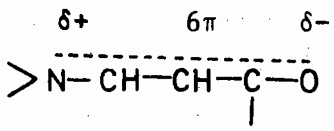
That these charged species are real contributors has been demonstrated in the case of 2,5-diaminated quinones; for example, structure (123), which is a resonance hybrid of the can onical forms (123) and (124). The extent of contribution of the quadrupolar form (124) in the ground state has been the subject of several papers. Dähne *et al*[53] have assumed the molecule to consist of two trimethine merocyanine structural units (125) which are coupled by the C_1-C_2 and C_4-C_5 bonds in the resulting quinone (126). Included in their evidence for this hypothesis are X-ray structural analyses which indicated that the C_1-C_2 and C_4-C_5 bond lengths were longer than those for the C_1-C_6 and C_3-C_4 bonds; also, the C-N bond length was shorter than that expected for C-N single bonds.



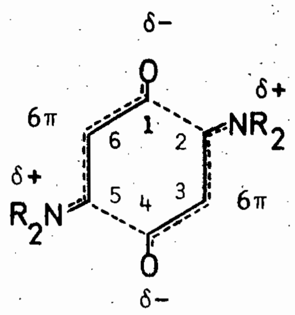
(123)



(124)



(125)

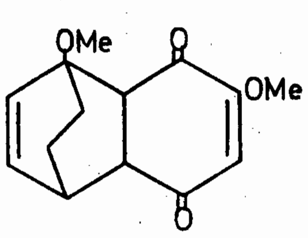


(126)

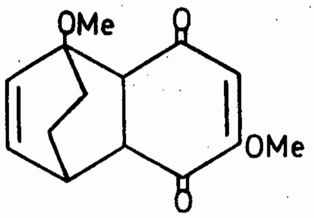
Diels-Alder addition of methoxycyclohexa-1,3-diene (98a)[†] to quinone (121) could formally take place to give either of the two adducts (127) or (128). However, that structure (127) should be preferred might be expected on inspection of (129), a resonance contributor to diene (98a). This stems from the fact that (127) requires a transition state in which the more nucleophilic C_4 end of the diene approaches the site on the dienophile more favourable to nucleophilic attack. When, quinone (121)[54] and diene (98a) were heated under reflux in benzene, only one adduct was isolated (60%)[‡].

[†] The range of dienes used in addition reactions in this chapter was readily obtained from the corresponding aromatic species by the method of Birch *et al*[46(a), 55].

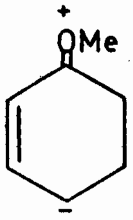
[‡] In the addition of (98a) to 1,4-benzoquinone, the adduct yield was a little less that 60%[46(b)]. Thus, yields of isolated material in each reaction are comparable.



(127)



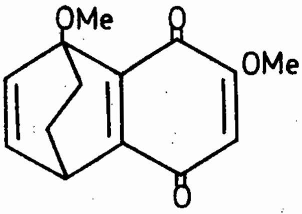
(128)



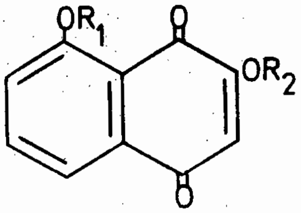
(129)

That the product was adduct (127) and not (128) was proved by its conversion into the known[56] 2,8-diacetoxy-1,4-napthaquinone (134), which can be distinguished[56] from the isomeric 2,5-diacetoxy compound (135). The dimethoxy napthaquinone (131) was formed in a manner similar to that outlined in Scheme (8). In this instance, the enolisation was carried out with potassium *t* - butoxide in dry tetrahydrofuran. Immediate oxidation to the bridged quinone (130) and subsequent elimination of the bridge, employing the methods outlined earlier, afforded the quinone (131) almost quantitatively. The quinonoid methoxyl of this compound was hydrolysed by treatment with aqueous base to afford quinone (132). Removal of the aromatic methoxyl of product (132) was accomplished with boron tribromide[†] to yield the hydroxy juglone (133), which was readily acetylated with pyridine and acetic anhydride. The melting point (136°C) of the diacetate obtained showed it to be the required diacetoxy compound (134) (lit. m.p.[56] 137°C) rather that its isomer (135) (lit. m.p.[56] 152°C).

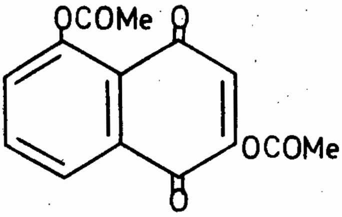
[†] See Chapter 1 page 21



(130)



(131) $R_1 = R_2 = Me$
(132) $R_1 = Me; R_2 = H$
(133) $R_1 = R_2 = H$
(134) $R_1 = R_2 = COCH_3$

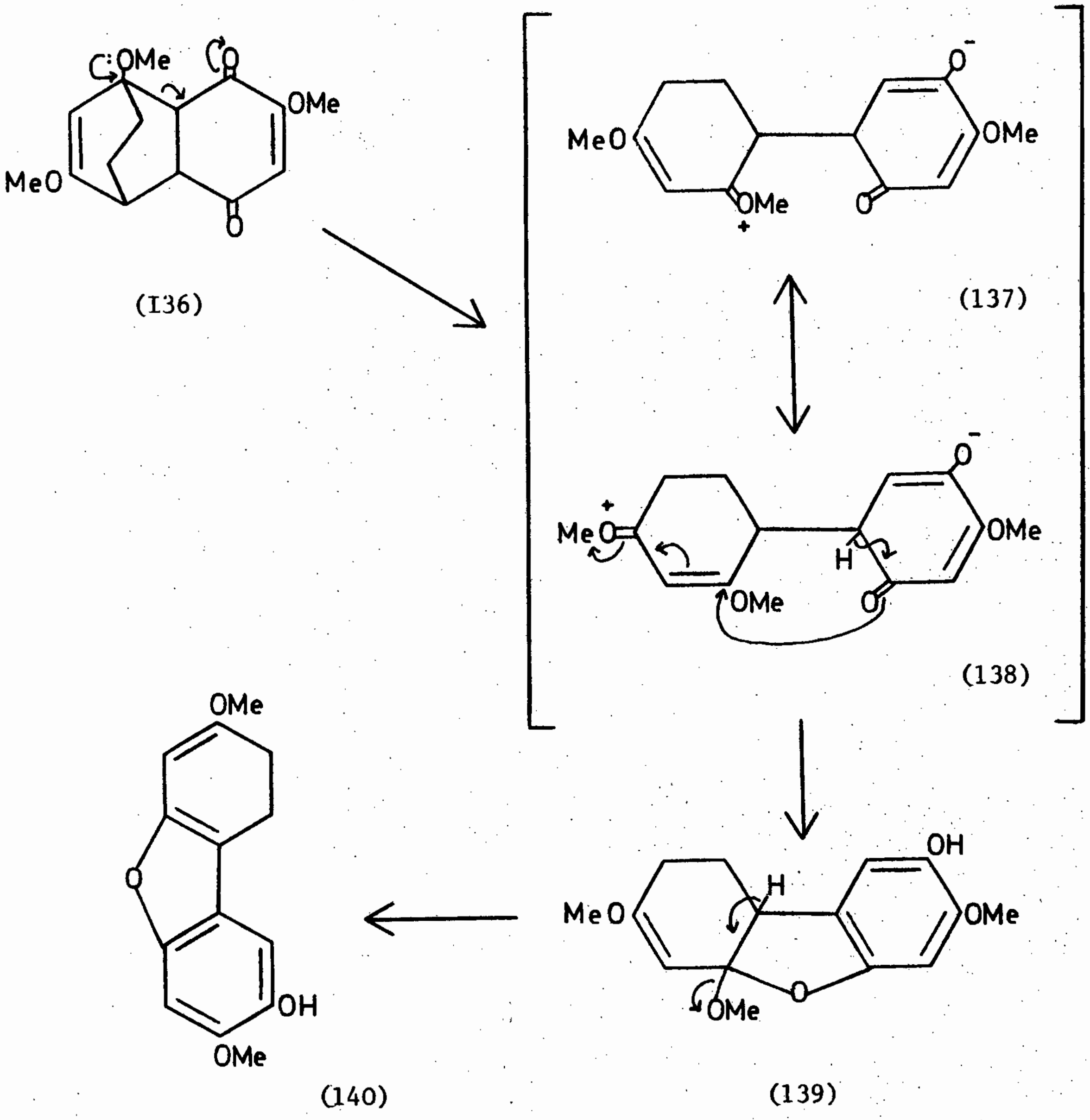


(135)

2.3 Attempts to synthesise 2,6,8-Trioxygenated Napthaquinones

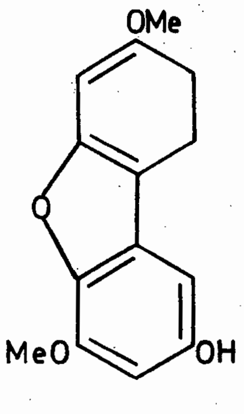
Analogous to the formation of adduct (127), the addition reaction between 1,3-dimethoxycyclohexa-1,3-diene (98b) and the methoxyquinone (121) was attempted. Instead of the desired adduct (136), this reaction afforded a white crystalline product which was characterised as the dihydrodibenzofuran (140).

Scheme (9)

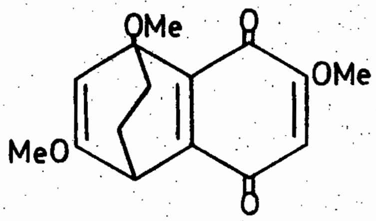


Two routes to the formation of the furan (140) can be envisaged. The first, as depicted in Scheme (9), is via the initially formed adduct (136), which could rearrange by a mechanism put forward by Birch[46(b)] to explain similar results that he obtained with related Diels-Alder adducts. He found that compounds (100) and (101) yielded corresponding furan structures under mildly acidic conditions.

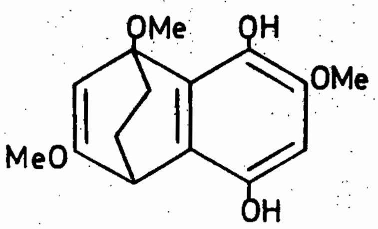
The proposed mechanism was shown to be dependant on the bridgehead methoxyl group in the adduct, since the rearrangement does not occur in the absence of this substituent. Further, it appears that the presence of two methoxy groups on the bridged ring in adduct (101) promoted the rearrangement over that of adduct (100), in which only one methoxyl was present. Other workers[57] have observed that the adduct (101) underwent rearrangement even on standing in deuteriochloroform.



(141)



(142)

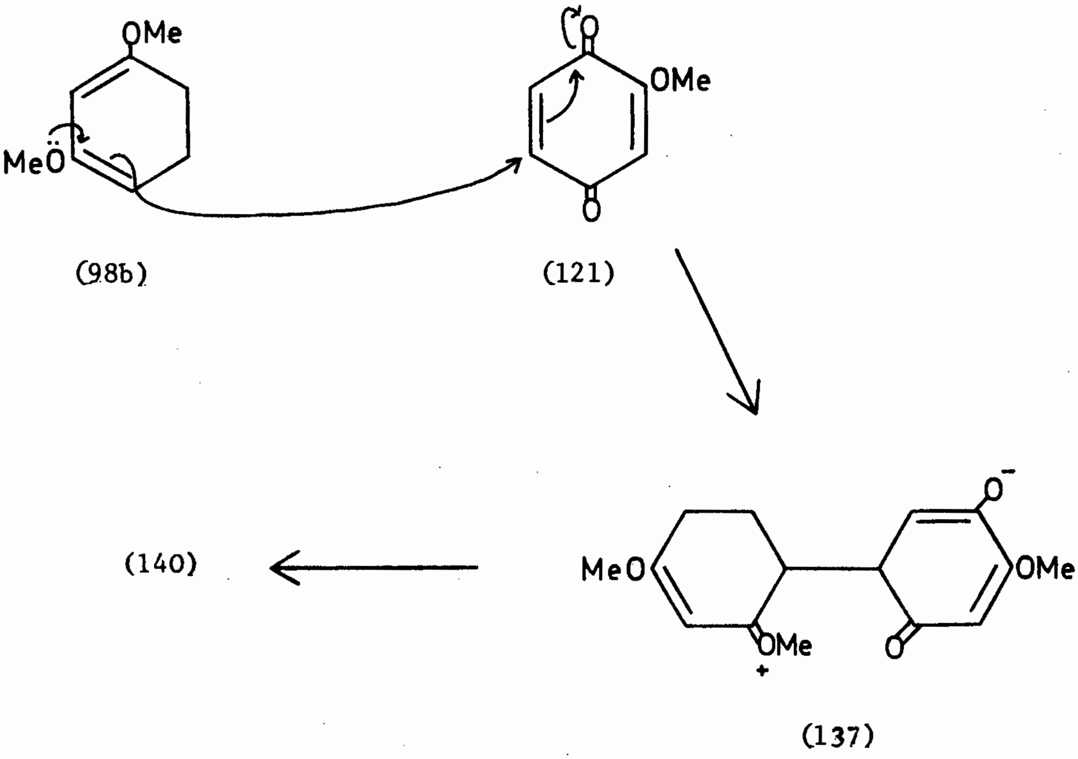


(143)

The ^{1}H n.m.r. spectrum of the white product included two three-proton methoxyl signals at τ 6.11 and 6.32 and two aromatic singlets at τ 3.07 and 3.18; the latter indicating a *para*-orientation of these aromatic protons to each other. Hence, if the route depicted in Scheme (9) to the dihydrobenzofuran structure operated in our case, the formation of the required adduct (136) could be inferred. Thus regiospecific addition would have occurred, since none of the alternative isomer (141) was detected.

The alternative route which could afford the product (140) is that outlined in Scheme (10). This envisages nucleophilic attack by the diene (98b) on C$_5$ of the quinone (121) and subsequent rearrangement to structure (140). This mechanism could not be excluded, since we failed to isolate the postulated adduct (136).

Scheme (10)

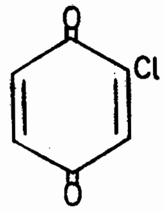


A variety of conditions was employed in attempts to prevent the rearrangement from occurring and so to allow the isolation of adduct (136) or the corresponding quinone (142). Additions performed at 0°C and at ambient temperature (20°C) were found to proceed at reduced rates, but again yielded the rearranged product exclusively. Further reactions were carried out in the presence of a base (e.g. potassium *t* - butoxide, 1 N ammonium hydroxide, sodium carbonate) in an effort to effect enolisation to the corresponding hydroquinone (143) before rearrangement could take place. Oxidation with silver (I) oxide of the residues of these reactions did not,however, afford quinone (142), but gave instead intractable gums.

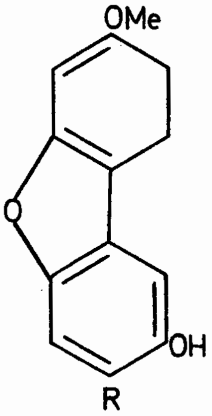
For comparison purposes, the reaction between the dimethoxy diene (98b) and benzoquinone, as described by Birch, was repeated, and no difficulty was experienced in isolating his adduct (101). This confirmed that the methoxyl substituent on benzoquinone (121) altered either the reaction mechanism, or the stability of the adduct (136). Quinonoid substituents other that methoxyl were therefore sought and reaction was attempted between the chloroquinone (144) and the diene (98b). This again gave rise to the rearranged product (145) exclusively. Once again, the presence of two aromatic singlets in the ^{1}H n.m.r. spectrum excluded the possibility of the isomeric compound (146). A similar result was obtained when 2-methylbenzoquinone (99c) was treated with the diene (98b) under the same conditions, and ^{1}H n.m.r. spectroscopy indicated structure (148) and not (146). Thus chlorine and methyl are similar to methoxyl in influencing a change in the nature of the observed product.

The addition reaction between 1-methoxy-3-methylcyclohexa-1,3-diene (98c) and 2-methoxybenzoquinone (121), however, afforded the stable adduct (149) as the sole product. This was converted to the napthaquinone

(151) via the bridged species (150) as described earlier for the quinone (131). Boron trichloride demethylation afforded 3-methoxy-7-methyljuglone (152), identical with an authentic sample[58, 59].

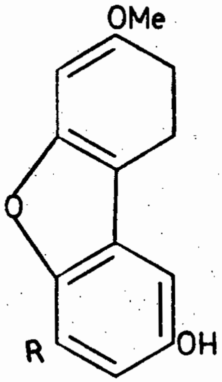


(144)



(145) R = Cl

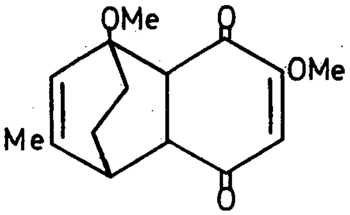
(147) R = Me



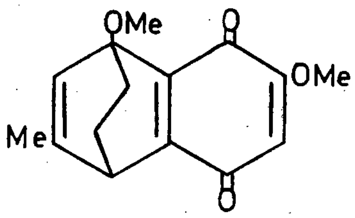
(146) R = Cl

(148) R = Me

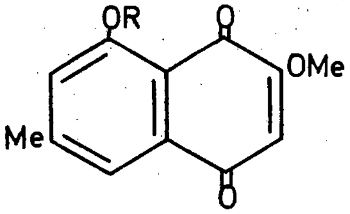
This reaction was of dual interest. Firstly, a methoxyl rather than hydrogen or methyl at C_3 on the diene (98) is necessary to alter the course of the reaction. This observation does not, however, permit distinction between the two mechanisms proposed for the formation of the dihydrobenzofurans (140), (145) and (147), since it can be argued that the presence of the additional methoxyl favours each.



(149)



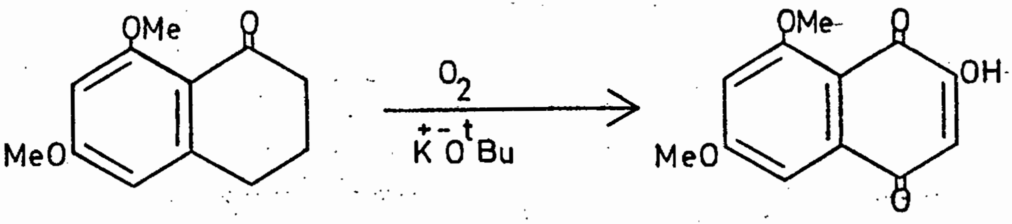
(150)



(151) R = Me
(152) R = H

Secondly, the napthaquinone (151) provided a potential route to the 3,5,7-trioxygenated species (91) with the conversion of the 7-methyl substituent into an oxygen function. This could possibly be achieved by its conversion into a hydroxymethyl function by bromination with N-bromosuccinimide (NBS) followed by replacement of bromine by hydroxyl; oxidation to the aldehyde and subsequent Baeyer-Villiger reaction could be expected to yield a workable oxygen function. However, since this extended the synthesis to a tedious length, comparable with that of Davies mentioned earlier, it was not explored.

While this work was being carried out, Coombe[60] published an improved synthesis in good yield of the required trioxygenated napthaquinone (97a) from the corresponding tetralone (153), analogous to that of Thomson mentioned earlier. Hence further attempts to accomplish this by our route were abandoned.

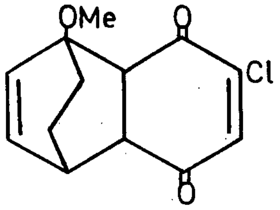


(153)

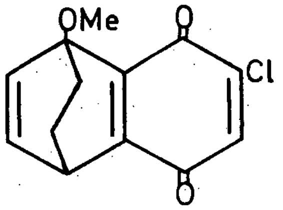
(97a)

2.4 Investigation of some further Addition Reactions:

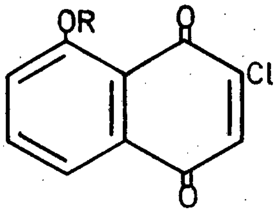
Since reaction of a 2-chlorobenzoquinone (144) with the dimethoxydiene (98b) gave the rearranged product (145) exclusively, it was of interest to investigate whether the chlorine substituent would direct addition of methoxycyclohexa-1,3-diene (98a) and lead to the regiospecifically formed adduct (154). This in turn might have provided the synthetically useful napthaquinone nucleus (156), with a readily modified chlorine substituent on the quinone ring. This reaction was carried out, but the sole product, adduct (154), was not isolated because of its instability. Instead, the crude product was converted by the usual sequence into the napthaquinone (156) via the bridged quinone (155). The orientation of the substituents in the final product was confirmed by demethylation with boron trichloride to afford the known 3-chlorojuglone (157) m.p. 166-167°C (lit.[61], 166°). 2-Chlorojuglone on the other hand has m.p. 112°C[62]. This napthaquinone has proved useful to us in other synthetic work described later.



(154)



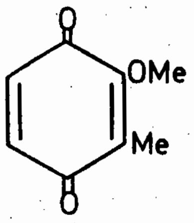
(155)



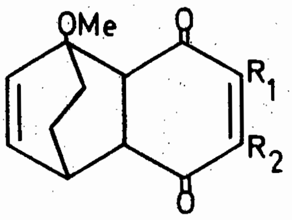
(156) R = Me

(157) R = H

The addition of diene (98a) to 2-methoxy-3-methyl-1,4-benzoquinone (158) would be of interest, as competition between the methoxyl and methyl substituents on the quinone might occur in determining which plays the dominant role in the favoured transition state leading to the Diels-Alder adduct. One might expect that the methoxyl should be more effective, giving rise to the adduct (159) in preference to its isomer (160). If this were the case, adduct (159) could be converted readily to the naturally occurring napthaquinone, droserone (168).

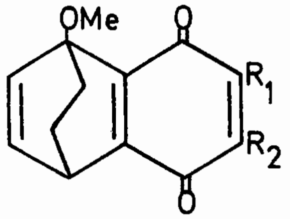


(158)

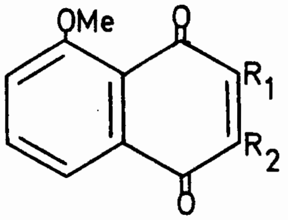


(159) R_1 = OMe; R_2 = Me
(160) R_1 = Me; R_2 = OMe

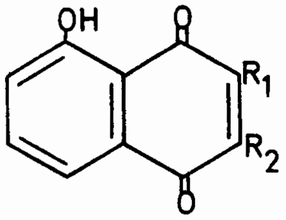
Addition of the diene (98a) to quinone (158) actually afforded a mixture of the adducts (159) and (160), as was suggested by the presence of two compounds with very similar R_f values on t.l.c. examination of the purified product. These proved difficult to separate and were converted as a mixture by enolisation and oxidation, as before, into the bridged quinones (161) and (162). Separation at that stage again proved difficult and, as a result, the mixture of bridged quinones was converted by pyrolysis into the corresponding napthaquinones (163) and (164)[†]. Removal of the *O* - methyls by boron tribromide treatment afforded the juglones (165) and (166).



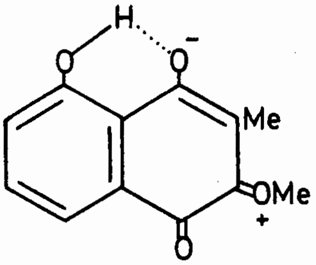
(161) R_1 = OMe; R_2 = Me
(162) R_1 = Me; R_2 = OMe



(163) R_1 = OMe; R_2 = Me
(164) R_1 = Me; R_2 = OMe



(165) R_1 = OMe; R_2 = Me
(166) R_1 = Me; R_2 = OMe



(167)

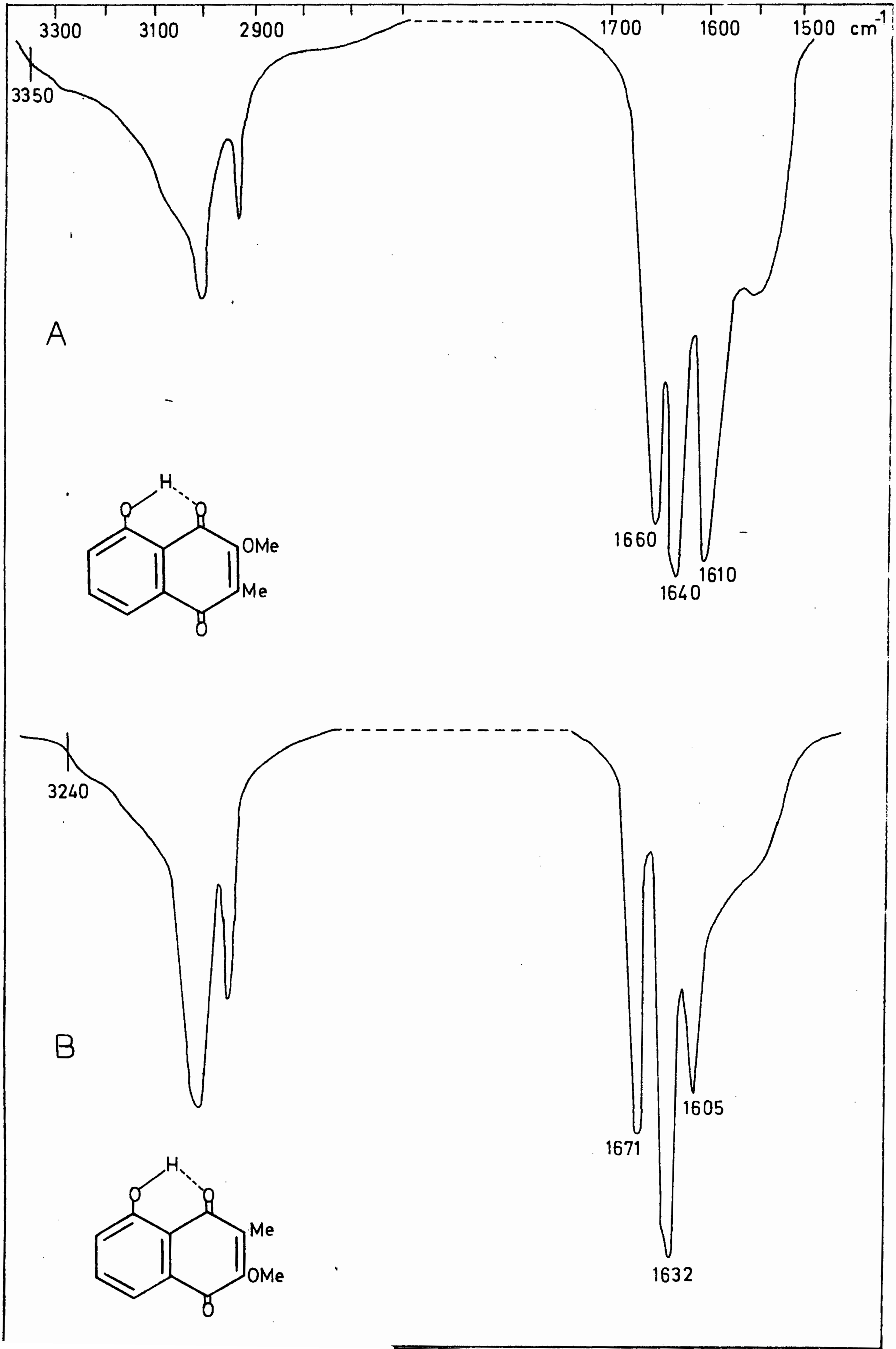
[†] Small quantities of the major component (161) were obtained in a pure form from the mixture of (161) and (162) by column chromatography, and this enabled full characterisation of the isomers (161) and (163). Microanalyses were also obtained and ^{1}H n.m.r. spectral data recorded for the mixtures of (161) and (162), and (163) and (164).

The mixture of compounds was most readily separated by chromatography as the juglones (165) and (166). These juglones were shown to occur in the approximate proportion of 4 : 1, which indicates the adduct (159) to be by far the major component of the initially formed mixture of adducts (159) and (160). Thus the reaction shows considerable regioselectivity, and, as might have been expected, the 2-methoxy substituent of quinone (158) overshadows the 3-methyl in directing the adduct formation.

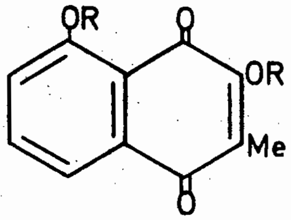
One might have expected that the minor component (166) of the juglone mixture would possess the more effective intramolecular hydrogen bond between the *peri*-hydroxyl and carbonyl groups through a resonance contribution from the canonical form (167). This manifests itself in compound (166) having a slightly higher R_f value which enables its separation from the isomeric compound (165). This difference in hydrogen bond strength is borne out by the H^1 n.m.r. and infrared spectra of compound (166). The former shows it to have a more strongly deshielded hydroxyl proton (τ -2.20) and *O* -methyl (τ 5.85) than does its isomer (165) (τ -1.74 and 5.90 respectively); Figure 3 shows that (166) has an absorption at a lower frequency for the hydrogen-bonded hydroxyl, at a higher frequency for the non-bonded carbonyl (1671 cm^{-1}), and at a lower frequency for the bonded carbonyl (1632 cm^{-1}) than has the lesser hydrogen-bonded isomer (165) (having respective carbonyl frequencies at 1660 and 1640 cm^{-1}).

Juglone (165) was converted into droserone (168) on its being stirred with dilute aqueous sodium hydroxide. Its m.p. 179-180°C, as well as that of its diacetate (169) 118.5-119°C, formed on treatment

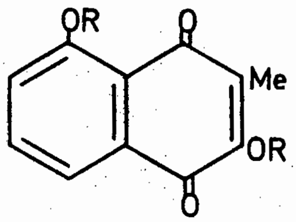
Figure 3


3300
3100
2900
1700
1600
1500
cm^{-1}
3350
A
H
O
O
OMe
Me
O
1660
1640
1610
3240
B
1671
1632
1605
H
O
O
Me
OMe
O

with acetic anhydride and pyridine, was found to be in accord with the literature^{63} values (181 and 119°C respectively). The isomer (170) and its diacetate (171), formed by similar treatment of the juglone (166), were easily distinguished by their melting points, 190-191°C (dec) (lit.^{63}, 189-190°C) and 157-159°C (lit.^{63}, 158-160°C) respectively.



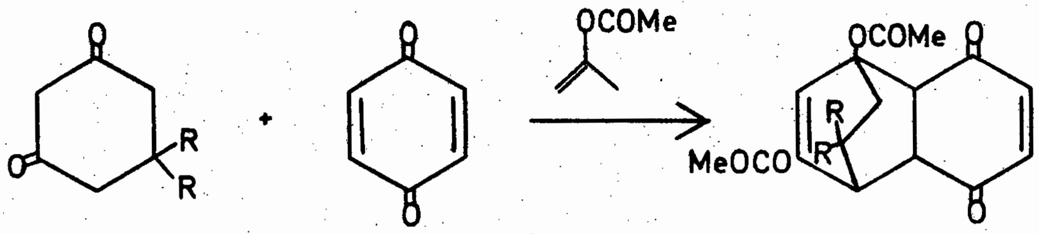
(168) R = H
(169) R = COMe



(170) R = H
(171) R = COMe

Recently, Wolinsky and Login^{57} have shown that cyclic acetoxy-1,3-dienes may be generated *in situ* from 1,3-cyclohexanediones or isophorone on heating in isopropenylacetate in the presence of a catalytic amount of *p* - toluenesulphonic acid (p - Ts). Further, these dienes undergo Diels-Alder reaction with 1,4-benzoquinone to afford 5,8-ethano-4a,5,8,8a-tetrahydro-1,4-napthaquinone derivatives as depicted in Scheme 11.

Scheme (11)

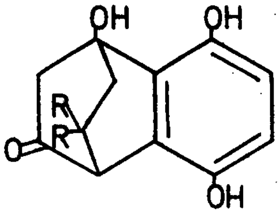


(172) R = Me
(173) R = H

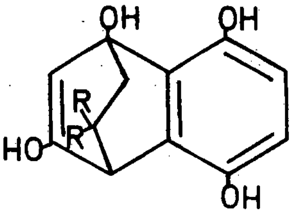
(99a)

(174) R = Me
(175) R = H

Acid or base treatment of adducts (174) and (175) resulted in aromatization to the ketoquinols (176) and (177), no doubt via the enol forms (178) and (179). In these cases, rearrangement to give benzofurans analogous to structure (140) does not compete favourably with aromatization since, unlike the methoxyl substituent, the bridgehead acetoxyl cannot support the positive charge which develops during the fragmentation reactions (viz: Scheme (9), intermediates (137) and (138)). It was of interest to us to investigate this route to structures of the type (174) and (175), employing appropriately substituted quinones, which might give rise to some synthetically useful intermediates.



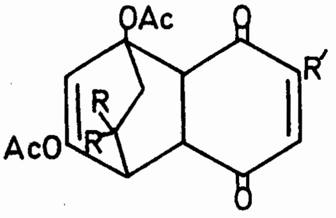
(176) R = Me
(177) R = H



(178) R = Me
(179) R = H

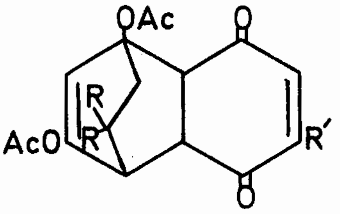
When methoxybenzoquinone (121) and dimedone (172) were heated under reflux in isopropenyl acetate in the presence of p - Ts, none of the proposed regiospecific adduct (180) or its isomer (181) was produced. Instead, workup yielded a dark resinous gum from which a small amount of the starting quinone was the only substance recovered.

However, similar reaction of chlorobenzoquinone (144) with dimedone afforded a dark oily residue which, after workup by column chromatography, yielded an off-white crystalline material. ^{1}H n.m.r. spectrometry and t.l.c. investigation of this product have shown it to be a mixture of the adducts (182) and (183). Calculations from ^{1}H n.m.r. spectra have shown the isomers to be present in the approximate ratio of 1 : 2 (overall 60% yield). Subsequent chromatography has allowed the collection of small amounts of the major isomer and separate characterisation thereof.



(180) R = Me; R' = OMe

(182) R = Me; R' = Cl



(181) R = Me; R' = OMe

(183) R = Me; R' = Cl

Ac = COMe

The substitution pattern of the adducts (182) and (183) was determined by the X-ray crystallographic analysis of the major component, which was subsequently shown to have structure (183) (viz: Figure (4)). When this was compared with the results obtained earlier for the reaction of methoxycyclohexa-1,3-dienes (98a) and (98b) with chlorobenzoquinone (144), which show regiospecific products (145) and (154) exclusively (if adduct formation takes place in the former case - as proposed on page 68), it appears that the change of diene substituents from methoxy to acetoxy leads to a loss of selectivity in the adduct formation.

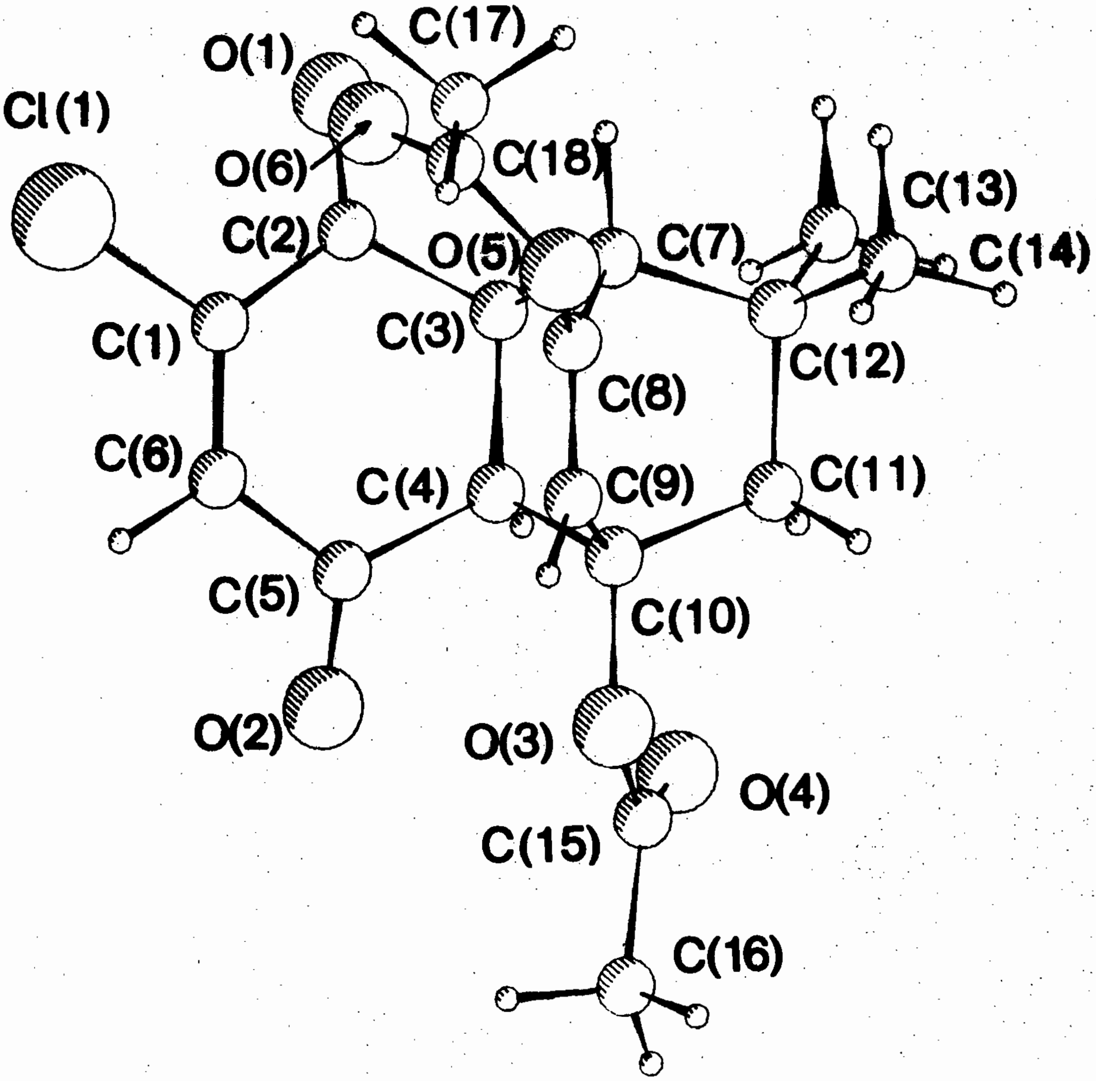
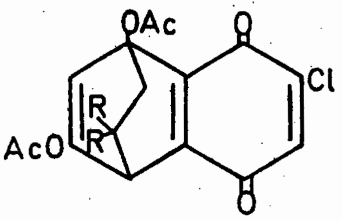
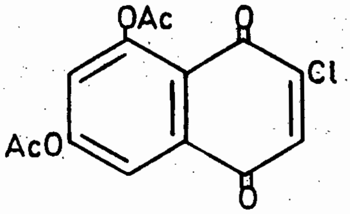


Figure 4

The molecular structure of compound (183) with atomic nomenclature. (Program "PLUTO", W.D.S. Motherwell, Cambridge).

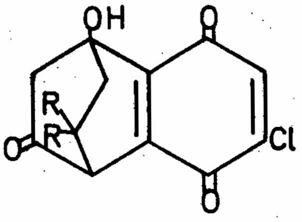


(184) R = Me

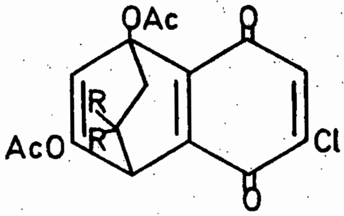


(185)

Ac = COMe



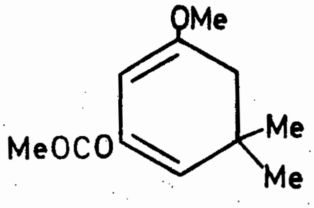
(186) R = Me



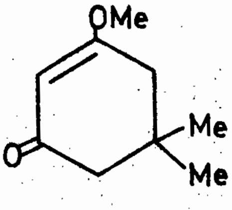
(187) R = Me

It was hoped that the isomer (182), on suitable treatment, might be converted via the bridged quinone (184) into the corresponding napthaquinone (185). This would provide a 2,6,8-trisubstituted napthaquinone which could be converted into the trioxygenated species (91) sought in Section 2.3, or could be used for further synthesis. However, several attempts at enolisation of the major adduct (183), followed by silver (I) oxide oxidation, afforded the ketoquinone (186) analogous to quinones (176) and (177) mentioned earlier. An unsuccessful attempt was made to generate quinone (187) from the ketoquinone (186) by heating the former under reflux in isopropenyl acetate in the presence of p - Ts. Further experiments could be performed on both the mixture (182) and (183), and compound (186) to see whether they can usefully be converted into the corresponding napthaquinones.

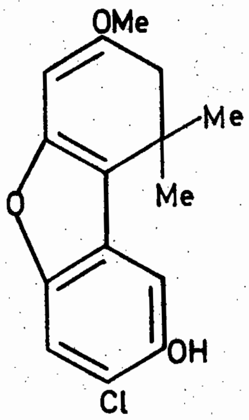
In an attempt to preclude the formation of mixtures such as (182) and (183), an alternative diene (188), generated *in situ* by analogous treatment of dimedone monomethylether (189), was reacted similarly with chlorobenzoquinone (144). Workup of the reaction mixture by chromatography, however, yielded only an off-white crystalline material whose H^1 n.m.r. indicated the rearranged product (190).



(188)



(189)



(190)

EXPERIMENTAL

Methoxycyclohexa-1,3-diene: (98a) 1,3-Dimethoxycyclohexa-1,3-diene: (98b) Methoxy-3-methylcyclohexa-1,3-diene: (98c)

The above dienes were prepared by the catalytic isomerisation of the corresponding 1,4-dienes, obtained by metal-ammonia reduction of the appropriate aromatic species as described by Birch *et al*[46(a)]. The isomerisation of the 1,4-dienes to give (98a) and (98c) was effected by heating under reflux in the presence of a catalytic amount of dichloromaleic anhydride[55(c)]; in the case of (98b) the interconversion was achieved by treatment with potassamide in liquid ammonia[46(d)]. These preparations gave the required 1,3-dienes as the major component of mixtures with the corresponding 1,4-isomers. ^{1}H n.m.r. spectroscopic measurements were used to determine the approximate ratios of the components in the mixtures.

Typical results obtained were as follows:

(98a) : isomer	4:1
(98b) : isomer	3:2
(98c) : isomer	4:1

2-Methoxy-1,4-benzoquinone: (121)

This was prepared in good yield (75%) from vanillin by the method of Jeffreys[54].

1,4,4a,8a-Tetrahydro-1,7-dimethoxy-1,4-ethanonapthalene-5,8-dione: (127)

The diene (98a) (6.4g) containing ca. 20% of the isomeric 1,4-diene, was heated under reflux in benzene (100 ml) containing the methoxy-1,4-benzoquinone (3g) for 1.5 h, at which stage t.l.c. showed that all the quinone was consumed. The solvent was evaporated and the residue chromatographed over a short dry column of neutral alumina with benzene as eluant, to give the product m.p. 117-119° (from benzene/light petroleum) (3.2g; 60% based on quinone). (Found: C, 67.7; H, 6.6 $C_{14}H_{16}O_4$ requires C, 67.8; H, 6.4%). ν_{max} 1691, 1650 and 1612 cm^{-1}, τ 3.83 (1H, d J 2Hz, 6 -H), 3.87 (1H, s, 7 -H), 4.12 (1H, s, 2 -H), 6.27 (3H, s, OCH_3), 6.55 (3H, s, OCH_3), 6.67 (1H, d J 8Hz, 4a -H), 6.88 (1H, m, 8 -H), 6.96 (1H, dd J 8 and 3Hz, 8a -H), and 7.9 - 8.5 (4H, m, CH_2CH_2).

1,4-Dihydro-1,7-dimethoxy-1,4-ethanonaptha-5,8-quinone: (130)

The foregoing adduct (1.0g) in dry tetrahydrofuran (40 ml) was stirred with an excess of potassium *t* - butoxide (1.2g) for 40 min. Water was added (10 ml), followed by dilute hydrochloric acid until weakly acidic. The solution was extracted with ether, dried (Na_2SO_4) and silver (I) oxide (3g) added. The reaction mixture was stirred for 3.5 h, filtered and evaporated to yield the orange quinone m.p. 118-118.5° (from benzene/light petroleum). (1.0g; 100%) (Found: C, 68.4; H, 5.9 $C_{14}H_{14}O_4$ requires C, 68.3; H, 5.7%), ν_{max} 1671, 1640 and 1579 cm^{-1}, τ 3.43 (1H, dd J 8 and 1Hz, 6 -H), 3.67 (1H, dd J 8 and 6Hz, 7 -H), 4.23 (1H, s, quinone H), 5.7(1H, m, bridgehead H), 6.19 (3H, s, OCH_3), 6.38 (3H, s, OCH_3) and 8.0-8.8 (4H, m, CH_2CH_2).

2,8-Dimethoxy-1,4-napthaquinone: (131)

The quinone (130) (0.31g) was heated at 120°/8 mm Hg under which conditions bubbling occurred as ethylene was eliminated. When bubbling ceased, sublimation at 140° (bath)/0.5 mm Hg afforded the light yellow product (0.27g, 98%) m.p. 202-202.5° (from methanol) (lit.,[64] 195°), (Found: C, 66.0; H, 4.6 $C_{12}H_{10}O_4$ requires C, 66.1; H, 4.6%),

ν_{max} 1674, 1642, 1612 and 1589 cm^{-1}, τ 2.2-2.5 (2H, m, 7- and 8-H), 2.75 (1H, dd J 2 and 7Hz, 6 -H), 3.93 (1H, s, quinonoid H), 6.00 (3H, s, OCH_3) and 6.12 (3H, s, OCH_3).

2-Hydroxy-8-methoxy-1,4-napthaquinone: (132)

Napthaquinone (131) (1.00g) was stirred with 1% aqueous sodium hydroxide (20 ml) until it had dissolved. The solution was washed with ether to remove any starting material and then acidified with dilute hydrochloric acid. This was extracted with chloroform, which was dried and evaporated to give the known[43, 65] quinone m.p. 209-211° (dec.) (lit.,[65] m.p. 211° (dec))(0.86g, 92%). τ 2.18-2.40 (2H, m, 7- and 8-H), 2.73 (1H, dd J 2 and 7Hz, 6 -H), 3.72 (1H, s, quinonoid H) and 5.95 (3H, s, OCH_3).

2,8-Diacetoxy-1,4-napthaquinone: (134)

The foregoing quinone (0.17g) in dry methylene chloride was stirred at -78° and treated dropwise with an excess of boron tribromide (1g) in the same solvent. The solution was allowed to warm to room temperature and then hydrolysed with water. The mixture was extracted with ether, then reextracted with aqueous potassium hydroxide. This aqueous layer was finally acidified and extracted with ether, which was dried and evaporated. The crude dihydroxyquinone (133) so formed (0.15g) was acetylated immediately (pyridine/acetic anhydride) to yield the diacetate, which was purified over a short column (ethyl acetate/chloroform 4:1). This gave pale yellow crystals, m.p. 136° (lit.[56] m.p. 137°) (0.09g, 42%). τ 1.95 (1H, d J 8Hz, 8 -H), 2.25 (1H, t J 8Hz, 7 -H), 2.63 (1H, d J 8Hz, 6H), 3.25 (1H, s, quinonoid H), 7.56 (3H, s, $COCH_3$) and 7.62 (3H, s, $COCH_3$).

8,9-Dihydro-2-hydroxy-3,7-dimethoxydibenzofuran: (140)

2-Methoxybenzoquinone (2g) and 1,3-dimethoxycyclohexa-1,3-diene (98b) (4g of a mixture containing about 33% of the alternative 1,4-isomer) were heated under reflux in benzene (50 ml) for 3 h. The solvent was evaporated and the product chromatographed over either an alumina or a silica column with benzene to give the white product (2.4g, 67%) m.p. 179-180^o (methylene chloride/light petroleum) (Found: C, 68.5; H, 5.8 $C_{14}H_{14}O_4$ requires C, 68.3; H, 5.7%), ν_{max} 3440 cm^{-1}, τ 3.07 and 3.18 (1H,each, s, 1- and 4-H), 4.51 br (2H, s, 6 -H and OH; the latter exhcanges with D_2O), 6.11 (3H, s, OCH_3). 6.31 (3H, s, OCH_3), and 7.0-7.6 (4H, m, CH_2CH_2). The same reaction was found to occur at room temperature and at 0^o.

8,9-Dihydro-3-chloro-2-hydroxy-7-methoxydibenzofuran: (145)

Chlorobenzoquinone (144) (1g) and diene (98b) (2g) were stirred together in benzene (50 ml) at room temperature for 20 min. The solvent was removed and the product chromatographed over a short column (10% ethyl acetate/light petroleum) to afford the white product (0.6g, 34%), m.p. 115-116^o (methylene chloride/light petroleum) (Found: C, 62.5 H, 4.7 $C_{13}H_{11}ClO_3$ requires C, 62.3; H, 4.4%), τ 2.72 (1H, s, 4 -H), 3.14 (1H, s, 1 -H), 4.54 (1H, s, OH, D_2O exchangeable), 4.64 (1H, s, 6 -H), 6.32 (3H, s, OCH_3), 7.0-7.6 (4H, m, CH_2CH_2).

8,9-Dihydro-3-methyl-2-hydroxy-7-methoxydibenzofuran: (147)

2-Methylbenzoquinone (1.00g) and diene (98b) (1.5g) were heated under reflux in benzene (60 ml) for 12 h. Workup as above by chromatography (eluant ethyl acetate) yielded an off-white crystalline material which was recrystallized from benzene/light petroleum. ^{1}H n.m.r. indicated the product which was hence not further characterised. A similar reaction carried out at room temperature over 48 h afforded the same material. τ 2.89 (1H, s, 4 -H), 3.30 (1H, s, 1 -H), 4.99 (1H, s, OH), 5.50 (1H, s, 6 -H), 6.29 (3H, s, OCH_3), 7.06-7.52 (4H, m, CH_2CH_2), 7.68 (3H, s, CCH_3).

4a,5,8,8a-Tetrahydro-3,5-dimethoxy-7-methyl-1,4-napthaquinone: (149)

Methoxybenzoquinone (121) (1.7g) and methoxy-3-methylcyclohexa-1,3-diene (98c) (2.9g) were heated under reflux in benzene (50 ml) for 4 h. The solvent was evaporated and the residue chromatographed over a silica column (eluant 30% ethyl acetate/light petroleum) to yield the adduct (2.6g, 81%), m.p. 111.5-112.5^o (benzene/light petroleum). (Found: C, 68.7; H, 6.8 $C_{15}H_{18}O_4$ requires C, 68.7; H, 6.9%) ν_{max} 1690, 1647 and 1610 cm^{-1}, τ 4.12 (1H, s, 2 -H), 4.26 br (1H, s, 6 -H), 6.27 (3H, s, OCH_3), 6.58 (3H, s, OCH_3), 6.70 (1H, d J 8Hz, 4a -H), 6.95 (1H, dd J 8 and 3Hz, 8a -H), 7.09 br (1H, s, 8 -H), 7.9-8.8 (4H, m, CH_2CH_2), 8.26 (3H, s, CCH_3).

5,8-Dihydro-3,5-dimethoxy-7-methyl-5,8-ethanonaptha-1,4-quinone: (150)

The foregoing adduct (149) (220 mg) was enolised as before with potassium t-butoxide (400 mg). Workup and oxidation in the usual way with silver (I) oxide (1g) afforded the product, which was chromatographed over a short silica column (eluant chloroform) to give the quinone (205 mg, 92%) m.p. 124-126^o (Found: C, 69.3; H, 6.3 $C_{15}H_{16}O_4$ requires C, 69.2; H, 6.1%), ν_{max} 1675, 1630 and 1584 cm^{-1}, τ 3.93 br (1H, s, 6 -H), 4.23 (1H, s, 2 -H), 5.96 br (1H, s, 8 -H), 6.18 (3H, s, OCH_3), 6.42

(3H, s, OCH_3), 7.95-8.8 (4H, m, CH_2CH_2), 8.10 (3H, s, CCH_3).

3,5-Dimethoxy-7-methyl-1,4-napthaquinone: (151)

The foregoing quinone (150) (200 mg) was aromatised as described earlier for compound (131) at a bath temperature of 80-110° and 10 mm Hg. Sublimation (135°/2 mm Hg) then afforded the product as yellow needles (164 mg, 92%) m.p. 174-176°. (Found: C, 66.9; H, 5.3 $C_{13}H_{12}O_4$ requires C, 67.2; H, 5.2%), ν_{max} 1678, 1655 and 1621 cm^{-1}, τ 2.47 (1H, s, 8 -H), 2.96 (1H, s, 6 -H), 3.96 (1H, s, 2 -H), 6.01 (3H, s, OCH_3), 6.13 (3H, s, OCH_3), 7.53 (3H, s, CCH_3).

3-Methoxy-5-hydroxy-7-methyl-1,4-napthaquinone: (152)

Quinone (151) (100 mg) in dry methylene chloride (6 ml) was treated with boron trichloride (100 mg) in the same solvent (6 ml) at -10°. The solution was stirred at that temperature for 30 min. and then allowed to warm to room temperature. The mixture was hydrolysed with water and extracted with methylene chloride. The organic layer was dried and evaporated to yield the product in an almost pure state. An analytical sample was prepared by chromatography over a short column (eluant 10% ethyl acetate/light petroleum), (87 mg, 92%) m.p. 209-210°. (lit.[58(a)] 209-210°) mixed m.p. undepressed by authentic sample. (Found: C, 66.2; H, 4.7 $C_{12}H_{10}O_4$ requires C, 66.1; H, 4.6%).

3-Chloro-5,8-dihydro-5-methoxy-5,8-ethanonapthaquinone: (155)

Chlorobenzoquinone (144) (5g) and an excess of the diene (98a) (7.5g) (containing about 30% of the isomeric 1,4-diene), were stirred in benzene (100 ml) at room temperature until all quinone had been consumed (as indicated by t.l.c.) (ca. 2h.). The solvent was evaporated and the residue dissolved in dry tetrahydrofuran (100 ml) to which an excess (8g) of potassium t-butoxide was added. The solution was stirred for 1h and then acidified and extracted as before. Oxidation of the organic layer with silver (I) oxide was carried out as before and the crude product chromatographed over silica (eluant 10% ethyl acetate/light petroleum) to give the orange quinone as an oil (2.58g, 30%) (Found: C, 62.1; H, 4.7 $C_{13}H_{11}ClO_3$ requires C, 62.3; H, 4.4%) ν_{max} (neat) 1678 and 1650 cm^{-1}. τ 3.14 (1H, s, quinonoid H), 3.41 (1H, dd J 8 and 1Hz, 6 -H), 3.69 (1H, dd J 8 and 6Hz, 7 -H), 5.7 (1H, m, bridgehead H), 6.37 (3H, s, OCH_3), 8.0-8.9 (4H, m, CH_2CH_2).

3-Chloro-5-methoxy-1,4-napthaquinone: (156)

The foregoing quinone was treated as described earlier for quinones (131) and (151). The product sublimed readily at 130°/1.5 mm Hg in quantitative yield, m.p. 159-160.5°. (Found: C, 59.5; H, 3.5 $C_{11}H_7ClO_3$ requires C, 59.35; H, 3.2%), ν_{max} ($CHCl_3$) 1680, 1668 and 1610 cm^{-1}, τ 2.3-2.9 (3H, m, 6-,7- and 8 -H), 2.90 (1H, s, quinonoid H), 6.00 (3H, s, OCH_3).

3-Chloro-5-hydroxy-1,4-napthaquinone: (157)

The quinone (156) (100 mg) in dry methylene chloride (10 ml) was treated at -78° with boron trichloride (48 mg, 1 mole equivalent) in the same solvent (10 ml). After workup, as described earlier for compound (60), the residue was chromatographed over a short silica column to afford the product (55 mg, 83% based on unrecovered starting material). A sample was sublimed at 100-105°/0.6 mm Hg, m.p. 166-167°; τ -1.77 (1H, s, OH), 2.1-2.9 (3H, m, 6-, 7-, and 8 -H), 2.83 (1H, s, quinonoid H). Further elution provided starting material (35 mg).

2-Methoxy-3-methyl-1,4-benzoquinone: (158)

2,6-Dimethoxytoluene (5.45g) in dry dimethylformamide (20 ml) was added at room temperature to a stirred solution of ethanethiol (7.1g) in the same solvent (100 ml) containing sodium hydride (4.2g of a 60% dispersion in oil). The solution was heated under reflux for 2 h, and then worked up according to the procedure of Mirrington[35] for the demethylation of anisoles, to give 3-methoxy-2-methylphenol (4.8g, 99%). This was oxidised to 2-methoxy-3-methyl-1,4-benzoquinone with Fremy's salt according to the literature[66].

5,8-Dihydro-3,5-dimethoxy-2-methyl-5,8-ethanonapthaquinone: (159)
5,8-Dihydro-2,5-dimethoxy-3-methyl-5,8-ethanonapthaquinone: (160)

The quinone (158) (1.85g) in benzene (150 ml) was treated with diene (98a) (4.2g) containing about 30% of the isomeric 1,4-diene. The solution was heated under reflux for 1.5 h, at which time t.l.c. indicated consumption of all the quinone. The solvent was evaporated and the pale orange residue chromatographed over a neutral alumina column. This was eluted with benzene to remove excess diene, and then with 20% ethyl acetate in benzene to afford the adduct mixture as an oil. This was dissolved in dry tetrahydrofuran (40 ml) and potassium *t* - butoxide (2.59g, an excess) was added. The mixture was stirred for 1 h, and then diluted with water (40 ml) and acidified with dilute hydrochloric acid. This was extracted with ether, the organic layer then washed with water, dried and treated with silver (I) oxide as described before (5g, an excess). The orange residue was chromatographed over a short silica column (eluant 5% ethyl acetate/benzene) to afford the quinone mixture (2.8g, 86% based on quinone (158)), as a partially crystalline orange oil. T.l.c. examination indicated two overlapping constituents. (Found: C, 69.2; H, 6.4 $C_{15}H_{16}O_4$ requires C, 69.2; H, 6.15%), ν_{max} (neat) 1665, 1645, 1615 and 1589 cm^{-1}, τ 3.44 (1H, dd J 8 and 1Hz, 6 -H), 3.67 (1H, dd J 8 and 6Hz, 7 -H), 5.7 (1H, m, bridgehead H), 6.01 (3H, s, OCH_3), 6.16 (3H, s, OCH_3), 8.08 (3H, s, CCH_3), 8.1-8.8 (4H, m, CH_2CH_2). Chromatography of a separate sample over a silica column with 5% ethyl acetate/light petroleum afforded fractions of the latter component which contained pure bridged quinone (161) with analytical and H^1 n.m.r. spectral data identical with the above.

3,5-Dimethoxy-2-methyl-1,4-napthaquinone: (163) 2,5-Dimethoxy-3-methyl-1,4-napthaquinone: (164)

The foregoing mixture (2.7g) was heated at 115° (bath)/8 mm Hg to eliminate the ethylene bridge as described earlier. When bubbling ceased, by which time the oil had solidified, sublimation at 140°/0.5 mm Hg afforded the light yellow napthaquinone mixture (2.23g, 94%). An analytical sample was prepared by p.l.c. (eluant 50% chloroform/light petroleum). (Found: C, 67.4; H, 5.1 $C_{13}H_{12}O_4$ requires C, 67.2; H, 5.2%), τ 2.22-2.52 (2H, m, 7- and 8 -H), 2.78 br (1H, d J 8Hz, 6 -H), 5.90 and 6.01 (major component) and 5.95 and 6.01 (minor component) (6H, all singlets, OCH_3), 7.94 (minor) and 7.97 (major) (3H, singlets, CCH_3).

3,5-Dimethoxy-2-methyl-1,4-napthaquinone: (163)

Prepared as above from the pure bridged quinone (161) as yellow crystals, m.p. 111-112°. (Found: C, 67.4; H, 5.2 $C_{13}H_{12}O_4$ requires C, 67.2; H, 5.2%), τ 2.28 (1H, dd J 8 and 2Hz, 8 -H), 2.41 (1H, t J 8Hz, 7 -H), 2.78 (1H, dd J 8 and 2Hz, 6 -H), 5.90 (3H, s, OCH_3), 6.01 (3H, s, OCH_3), 7.97 (3H, s, CCH_3).

5-Hydroxy-3-methoxy-2-methyl-1,4-napthaquinone: (165) 5-Hydroxy-2-methoxy-3-methyl-1,4-napthaquinone: (166)

The mixture of quinones (163) and (164) (100 mg) was stirred at -78° in methylene chloride (10 ml) and boron tribromide (140 mg, 1.2 mole equivalents) in methylene chloride (10 ml) , was added. After 10 min. the temperature was allowed to become ambient. The mixture was thrown into water, extracted with methylene chloride, and the organic layer dried and evaporated. The solid residue was chromatographed (p.l.c. eluant 5% ethyl acetate/light petroleum) to give, in the band of highest R_f. the quinone (166) as orange needles (15 mg, 16%) m.p. 127.5-128° (light petroleum). (Found: C, 66.1; H, 4.7 $C_{12}H_{10}O_4$ requires C, 66.1; H, 4.6%), ν_{max} see Figure (3), τ -2.20 (1H, s, OH), 2.16-2.90 (3H, m, 6-, 7-, and 8 -H), 5.85 (3H, s, OCH_3), 7.93 (3H, s, CCH_3). A second band afforded the quinone (165) as yellow needles (60 mg, 64%) m.p. 107.5-109° (light petroleum). (Found: C, 65.8; H, 4.7 $C_{12}H_{10}O_4$ requires C, 66.1; H, 4.6%) ν_{max} see Figure (3), τ -1.74 (1H, s, OH), 2.15-2.97 (3H, m, 6-, 7-, and 8 -H), 5.90 (3H, s, OCH_3), 7.92 (3H, s, CCH_3).

Droserone [3,5-Dihydroxy-2-methyl-1,4-napthaquinone]: (168)

The quinone (165) (80 mg) was stirred with aqueous sodium hydroxide (10 ml, 5%) until all starting material had dissolved. The solution was washed with ether, acidified with dilute hydrochloric acid, and extracted with chloroform. The organic layer was dried, evaporated, and chromatographed (p.l.c. eluant 10% ethyl acetate/light petroleum) to give droserone (75 mg) m.p. 179-180^o (methylene chloride/light petroleum) (Found: C, 65.0; H, 4.3 $C_{11}H_8O_4$ requires C, 64.7; H, 3.9%) ν_{max} ($CHCl_3$) 3445, 1650 and 1628 cm^{-1}, τ -1.08 (1H, s, bonded OH), 2.06-2.90 (3H, m, 6-, 7-, and -8H), 2.36 (1H, s, quinonoid OH), 7.90 (3H, s, CH_3). This was converted into its diacetate (169) (pyridine/acetic anhydride) m.p. 118.5-119^o. τ 1.94 (1H, d J 8Hz, 8 -H), 2.30 (1H, t J 8Hz, 7 -H), 2.65 (1H, d J 8Hz, 6H), 7.56 (3H, s, $COCH_3$), 7.60 (3H, s, $COCH_3$), 7.92 (3H, s, quinonoid CH_3).

2,5-Dihydroxy-3-methyl-1,4-napthaquinone: (170)

The quinone (166) (75 mg) was treated as for its isomer (165). Workup as before gave the quinone (170) (55 mg, 77%) m.p. 190-191^o (dec.), τ -2.39 (1H, s, bonded OH), 2.30-2.84 (4H, m, 6-, 7-, 8 -H, and quinonoid OH), 7.91 (3H, s, CH_3). This was converted to its diacetate (171), m.p. 157-159^o. τ 1.96 (1H, d J 8Hz, 8 -H), 2.32 (1H, t J 8Hz, 7 -H), 2.66 (1H, d J 8Hz, 6 -H), 7.55 (3H, s, $COCH_3$), 7.61 (3H, s, $COCH_3$), 7.95 (3H, s, quinonoid CH_3).

4a,5,8,8a-Tetrahydro-3-chloro-5,7-diacetoxy-5,8-ethanonapthalene-1,4-dione: (182) 4a,5,8,8a-Tetrahydro-2-chloro-5,7-diacetoxy-5,8-ethanonapthalene-1,4-dione: (183)

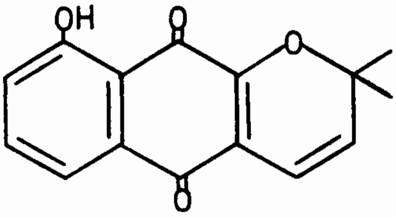
Chlorobenzoquinone (144) (1.0g) and dimedone (172) (1.2g) were heated under reflux in isopropenyl acetate (15 ml) in the presence of a catalytic amount of p - Ts (0.02g) until t.l.c. indicated consumption of quinone. (ca. 50 h.). The solvent was removed and the residue chromatographed over a short silica column (eluant 10% ethyl acetate/ light petroleum) to afford the mixture of adducts as an off-white powder. (1.7g, 66%). (Found: C, 58.70; H, 5.25 $C_{18}H_{19}ClO_6$ requires C, 58.94; H, 5.22%). Rechromatography (eluant as above) allowed fractions of the major compound to be collected separately. This same result was obtained in a later preparation by crystallisation from the reaction solvent on cooling after concentration of the reaction mixture. These afforded portions of the major adduct (183) as off-white prisms (methylene chloride/light petroleum), m.p. 181-183^{o} (Found: C, 58.70; H, 5.20 $C_{18}H_{19}ClO_6$ requires C, 58.94; H, 5.22%) ν_{max} 1774, 1740, 1695 and 1670 cm^{-1}, τ 3.07 (1H, s, 3 -H), 4.16 (1H, s, 6H), 6.00 (1H, d J = 10Hz, 4a -H), 6.48 (1H, dd J = 10 and 3Hz, 8a -H), 7.36 (1H, m, 8 -H), 7.55 and 8.52 (1H each, 2 doublets J = 12Hz, CH_2), 7.89 (6H, s, 2 x acetyl), 8.78 (3H, s, CH_3) and 8.98 (3H, s, CH_3).

CHAPTER III

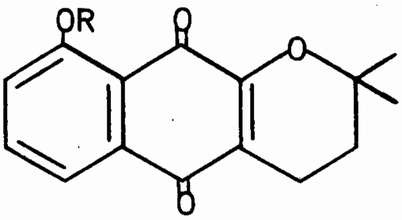
Syntheses of Some Selected Naturally Occurring Napthaquinones.

3.1 Introduction:

Several prenylated juglones have recently been discovered in Nature. These include α - caryopterone (191), isolated by Eugster *et al*[67] from *Caryopteris clandonensis* Bunge (Verbenaceae), dihydro - α - caryopterone (192) (9 - hydroxy - α - lapachone), and the latters methyl ether, *o* - methyldihydro - α - caryopterone (193), isolated by Inouye *et al*[68] from the wood of the *Catalpa ovata*. Quinone (192), prior to its isolation from a natural source, had been reported by Eugster[67] who had derived it from the catalytic reduction of α - caryopterone.



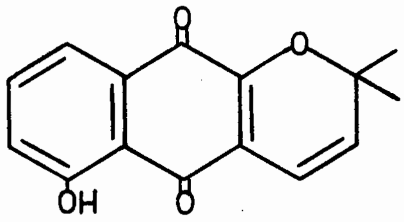
(191)



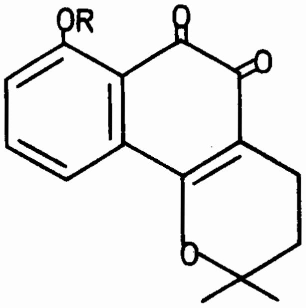
(192) R = H

(193) R = Me

This reduction had been employed to establish the structure of α - caryopterone as (191) and not as its isomer (194) with the hydroxyl in the alternative *peri* - position. This was shown by the rearrangement of compound (192) with concentrated acid, which afforded an orange *ortho* - quinone in which the aromatic hydroxyl was still hydrogen bonded. The hydroxyl in the *ortho* - quinone derived from compound (194) would not be hydrogen bonded. Methylation of the *ortho* - quinone gave a methyl ether (196) with spectra very similar to those of the known β - lapachone (197). This *ortho* - quinone obtained by the rearrangement of dihydro - α - caryopterone (192) was thus shown to have structure (195) (dihydro - β - caryopterone). Hence, the natural compound must possess structure (191) and its dihydro derivative structure (192); final structural confirmation by synthesis had not been carried out.

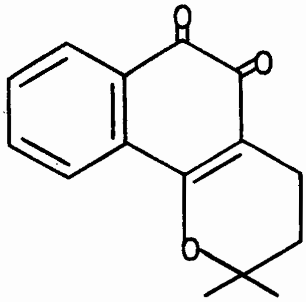


(194)



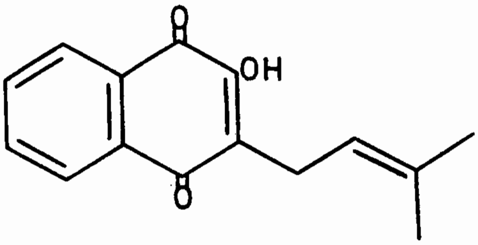
(195) R = H

(196) R = Me



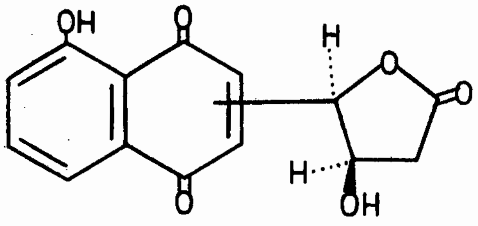
(197)

These natural products were of interest to us since they might be derived from the corresponding dioxygenated napthaquinone nucleus (90) by suitable quinone alkylation and subsequent ring closure. The appropriate hydroxy juglone (133) and its methyl ether (132) were readily available from the regiospecific reaction sequence described in Chapter II. Additional interest in these syntheses was stimulated by the fact that lapachol (198), the subject of a series of researches[69] culminating in the discovery of a new class of antimalarial agents[70], has aroused renewed interest as a consequence of its activity against the Walker carcinosarcoma 256 (intramuscular) and as a favourable preclinical toxicological evaluation[71]. Since the synthetic routes that were envisaged would involve intermediate structures similar to that of lapachol, it was thought that some may be worthy of further study along those lines.

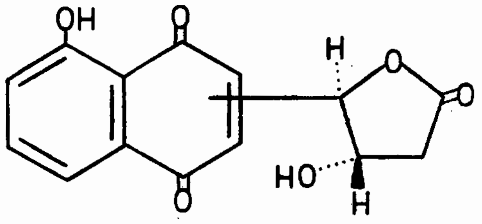


(198)

Recently, Japanese workers[72] have reported the isolation and characterisation of two new antibiotics, Juglomycins A and B, from the culture filtrate of Streptomyces sp. 190-2. From spectral and analytical data, the structures (199) and (200) have been assigned to the two isomers A and B.

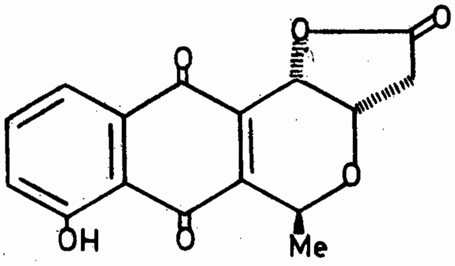


(199)

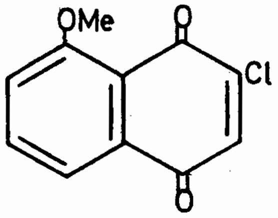


(200)

The stereoisomeric relationship between the two structures was supported by mass spectral fragmentation patterns and equilibration experiments. The naturally occurring compound Kalafungin[73] (201) has a structure similar to that of the Juglomycins and, based on biogenetic considerations, it has been proposed that the lactonic group in structures (199) and (200) may be attached to the 5-hydroxynapthaquinone nucleus at the 2 - position. Thus, the Juglomycins A and B were considered to be epimers at the γ - position of the lactone substituent. Because of the doubt that exists as to the exact structures (199) and (200), the syntheses of the Juglomycins were investigated. 2-Chloro-8-methoxynapthaquinone (156), whose synthesis was described in Chapter II, was proposed as the starting material.



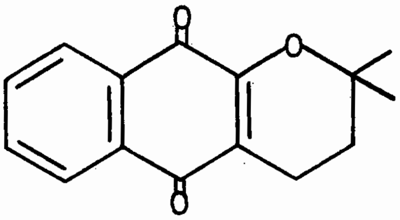
(201)



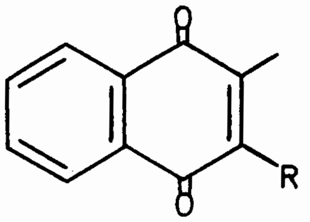
(156)

3.2 Syntheses of some Prenyl Juglones:

Numerous attempts have been made over the years to synthesise a wide variety of napthaquinones which were suitably alkylated on the quinone nucleus. Of these, lapachol (198) and related compounds such as α - lapachone (202) and β - lapachone (197), and the wide series of naturally occurring quinones known commonly as menaquinones (203), have received most attention. A major obstacle in these syntheses has been the development of suitable quinone C - alkylation methods.

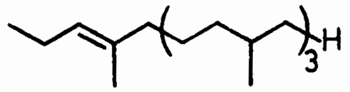


(202)



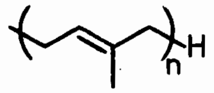
(203) (a) Phylloquinone

R =



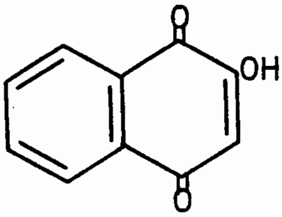
(b) (MK-n)

R =

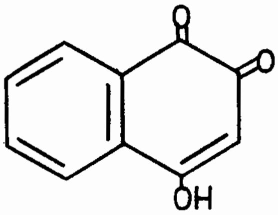


Our knowledge of the chemistry of lapachol and its family of compounds is largely the result of a long series of careful researches carried out by Hooker and his co-workers[74]. During these studies, various attempts to synthesise lapachol by suitable alkylation of 2-hydroxy-1,4-napthaquinone (lawsone) (204) were made. Lawsone is tautomeric with 4-hydroxy-1,2-napthaquinone (205), and ethers of both forms can be obtained by reaction of their silver salts with alkyl halides. The ambident anion can also react on carbon (C - 3) if an allyl or benzyl halide is used[75], and this was exploited by Fieser[76] in his synthesis of lapachol.

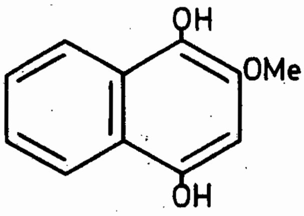
An improved yield is obtained by alkylation of 2-methoxy-1,4-dihydroxynapthalene (206) with 2-methylbut-3-en-2-ol in the presence of boron trifluoride, followed by oxidation with silver (I) oxide and then alkaline hydrolysis[77]. This latter alkylation procedure is similar to that which was earlier employed in the syntheses of menaquinones[78]. This route has the advantage of employing conditions which usually avoided side chain isomerisations and chromanol cyclisation and have also been optimised to avoid *o* - alkylation. However, as a method of alkylation it remains fundamentally limited by the inherent instability of the allylic alcohol component under the acid conditions employed[79]. As a result, low yields are normally obtained.



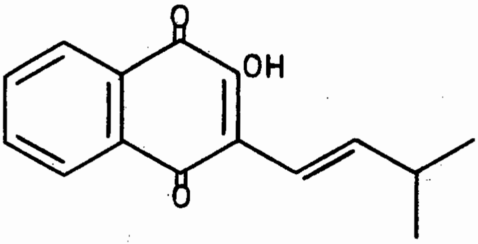
(204)



(205)



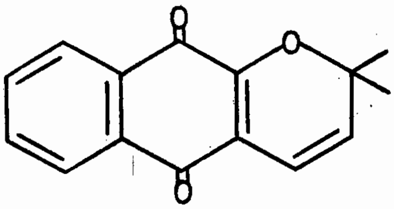
(206)



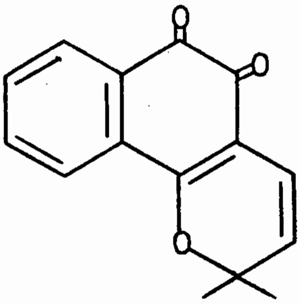
(207)

During his researches towards a synthesis of lapachol, Hooker[69] investigated, amongst others, the reaction of isovaleraldehyde with lawsone, and isolated a compound that was isomeric with lapachol viz: isolapachol (207). This reaction has since proved to be one of considerable generality, and so it presents a high yield method of napthaquinone C - alkylation adjacent to a hydroxyl function. However, since compound (207) was not interconvertible with the cyclic α - or β - lapachones (202) and (197) by the methods employed by a number of workers, because of the Δ^1 - position of the double bond in the side chain, this alkylation procedure did not constitute a route to lapachol (198). In view of the difficulties encountered in attempts to directly introduce the Δ^2 - isopentenyl side chain[76, 80], which might be caused to cyclise readily under acidic conditions, to continue with this alkylation procedure, as a route to structures of the lapachone type was futile.

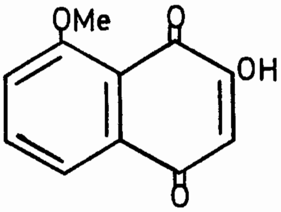
More recently, Dudley and Chiang[81] have reported a route for the deconjugation of isolapachol (207) into lapachol (198). This employs the cyclisation of the former compound, with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), to give the α - and β - dehydrolapachones (208) and (209). Birch reduction of compound (208) then yields a mixture of lapachol and isolapachol (approximately 3:2 ratio). This then provided us with a suitable ring closure which might be employed to synthesise α - caryopterone from the appropriate open chain structure.



(208)

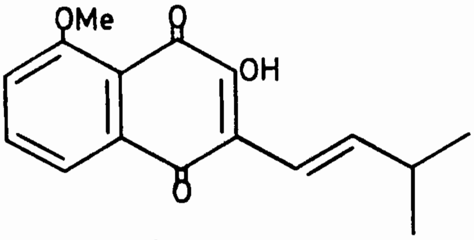


(209)

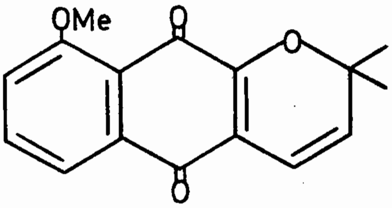


(132)

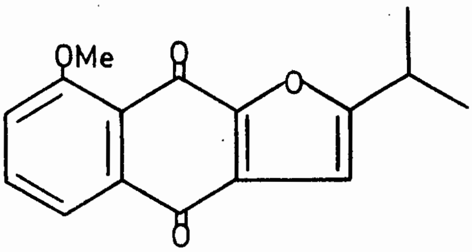
In our case, 2-hydroxy-8-methoxy-1,4-napthaquinone (132) was subjected to a Hooker alkylation with isovaleraldehyde in acetic acid. This afforded the required product (210) in good yield (86%).
This compound was readily oxidatively cyclised by stirring at room temperature with DDQ in benzene. Workup gave the chromene quinone (211) and the furan quinone (212) in yields of 47% and 8% respectively. In addition, analogous to the products isolated when isolapachol was similarly treated, a deep purple product thought to be the *ortho* - quinone (213) was obtained in 28% yield. This product was not characterised as the *ortho* - quinone (213) because of its ready conversion into quinone (211) on treatment with warm ethanol containing concentrated hydrochloric acid. This corresponds to the interconversion of α - and β - lapachone, in varied acidic media, as observed by earlier workers[82] and later related to the basicities of the two lapachones[83].



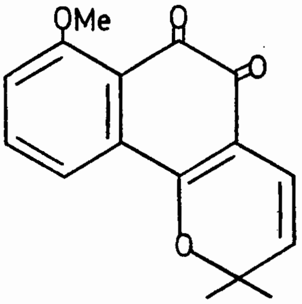
(210)



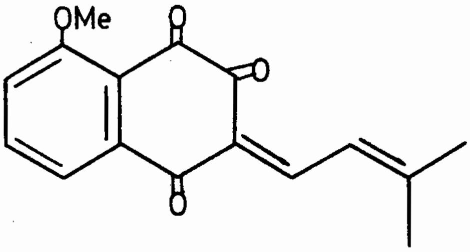
(211)



(212)



(213)



(214)

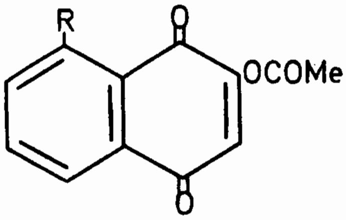
The formation of the compounds (211) and (213) can be rationalised in terms of cyclisation of the intermediate oxidation product (214)[81]. On the other hand, ring closure of compound (210), followed by oxidation, would afford the product (212). Analogous furan quinones have been described in connection with experiments on lapachol[82(b)].

When treated with boron tribromide in methylene chloride at low temperature, the quinone (211) underwent demethylation to yield α - caryopterone (191), identical with a sample of the natural product kindly provided by Professor Eugster.

Subsequent to the completion of the above work, a further, highly efficient quinone _C_ - alkylation procedure appeared in the literature[84]. This involves the use of radicals, generated by decarboxylation of carboxylic acids with silver ions and peroxodisulphate (Equations (1) and (2)), to alkylate the quinone nucleus. This reaction has been employed successfully in the syntheses of a number of naturally occurring quinones, including lapachol (198). In the case of lapachol (198), the reaction made possible the direct introduction of the Δ^2 - isopentenyl side chain, by the generation of the radical (215). This radical was derived when 4-methylpent-3-enoic acid was heated in an acetonitrile/water mixture in the presence of silver nitrate and ammonium peroxodisulphate. Lawsone acetate (217) was used as the quinone substrate.

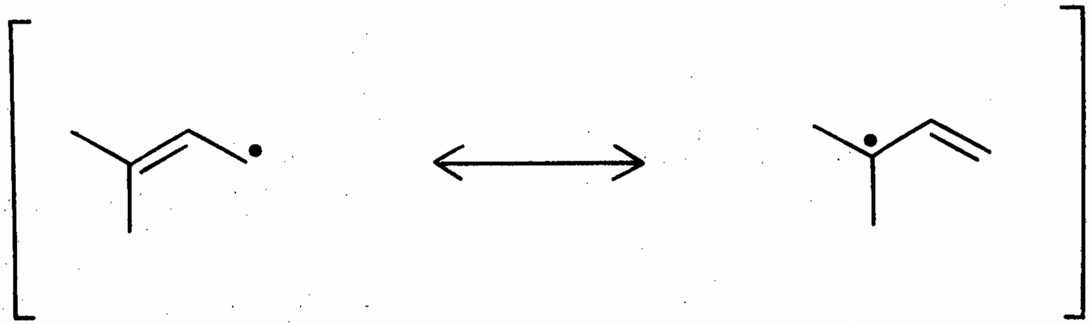
Equation (1) $Ag^{+} + S_2O_8^{2-} \longrightarrow Ag^{2+} + SO_4^{\cdot -} + SO_4^{2-}$

Equation (2) $Ag^{2+} + RCOOH \longrightarrow R^{\cdot} + CO_2 + H^{+} + Ag^{+}$



(217) R = H

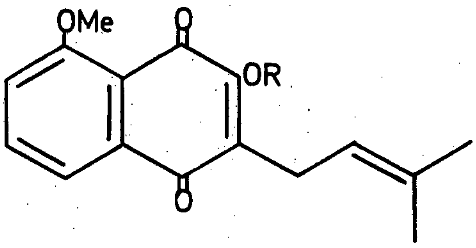
(218) R = OMe



(215) (216)

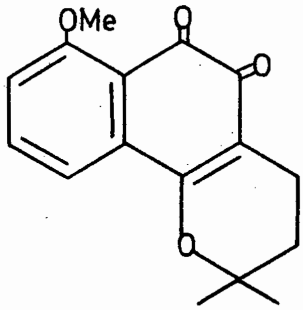
Features of the reaction, when γ, γ - dimethylallylquinones are being prepared, are the good yields and the selectivity of products formed. In principle, the quinone molecule could be attacked by the radicals (215) or (216), with either of the two carbon atoms bearing high spin density as shown. This would give rise to either an α, α - dimethylallyl- or a γ, γ - dimethylallylquinone. However, experience with various quinones has shown that only the latter is isolated. This selectivity holds true for various other acids which can form two possible radicals.

A route to the naturally occurring dihydro-α-caryopterone (192) and *o* - methyldihydro-α-caryopterone (193) was thus readily available from the quinone (132). As mentioned earlier, compound (192) had previously been reported as derived from the natural α - caryopterone, prior to its natural isolation. The application of the radical alkylation procedure required the quinone (132) to be modified to its acetate (218). This was easily achieved with acetic anhydride and sulphuric acid. Treatment of the acetate (218) with 4-methylpent-3-enoic acid, under the conditions used for alkylation, readily afforded the required prenylated product (219) in good yield (75%). Hydrolysis of this product with aqueous sodium carbonate gave the methoxylapachol (220), isomeric with the quinone (210) from the Hooker reaction.



(219) R = COMe

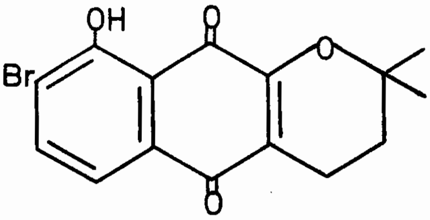
(220) R = H



(221)

Because of the Δ^2 - position of the exocyclic double bond, cyclisation of quinone (220) was carried out with a mixture of hydrochloric acid and acetic acid. These were the conditions that Hooker had employed to obtain the lapachones (197) and (202) from lapachol (198). As expected, this yielded a mixture of the α - and β - methoxylapachones, (193) and (221) respectively. These proved readily separable by column chromatography, and they could easily be distinguished by their different colours and infrared spectra. The former, (193), was identical with a sample of the naturally occurring 9-methoxy-α-lapachone[68]. The physical properties and spectral data of the latter, (221), corresponded to those reported for *o*-methyldihydro-β-caryopterone by Eugster[67]. This β - form was readily isomerised to the α - lapachone (193) with concentrated hydrochloric acid in ethanol. Interestingly, attempts to demethylate the methyl ether (193) with the Lewis acid boron trichloride, effected, presumably by acid catalysis, its reverse transformation into the β - form (221). However, reaction of the methyl ether (193) with boron tribromide in methylene chloride at room temperature, afforded dihydro-α-caryopterone (192), identical with a sample of the natural product. Both the above natural samples of compounds (193) and (192), were kindly provided by Professor Inouye.

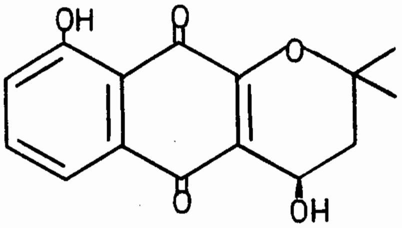
Under the more vigorous conditions of reflux with an excess of boron tribromide, compound (193) afforded a second product in addition to the required quinone (192). This darker-coloured material was characterised as having the structure (222), where the aromatic nucleus had undergone bromination. The position of bromination was indicated by the ^{1}H n.m.r. spectrum, which included two aromatic doublets at τ 2.16 and 2.53 with a coupling constant of 8Hz.



(222)

Burnett and Thomson[85] have reported that α - lapachone (202) can readily be converted to dehydro-α-lapachone (208) by the heating of the former under reflux in dioxan in the presence of DDQ. Similar treatment of 9-methoxy-α-lapachone (193) could then possibly afford *o*-methyl-α-caryopterone (211), and thus provide an alternative route to α - caryopterone (191). Extended treatment of quinone (193) under these conditions, however, returned starting material only. Interestingly, an alternative route to α - caryopterone did arise, since reaction of the methoxylapachol (220) with DDQ at room temperature in benzene afforded a mixture of quinones (211) and (213). These were separated by column chromatography and the β - form (213) was converted as before into compound (211) with the use of ethanolic hydrochloric acid. This oxidative cyclisation presumably proceeds via the same intermediate (214), thought to be involved in the earlier production of these quinones.

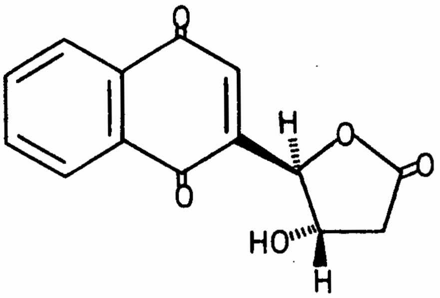
Inouye *et al*[68] have further reported the isolation of the quinone (223) from *Catalpa* wood along with five other napthaquinones including compounds (202) and (192). Since we had available α - caryopterone (191), as a reasonable precursor to compound (223), an attempt was made to produce this hydroxy-derivative. However, this proved unsuccessful and was set aside for the time being.



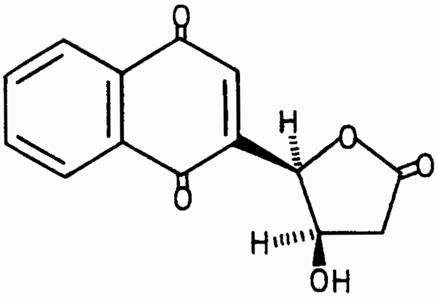
(223)

3.3 Models for the Syntheses of Juglomycins A and B:

As mentioned earlier, it was thought that synthetic routes to the Juglomycins A and B, (199) and (200), might employ a 2-chloro-8-methoxy-napthaquinone (156) as a starting material. Because of the relative complexity of the synthesis of this precursor (six steps from 1,4-benzoquinone), it was decided to prepare the models (224) and (225) to establish viable routes to the desired antibiotics.

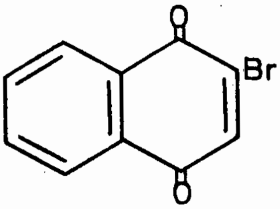


(224)

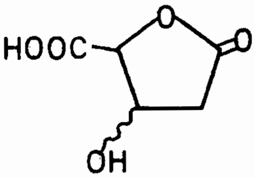


(225)

As it is readily prepared in large quantities, 2-bromo-1,4-napthaquinone[86] (226) was chosen for these purposes. It was supposed that substitution of chlorine in compound(156) by bromine in the models would not alter drastically the properties of the napthaquinone nucleus.



(226)

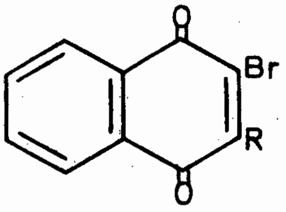


(227)

Two possible synthetic routes were readily envisaged. The first involved the generation of the acid (227). Subsequent addition of this to the napthaquinone nucleus, in the presence of ammonium peroxodisulphate and silver nitrate, could provide a diastereoisomeric mixture of the required compounds. These could prove tedious to separate. In any case, certain problems could be expected in any attempts to prepare the required hydroxylactone acid (227).

The second proposed route involved the addition of an appropriate side chain to the napthaquinone nucleus. Subsequent modifications of this product could lead to stereochemically correct ring closure and thus provide the separate diastereoisomers. This latter approach was deemed to be the better one to adopt.

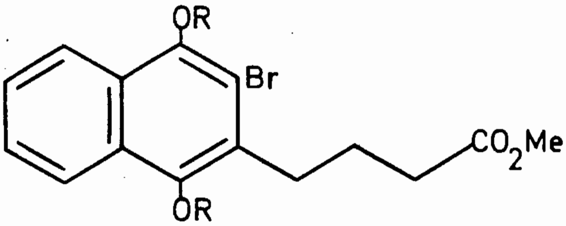
Two reaction sequences were developed simultaneously from the quinone (226). These involved the initial conversion of compound (226) into alkylated product (228). In the literature concerning the radical C - alkylation method mentioned earlier, no mention is made of reactions that involved 1,4-quinones bearing halogen substituents in the 2 - position. However, since this alkylation procedure offered the most direct route to compound (228), a trial reaction was attempted. Here, quinone (226) was reacted with hexanoic acid under the conditions mentioned earlier. Workup of the reaction afforded the desired quinone (229) in good yield (90%). Subsequent reaction of monomethyl glutarate with the bromoquinone (226) proved as successful and gave the alkylated quinone (228).



(228) R = $CH_2CH_2CH_2CO_2Me$

(229) R = $CH_2CH_2CH_2CH_2CH_3$

At this stage, the two model routes diverged. Firstly, the quinone (228) was reductively acetylated to afford the diacetoxy compound (230). Secondly, further quantities of the quinone were converted into the corresponding hydroquinone (231) with sodium dithionite, and then methylated with potassium carbonate and dimethyl sulphate. This gave the dimethoxy product (232).

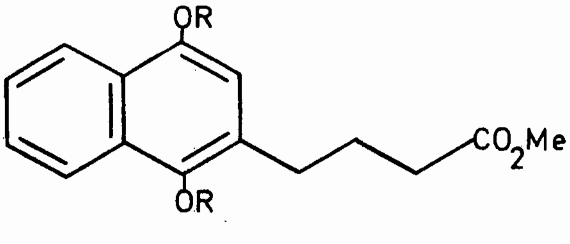


(230) R = COMe

(231) R = H

(232) R = CH_3

Both compounds (230) and (232) were then catalytically hydrogenolysed to remove the bromine substituent and to generate structures (233) and (234) respectively. These reactions were most readily performed in glacial acetic acid with 10% palladium on carbon as catalyst. The diacetoxy species (230) was found to require a higher reaction temperature (65-70°C) than did the dimethoxy compound (232) (35°C). Nevertheless, the removal of bromine proceeded quantitatively in both instances.

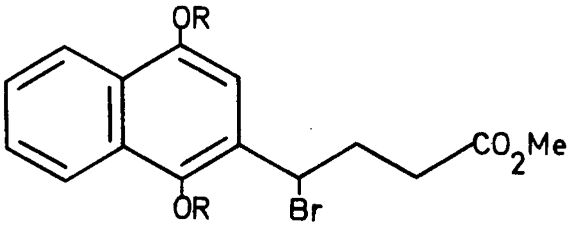


(233) R = COMe

(234) R = CH_3

Compound (234) was also synthesised in fewer steps by alkylation of napthaquinone itself with monomethyl glutarate, followed by reductive methylation of the product. However, its synthesis from 2-bromonapthaquinone as described was undertaken to follow closely the route proposed for the juglomycins from 2-chloro-8-methoxynapthaquinone. In addition, the alkylation of bromonapthaquinone had the advantage that it gave one product cleanly, while similar reaction of napthaquinone afforded the monoalkylated material contaminated by some unwanted dialkylated quinone, which had to be removed.

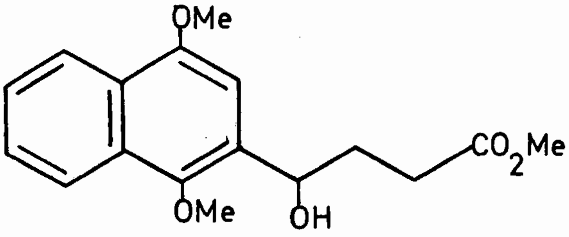
The next step in the reaction schemes involved the formation of a double bond between C_1 and C_2 of the side chain. Of the methods available for the introduction of this unsaturated function, the most direct appeared to be that of a bromination-dehydrobromination sequence. This procedure is one that is well established in the literature[87]. The initial benzylic bromination of both compounds (233) and (234), with N-bromosuccinimide (NBS) and benzoyl peroxide, proceeded smoothly to afford the required products (235) and (236) quantitatively.



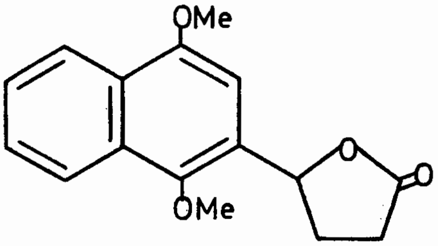
(235) R = COMe

(236) R = CH_3

During the purification of the bromide (236), some transformations of interest were observed. While the bromide (235) proved stable to the chromatographic techniques employed in purification, the corresponding compound (236) did not. Elution of bromide (236) on p.l.c., with solvents which had not been rigorously dried, rapidly afforded a mixture of bands. These new products were identified as the hydroxy compound (237) and the lactone (238). This chromatography was repeated on further samples of compound (236), and identical results were obtained. It was also found that by further elutions of the same p.l.c. plate, the hydroxy compound (237) converted steadily into the lactone (238). The same conversion, via ring closure, was found to occur when an independent sample of compound (237) was treated with dilute hydrochloric acid[†]. This difference in behaviour between the diacetate (235) and the dimethyl ether (236) may be rationalised in terms of the activation of benzylic bromine in the latter by the *ortho* methoxyl, as in structure (239).

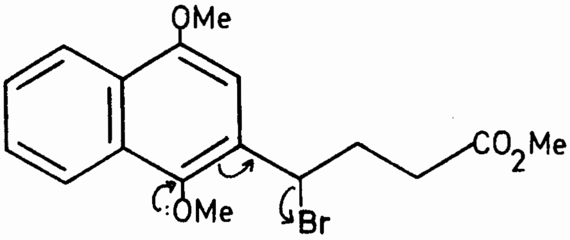


(237)



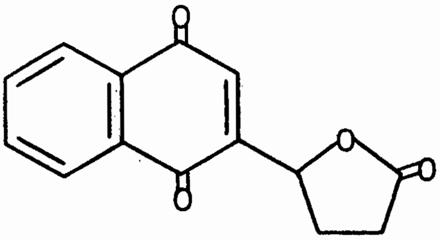
(238)

[†] See Experimental Section for details



(239)

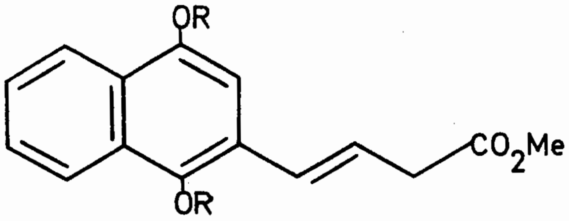
The lactone (238) possessed a structure similar to the final model compounds being sought. It therefore provided a suitable molecule on which to try the final oxidation to the quinone. Since, in the case of the dimethoxy model, this involved the relatively vigorous conditions of silver (II) oxide catalysed by 6M nitric acid, it was of interest to see whether the lactone ring survived. Treatment of lactone (238) with silver (II) oxide, using oxidative demethylation conditions, readily afforded the pale yellow quinone (240). The success of this oxidation augered well for the proposed oxidative demethylation of the final model lactones. However, the presence of the free hydroxyl in those models could interfere in the generation of the quinones.



(240)

As a result of the relative instability of the bromide (236), no further attempts were made to prepare an analytical sample. Evidence for the existence of this intermediate bromide was obtained by measuring the ^1H n.m.r. spectrum of the bromination product as obtained from the NBS reaction. This product was collected in relatively pure form after removal of the succinimide by filtration - the spectrum obtained was wholly consistent with that required for structure (236).

The next step in the generation of the required olefins (241) and (242), was the dehydrohalogenation of the bromides (235) and (236). This procedure is normally readily effected by treatment of the halogenated species with a suitable base. In the case of the diacetoxy species (235), the choice of base was limited by the presence of the easily hydrolysed acetate groups. A further restriction on the choice of base was imposed by the presence of the ester function in both bromides. Hydrolysis of the ester at this stage was not desired.

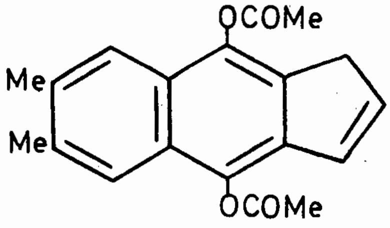


(241) R = COMe

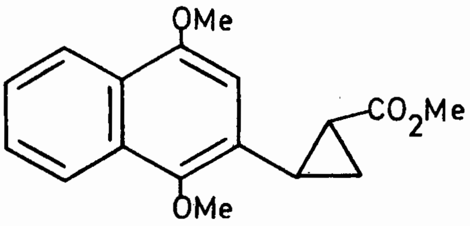
(242) R = Me

Giles,[88] when he prepared 6,7-dimethylbenz[f]indene-4,9-diyl diacetate (243) from the corresponding 1-bromoindane, showed that 2,6-lutidine may be employed for dehydrobromination. Compound (235) was thus treated with lutidine under conditions of reflux and this afforded the required olefin (241) in 65% yield. In the light of the moderate yield and tedious workup involved, an attempt was made to use the powerful base 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) instead of lutidine. This, however, gave even lower yields of the required olefin.

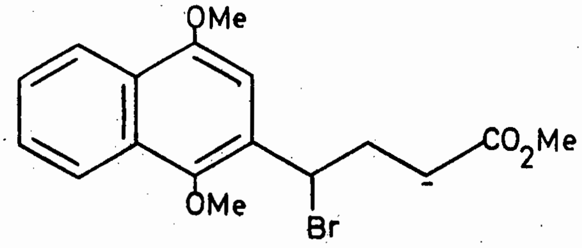
Firstly, because of the difficulty encountered in purification of the product after lutidine treatment, and secondly, since the bromide (236) contained the more stable methoxy substituents, it was decided to attempt dehydrobromination of that compound with other bases. Treatment of compound (236) with DBN returned only starting material. The same result was obtained when potassium *t* - butoxide in dry tetrahydrofuran was used at room temperature. However, when this latter base was employed under conditions of reflux, neither starting bromide nor required olefin could be found. Instead, the only product of the reaction was the cyclopropyl ester (244). It is reasonable to assume that this product forms via the proposed intermediate (245). This intermediate may be generated in preference to the required anion (246).



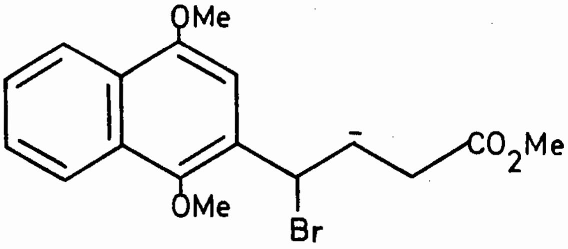
(243)



(244)



(245)



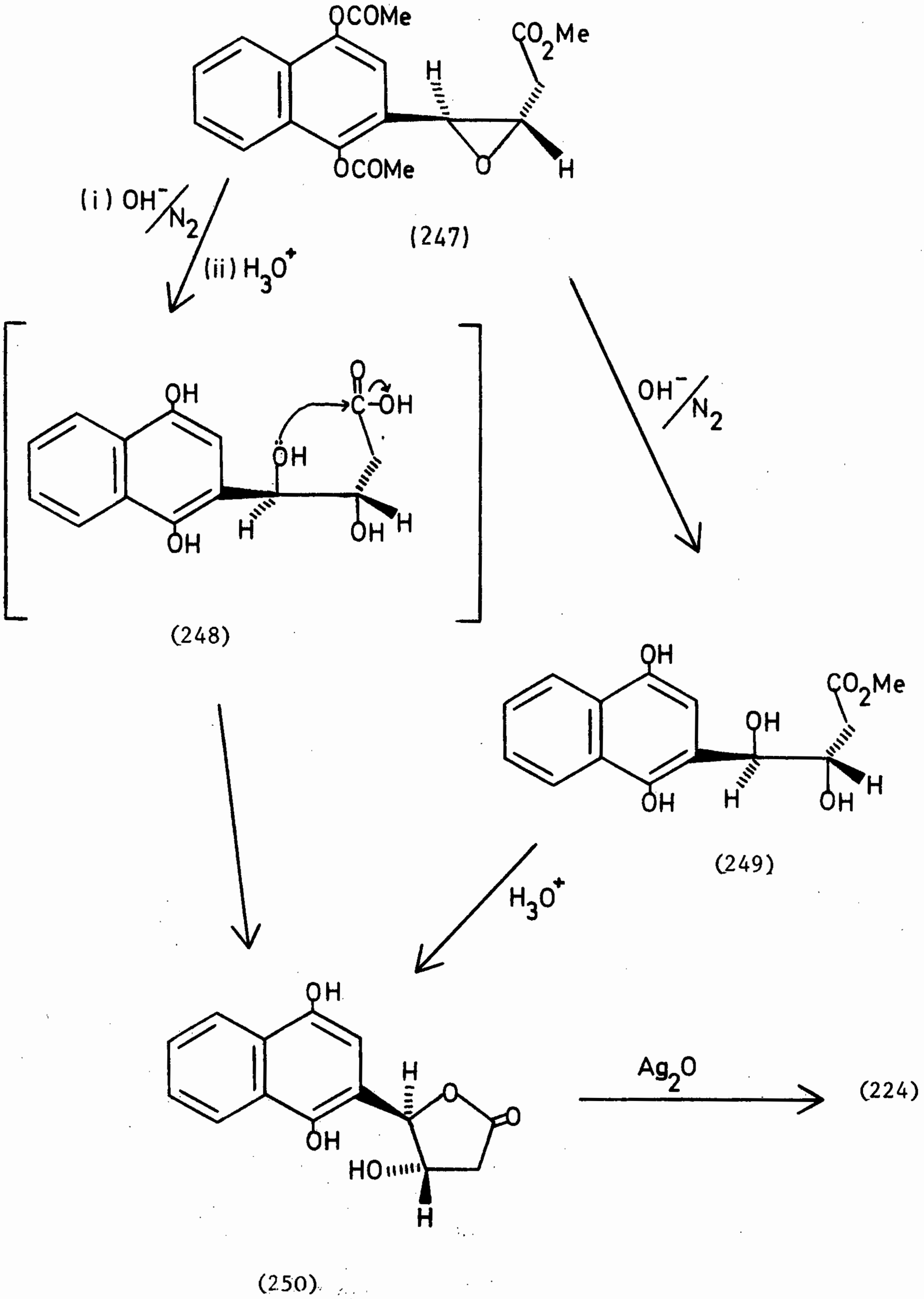
(246)

In the light of the above results, it was decided to revert to the use of lutidine as the base. When compound (236) was heated under reflux in lutidine, dehydrobromination proceeded far more readily than in the case of the diacetate (235). Workup afforded the required olefin (242) in 92% yield. Thus, both model olefins (241) and (242) were available, and suitable methods were then sought for their conversion into the desired model structures (224) and (225). The ^{1}H n.m.r. spectrum of each olefin showed a coupling constant of 16Hz for the olefinic protons, thus verifying a *trans* arrangement about each double bond.

The preparation of isomer (224) via the following sequence was envisaged. Conversion of the olefin function into an epoxide and subsequent ring closure should lead exclusively to the product with the stereochemistry of (224). Under either basic or acidic conditions, epoxide ring opening would be expected at the benzylic position.

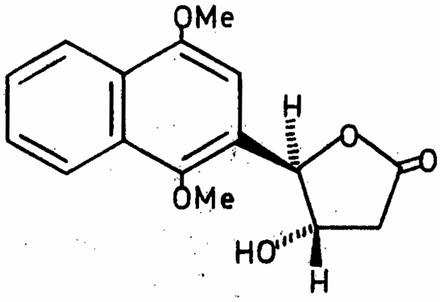
Reaction of the olefin (235) and *m*-chloroperbenzoic acid in methylene chloride, readily afforded the epoxide (247). It was hoped that the treatment of this with the base under nitrogen would follow the reaction sequence outlined in Scheme (12). However, reaction of the epoxide (247) with aqueous base under a variety of conditions led only to extensive decomposition. No single product could be isolated from the reaction mixtures.

Scheme (12)

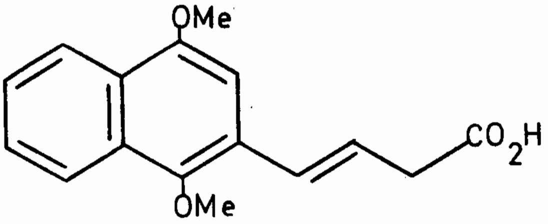


As a result of the difficulties experienced with the diacetate model, it was decided to continue only with the more stable dimethoxy analogue. Furthermore, the diacetate model had been prepared initially to facilitate the final generation of the quinones (224) and (225) under mild conditions; whereas in the dimethoxy case, the relatively more vigorous conditions of silver (II) oxide were required. However, it had been found that quinone (240) was readily produced from its dimethoxy precursor (238), under the acidic conditions of silver (II) oxide. It might then have been possible to oxidise similarly the hydroxylactone dimethyl ether (251) to the corresponding quinone, in spite of the unprotected lactone hydroxyl function. In this circumstance, the diacetate model would no longer be essential. The route to compound (251) from the alternative olefin (242) should then proceed by a pathway similar to that outlined in Scheme (12) for the diacetate model.

One pathway in Scheme (12) envisages both nucleophilic ring opening of the epoxide and basic hydrolysis of the ester function. To exclude the possibility that the basic conditions could upset the required lactone (251) after formation, it was decided to carry out the reaction sequence on the free acid product (252) as well. This would eliminate the necessity of the fairly vigorous base treatment required for ester hydrolysis, thus allowing lactone formation under milder conditions. The free acid (252) was easily obtained from the hydrolysis of the ester (242) with aqueous potassium hydroxide.

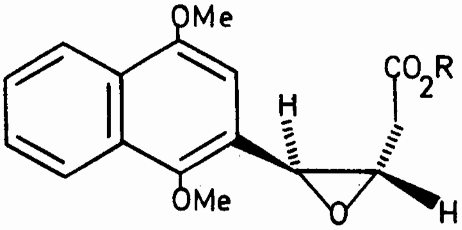


(251)



(252)

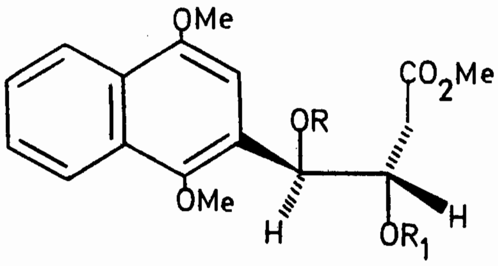
A number of attempts were made to epoxidise both the ester (242) and acid (252) with *m*-chloroperbenzoic acid in methylene chloride. However, these proved to be unsuccessful, with extensive decomposition occurring. Neither starting material nor epoxide could be found[†]. Similar attempts were made to prepare the *trans* hydroxylated product using performic acid. Because of the acidic strength of this reagent, one or other of the monoformate esters (255) or (256), or a mixture of these would be isolated instead of the epoxide[90]. In general, such monoformate esters readily yield vicinal diols on alkaline hydrolysis. However, this reaction was also unsuccessful.



(253) R = H

(254) R = Me

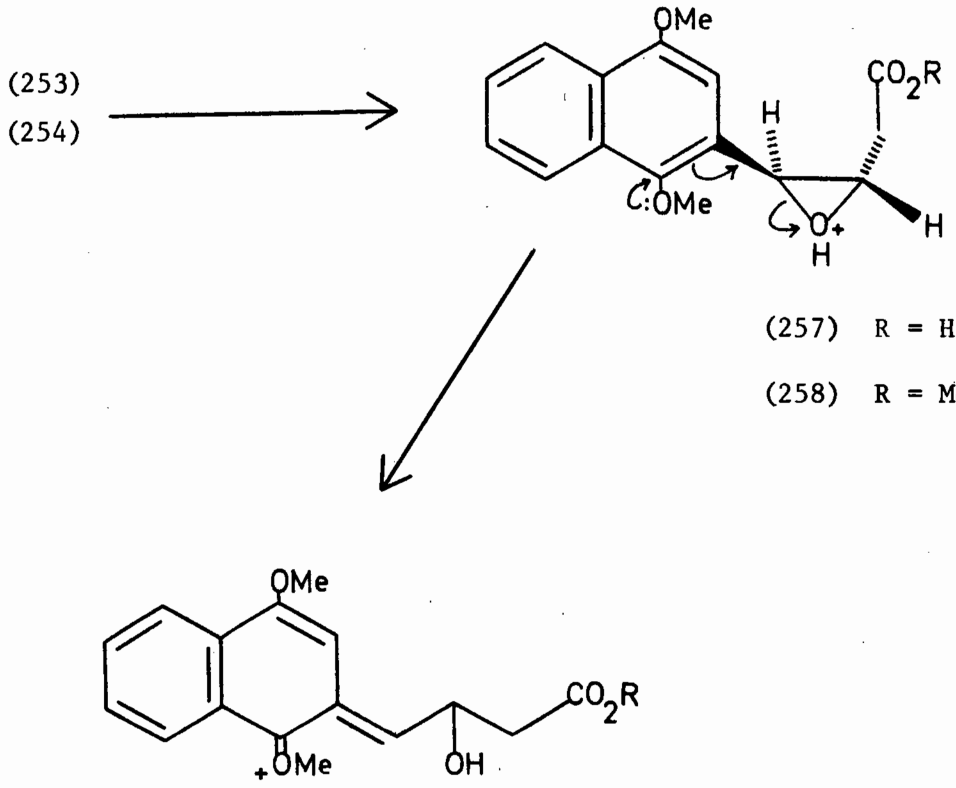
[†] No steps had been taken to remove any *m*-chlorobenzoic acid which could contaminate the peracid. This acid is more strongly acidic than the peracid[89].



(255) R = H, R_1 = CHO

(256) R = CHO, R_1 = H

Scheme (13)



(253)

(254)

(257) R = H

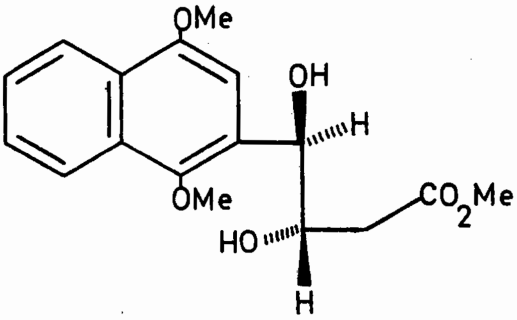
(258) R = Me

(259) R = H

(260) R = Me

A possible reason for the failure of these epoxidation procedures in acidic medium can be advanced by consideration of the intermediates (257) and (258). These species could rapidly undergo ring opening as shown in Scheme (13). The resulting intermediates (259) and (260) could undergo further transformations. The lesser electron availability in the case of the acetate protecting groups in epoxide (247) would explain why the epoxide could be isolated for the diacetate model.

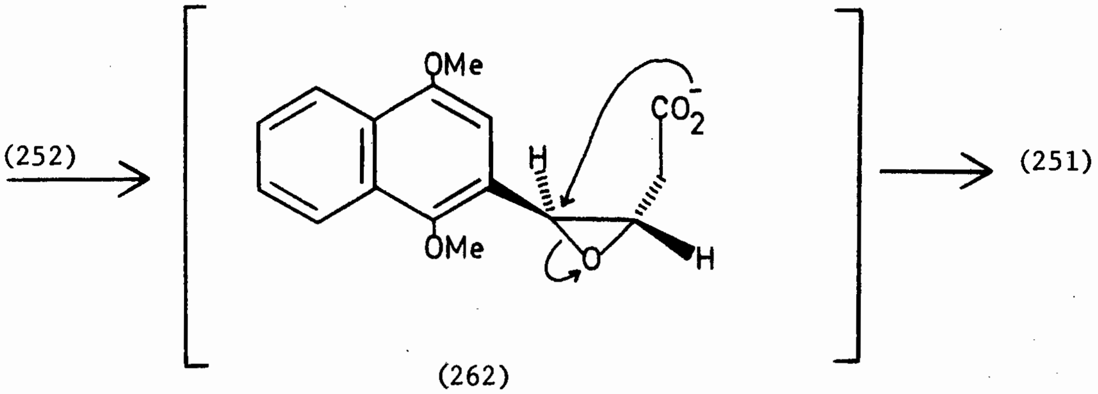
Anderson[91], has recently reported an epoxidation procedure in basic medium designed specifically for acid sensitive epoxides. This involves reaction of *m*-chloroperbenzoic acid with the olefin in a biphasic system of methylene chloride and aqueous sodium bicarbonate. Treatment of the ester (242) under these conditions readily afforded the epoxide (254)[†]. It was hoped that ring opening of the epoxide with base would afford the *trans* hydroxylated product (261). Subsequent treatment of this with dilute hydrochloric acid could be expected to yield the required lactone (251) in a manner analogous to the formation of lactone (238). However, treatment of epoxide (254) with aqueous base under mild conditions returned starting material. Under more vigorous conditions, extensive decomposition occurred and none of the required product could be isolated.



(261)

[†] This product was not purified further because extensive decomposition occurs on chromatography. ^{1}H n.m.r. spectral evidence was consistent with the required structure.

In view of the above failure, it was decided to attempt epoxidation of the free acid (252) under basic conditions. This procedure would generate the intermediate (262) and ring closure might then occur intramolecularly to give the required lactone (251) in one reaction.



(262)

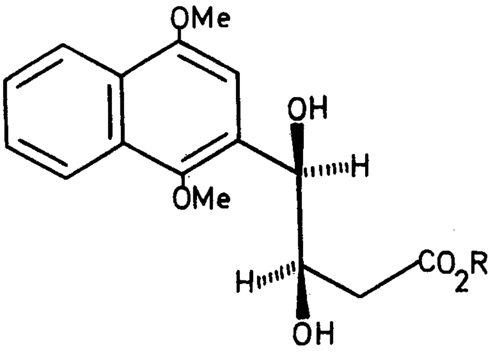
The biphasic conditions for epoxidation as described earlier were not expected to be very successful, since the acid would go into the aqueous phase. The resulting carboxylate anion might never come into contact with the peracid, dissolved in the organic phase. However, reaction of acid (252) under these conditions with *m*-chloroperbenzoic acid, in fact gave the required lactone (251) in moderate yield (47%). Other workers[92] have reported epoxidation in basic medium, using a monophasic system of acetonitrile and aqueous base. It was hoped that these homogenous conditions might improve the yield of the lactone. A number of reactions, using this solvent system, were thus carried out under a variety of basic strengths, *m*-chloroperbenzoic ratios and reaction times. However, the best yield of lactone obtained was 50%. Experiments to optimise this yield are still being performed.

Oxidation of the lactone (251), with silver (II) oxide, afforded the quinone (224), in spite of the free hydroxyl group. This reaction further illustrates the versatility of this reagent for the production of quinones from the corresponding dialkyl ethers. Figure 7 (page 129) shows the ^{1}H n.m.r. spectrum of quinone (224), which compares favourably with those in Figure 9 (page 131) for Juglomycins A and B. The mass spectral fragmentation pattern of quinone (224) also displays a good correlation with that reported for the Juglomycins.

Model quinone (224) $^{m}/_{e}$ 258 (M^+), 240, 188, 187, 159.

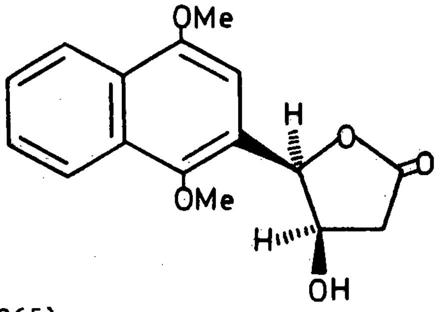
Juglomycins A and B $^{m}/_{e}$ 274 (M^+), 256, 204, 203, 175.

The synthesis of the alternative isomer (225) required the generation of the *cis* hydroxylated product (263). The production of *cis* diols from olefins has been accomplished most readily with osmium tetroxide[93]. Baran[94] has shown this process to be a particularly facile one when carried out with his improved conditions for the cleavage of the initially formed osmate esters. Workup, which employs pyridine and aqueous sodium bisulphite, allows for the smooth transformation of osmate esters to *cis* glycols under mild conditions. These conditions avoid the often troublesome separation of products from osmium and its inorganic derivatives.



(263) R = Me

(264) R = H



(265)

Reaction of the olefin (242) with osmium tetroxide in pyridine, followed by workup as described above, afforded the required *cis* diol (263) in almost quantitative yield. This product was cyclised immediately in mildly acidic medium, analogous to the earlier lactonisation of compound (237). This gave the desired lactone (265), with the stereochemistry shown[†]. Subsequently, it was shown that the lactone (265) could be obtained alternatively by similar *cis* dihydroxylation of the acid (252), followed by acid catalysed cyclisation of the resulting diol (264).

Figures 5 and 6 show the ^{1}H n.m.r. spectra of the two dimethoxy-lactones (251) and (265) respectively. The *cis* and *trans* isomers are readily distinguished by their different vicinal coupling constants.

Oxidation of the lactone (265), with silver (II) oxide, readily afforded the quinone (225) in good yield (86%). Figure 8 shows the ^{1}H n.m.r. spectrum of the quinone (225). This again compares favourably with the spectra of Juglomycins A and B, shown in Figure 9. The mass spectral fragmentation pattern for quinone (225) also follows closely that reported for the Juglomycins (see page 125).

Model quinone (225) $^m/_e$ 258 (M^+), 240, 188, 187, 159.

At present, the syntheses of the actual antibiotics, Juglomycins A and B, are being undertaken.

[†] No change in the stereochemistry was assumed to occur under the mild conditions employed viz: hydrochloric acid in tetrahydrofuran.

Figure 5

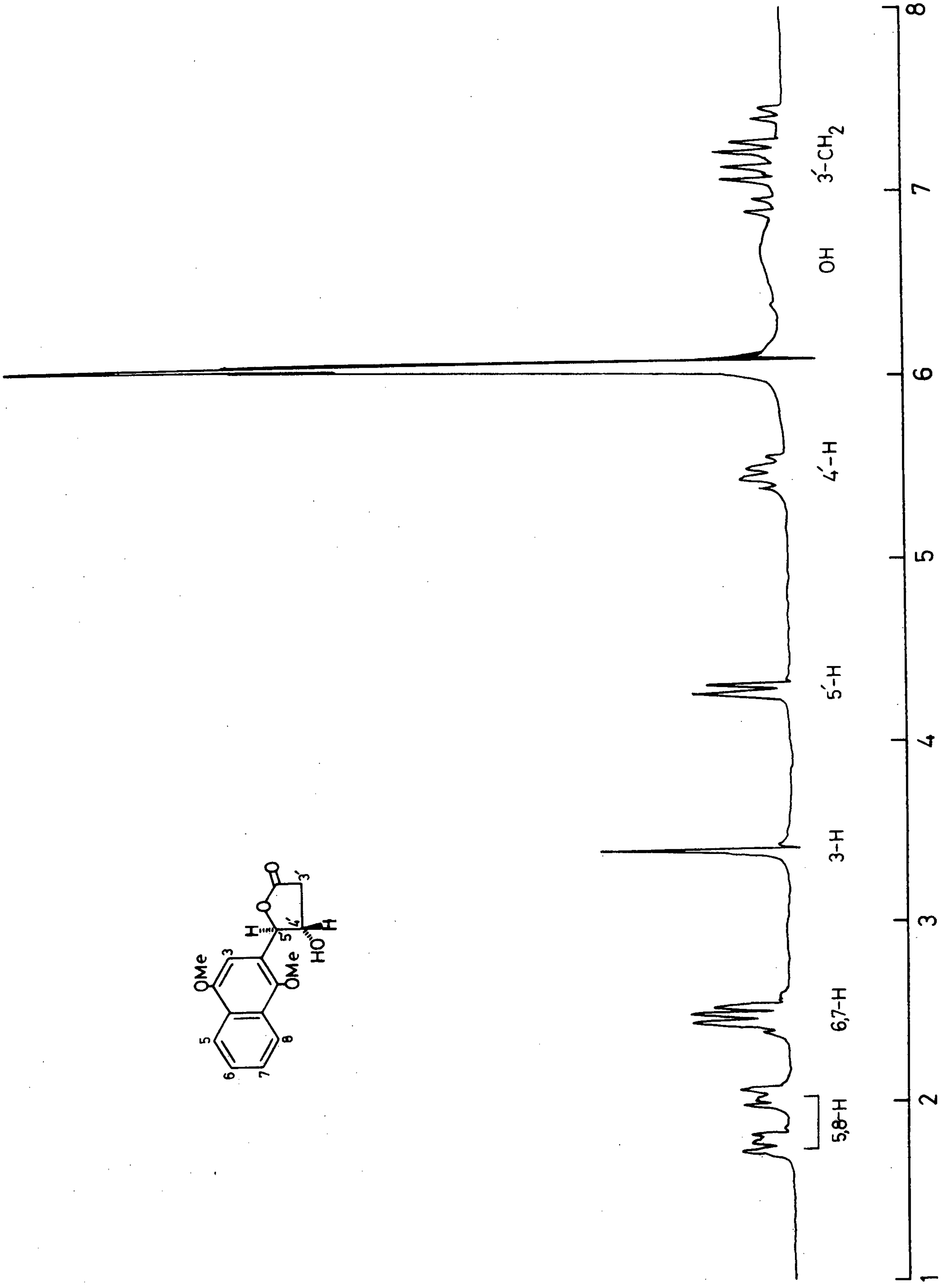


Figure 6

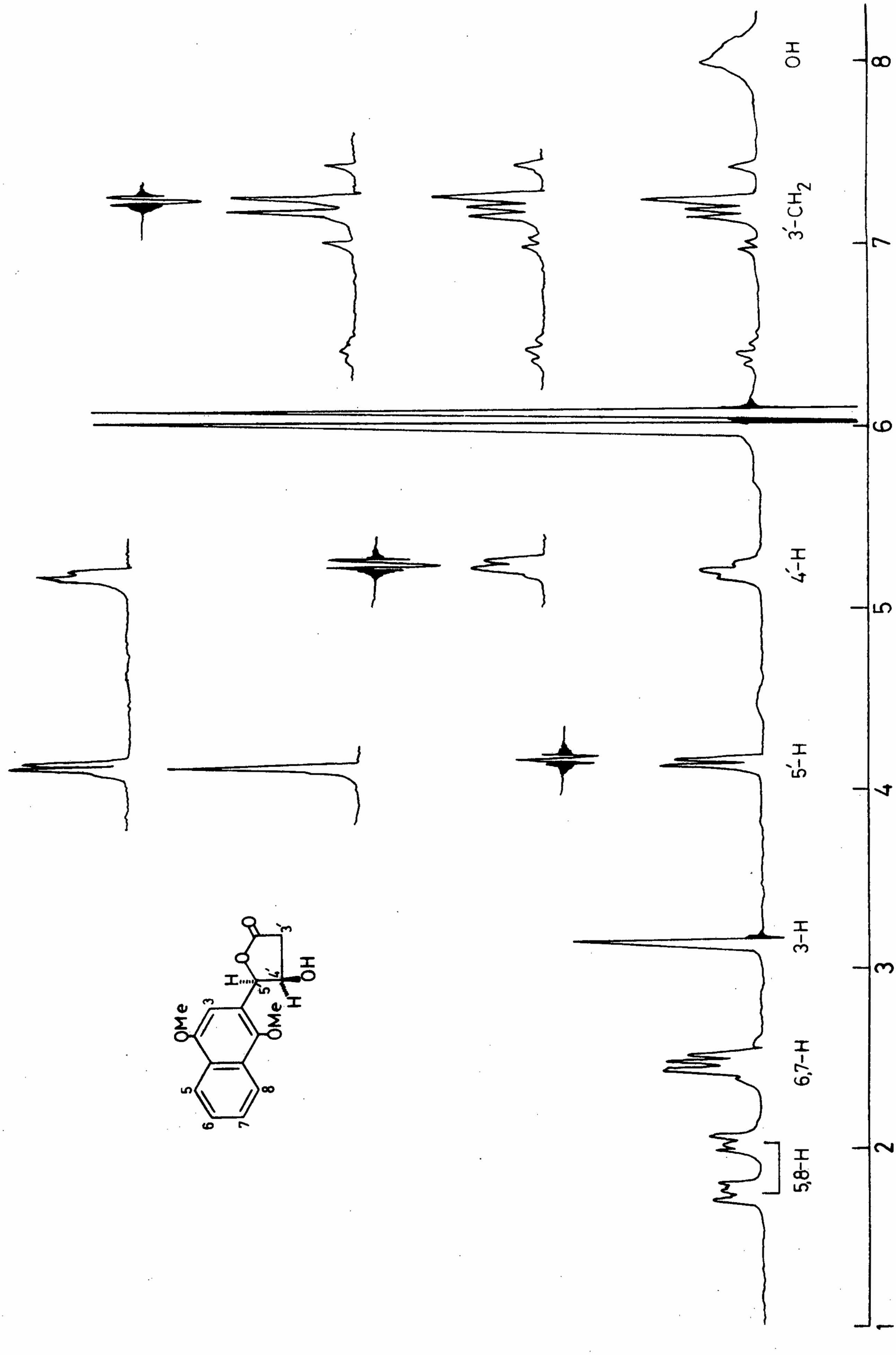


Figure 7

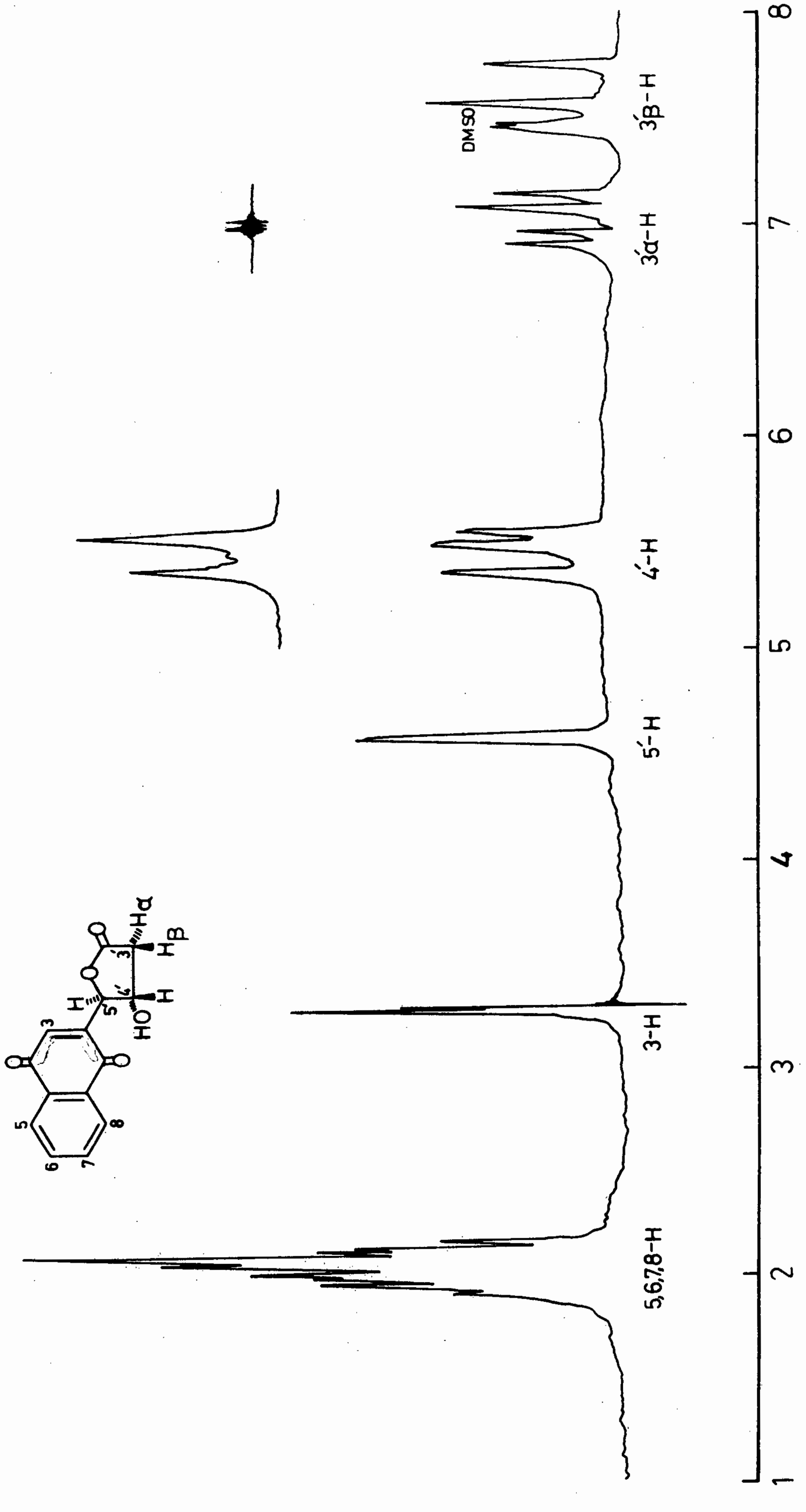


Figure 8

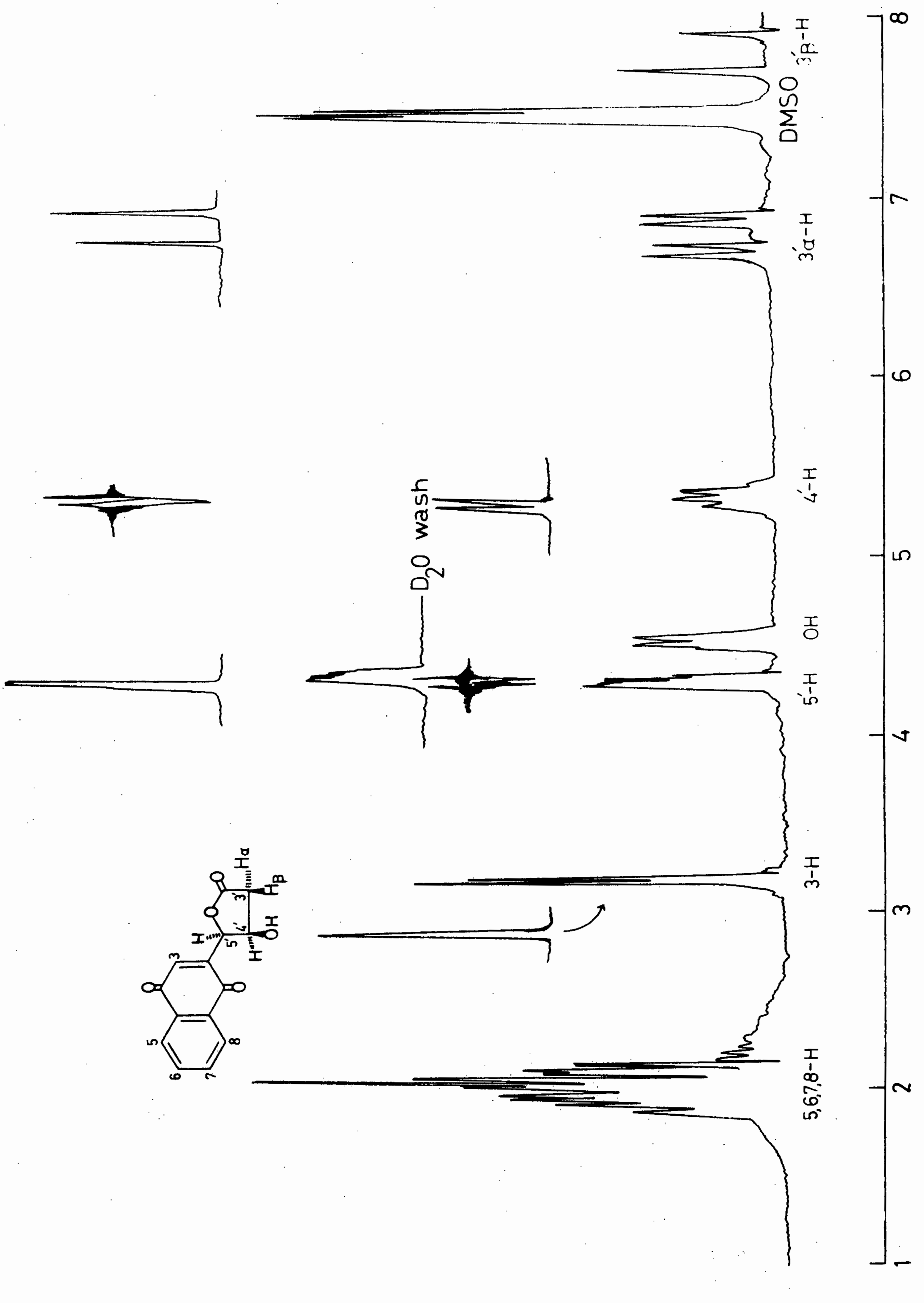
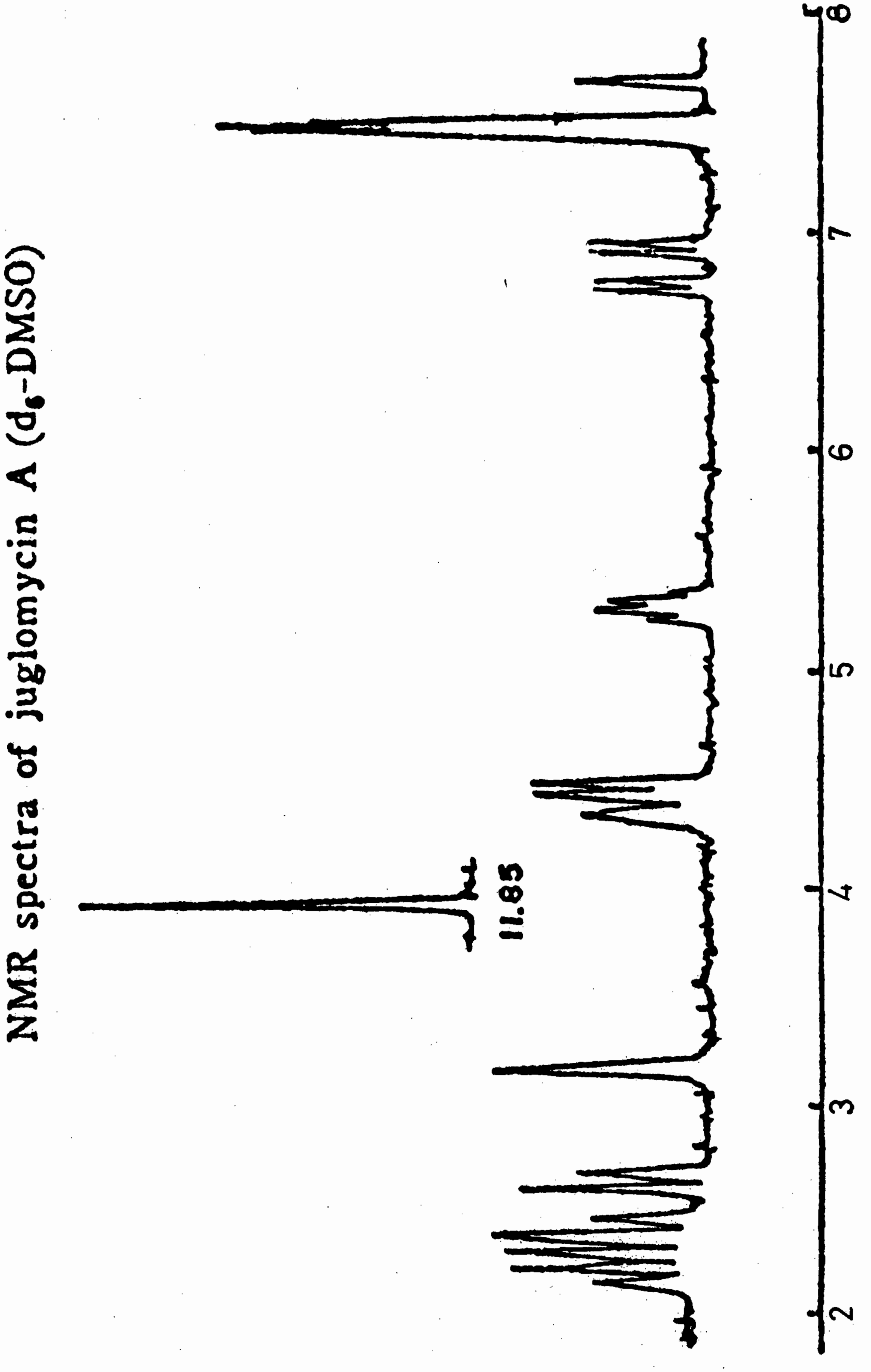
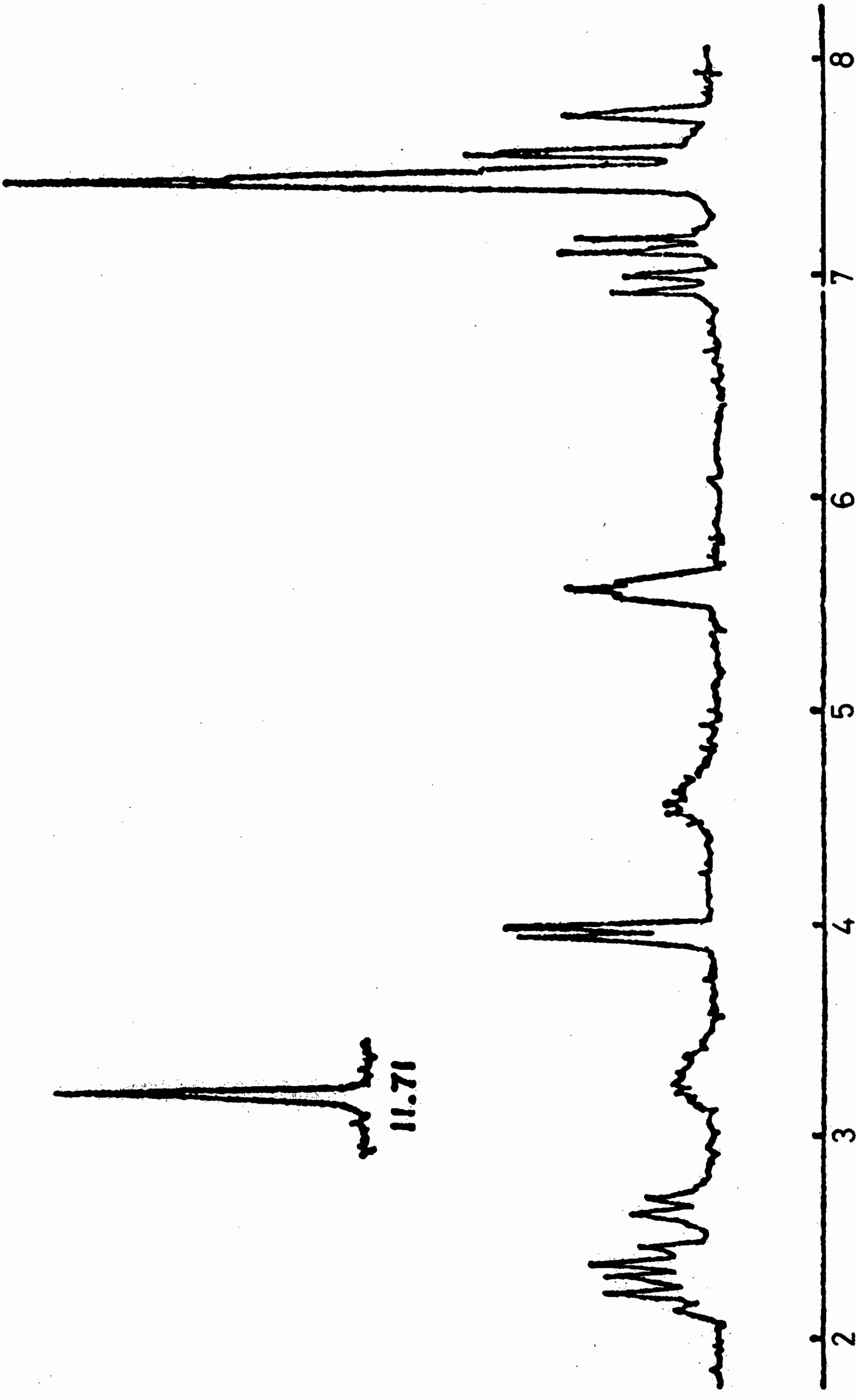

5,6,7,8-H
3-H
5'-H
OH
4'-H
3'α-H
DMSO
3'β-H
D$_2$O wash
1
2
3
4
5
6
7
8
3
5
6
7
8
5'
4'
3'
H
Hα
Hβ
OH

Figure 9 Reprinted from the Japanese Journal of Antibiotics 1971, 24, 223



NMR spectra of juglomycin A (d_6-DMSO)

Figure 9 Reprinted from the Japanese Journal of Antibiotics 1971, 24, 223



NMR spectra of juglomycin B (d_6-DMSO)

EXPERIMENTAL

2-(3-Methylbut-1-enyl)-3-hydroxy-5-methoxy-1,4-napthaquinone: (210)

2-Hydroxy-8-methoxy-1,4-napthaquinone (132) (0.40g) in hot (80°) glacial acetic acid (10 ml) was treated with concentrated hydrochloric acid (1 ml) followed immediately by isovaleraldehyde (1.25 ml). The dark solution was heated under gentle reflux for 1 h, then thrown into water (200 ml) and extracted with chloroform. The organic layer was dried and evaporated and the residue chromatographed over a short silica column with methylene chloride as eluant. This yielded the orange product, which was sublimed at 150° (bath)/1.2 mm Hg, m.p. 179.5-180° (0.45g, 86%). (Found: C, 70.7; H, 6.0 $C_{16}H_{16}O_4$ requires C, 70.6; H, 5.9%), ν_{max} (CCl_4) 3320, 1736, 1658, 1618 and 1584 cm^{-1}, τ 2.14-2.44 (2H, m, 6- and 7 -H), 2.79 (1H, dd J 2 and 8Hz, 8 -H), 3.02 (1H, dd J 7 and 16Hz, 2 -H), 3.48 (1H, d J 16Hz, 1 -H), 5.98 (3H, s, OCH_3), 7.47 (1H, octet J 7Hz, 3 -H) and 8.89 (6H, d J 7Hz, CH_3).

9-Methoxy-2,2dimethylnaptha[2,3-b]pyran-5,10-dione: (211) and
2-(Isopropyl)-8-methoxynaptha[2,3-b]furan-4,9-dione: (212)

The foregoing quinone (210) (300 mg) in benzene (50 ml) was added to a solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (300 mg) in benzene (100 ml) and the mixture stirred overnight at room temperature. The precipitate (H_2DDQ) was filtered and washed with benzene. The solvent was evaporated and the residue chromatographed (eluant methylene chloride). A pale yellow band afforded the furanquinone (212) which was sublimed at 150° (bath)/2.2 mm Hg, m.p. 157-158.5° (25 mg, 8%). (Found: C, 71.1; H, 5.2 $C_{16}H_{14}O_4$ requires C, 71.1; H, 5.2%), ν_{max} (CCl_4), 1726 and 1668 cm^{-1}, τ 2.10-2.56 (2H, m, 6- and 7 -H), 2.72 (1H, dd J 2 and 8Hz, 8 -H), 3.49 (1H, s, 3 -H), 5.99 (3H, s, OCH_3), 6.90 (1H, septet J 7Hz, C<u>H</u>Me_2) and 8.65 (6H, d J 7Hz, CH_3).

An orange-yellow band gave the pyranquinone (211) which was sublimed at 150° (bath)/2 mm Hg, m.p. 132-134°C (140 mg, 47%). (Found: C, 71.1; H, 5.6 $C_{16}H_{14}O_4$ requires C, 71.1; H, 5.2%), ν_{max} (CCl_4) 1727, 1677, 1650 and 1636 cm^{-1}, τ 2.18 -2.50 (2H, m, 6- and 5 -H), 2.78 (1H, dd J 2 and 8Hz, 7 -H), 3.39 (1H, d J 9Hz, 3 -H), 4.35 (1H, d J 9Hz, 4 -H), 6.01 (3H, s, OCH_3), and 8.46 (6H, s, CH_3).

Further fractions afforded a red crystalline material, assumed to be the *ortho*-quinone (213) (85 mg, 28%), which was readily converted to quinone (211) with concentrated hydrochloric acid (1 ml) in ethanol (10 ml) on warming on a water-bath.

α-Caryopterone [9-Hydroxy-2,2-dimethylnaptha[2,3-b]pyran-5,10-dione]: (191)

The quinone (211) (300 mg) in dry methylene chloride (5ml) was treated at -78° with an excess of boron tribromide (500 mg) in the same solvent (10 ml). Workup as described in the previous experimental section afforded a crude residue which was chromatographed on a short silica column (eluant methylene chloride). This gave α - caryopterone (160 mg, 55%) from which an analytical sample was prepared by p.l.c. with 10% ethyl acetate/light petroleum as solvent, m.p. (toluene/light petroleum) 170-172° (dec) with darkening at 143° (lit[67] 143.5-145° (dec)). (Found: C, 70.2; H, 5.0 $C_{15}H_{12}O_4$ requires C, 70.3; H, 4.7%). The i.r. and ^1H n.m.r. spectra were identical with those recorded for the natural material. The synthetic and natural materials had the same R_f on t.l.c. in several solvent systems.

3-Acetoxy-5-methoxy-2-(3-methylbut-2-enyl)-1,4-napthaquinone: (219)

2-Hydroxy-8-methoxy-1,4-napthaquinone (132) (0.96g) was acetylated with acetic anhydride (5 ml) containing concentrated sulphuric acid (0.2 ml) to give 3-acetoxy-5-methoxy-1,4-napthaquinone (218) (0.65g, 53%), τ 2.2-2.5 (2H, m, 7- and 8 -H), 2.6-2.8 (1H, m, 6 -H), 3.36 (1H, s, quinonoid H), 6.01 (1H, s, OCH_3) and 7.62 (3H, s, $COCH_3$). Because of its ready hydrolysis, the crude acetate was alkylated directly with 4-methylpent-3-enoic acid (0.30g) and silver nitrate (0.30g) in a mixture of acetonitrile (12 ml) and water (15 ml) to which was added a solution of ammonium peroxodisulphate (1.12g) in water (10 ml) at 60-65^o with vigorous stirring over a period of 1 h. At the completion of addition, the solution was stirred for a further 10 mins at the same temperature, then cooled and the excess acid neutralised with solid sodium carbonate. The dark mixture was extracted with ether and the organic layer dried and evaporated. The residue was chromatographed over a short silica column (eluant methylene chloride) to afford the quinone (0.65g, 75%). An analytical sample was prepared by p.l.c. with methylene chloride as solvent, m.p. 103-104^o. (Found: C, 68.8; H, 5.9 $C_{18}H_{18}O_5$ requires C, 68.8; H, 5.7%), ν_{max} (CCl_4) 1785, 1727, 1675 and 1650 cm^{-1}, τ 2.16-2.50 (2H, m, 7- and 8 -H), 2.66-2.83 (1H, m, 6 -H), 4.92 (1H, t J 8Hz, 2′ -H), 6.02 (3H, s, OCH_3), 6.76 (2H, d J 8Hz, CH_2), 7.62 (3H, s, $COCH_3$), 8.25 (3H, s, CH_3) and 8.32 (3H, s, CH_3).

3-Hydroxy-5-methoxy-2-(3-methylbut-2-enyl)-1,4-napthaquinone: (220)

The above acetate (219) (0.65g) was heated under gentle reflux with

N sodium carbonate (50 ml) until all material was dissolved. The solution was cooled in ice, acidified carefully with concentrated hydrochloric acid and extracted with methylene chloride. The organic layer was dried and evaporated and the residue chromatographed over a short silica column (eluant methylene chloride). A small quantity of starting material eluted first, followed by the product (0.25g, 55% based on unrecovered starting material). This was sublimed at 130^{o} (bath)/1.3 mm Hg, m.p. 155.5-156.5^{o}. (Found: C, 70.8; H, 6.1 $C_{16}H_{16}O_4$ requires C, 70.6; H, 5.9%), ν_{max} (CCl_4) 3360, 1728 and 1653 cm^{-1}, τ 2.1-2.5 (2H, m, 7- and 8 -H), 2.79 (1H, dd J 2 and 8Hz, 6 -H), 4.79 (1H, t J 8Hz, 2′-H), 5.98 (3H, s, OCH_3), 6.72 (2H, d J 8Hz, CH_2), 8.21 (3H, s, CH_3) and 8.31 (3H, s, CH_3).

O-Methyldihydro-α-caryopterone [3,4-Dihydro-9-methoxy-2,2-dimethylnaptha[2,3-b]pyran-5,10-dione]: (193) and 3,4-dihydro-7-methoxy-2,2-dimethylnaptha[1,2-b]pyran-5,6-dione: (221)

Quinone (220) (210 mg) in acetic acid (5 ml) and concentrated hydrochloric acid (0.75 ml) was heated on a water bath for 75 mins. The solution was cooled, water gradually added, and the whole extracted with methylene chloride. The organic layer was dried and evaporated, and the residue chromatographed (eluant methylene chloride) over silica to give, starting material (4 mg), followed by the quinone (193) (101 mg, 49%) which was sublimed at 150-155^{o} (bath)/1.8 mm Hg, m.p. and mixed m.p. 165-167^{o} (lit[68] 168-169^{o}). (Found: C, 70.5, H, 6.0 $C_{16}H_{16}O_4$ requires C, 70.6; H, 5.9%), ν_{max} ($CHCl_3$) 1671, 1640, 1623 and 1587 cm^{-1}, τ 2.22-2.54 (2H, m, 6- and 7 -H), 2.82 (1H, dd J 2 and 8Hz, 8-H), 6.04 (3H, s, OCH_3), 7.43 (2H, t J 7Hz, 4-CH_2), 8.20 (2H, t J 7Hz, 3-CH_2) and 8.59 (6H, s, CH_3). The synthetic and natural materials had the same R_f on t.l.c. in various solvents.

A third band afforded the *ortho*-quinone (221) (100 mg, 49%), m.p.160-161° (lit[67], 162-163°). The i.r. and ^1H n.m.r. data were identical with those reported[67]. Quinone (221) was quantitatively converted into the quinone (193) by treatment with concentrated hydrochloric acid in hot ethanol.

Dihydro-α-caryopterone [3,4-Dihydro-9-hydroxy-2,2-dimethylnaptha-[2,3-b]pyran-5,10-quinone]: (192)

(a) The quinone (193) (30 mg) in dry methylene chloride (10 ml) was treated at -78° with boron tribromide (1.5 molar equivalents) in the same solvent (10 ml). This was allowed to warm to room temperature and then stirred overnight. Water was cautiously added, and the solution extracted with chloroform. The contents of the organic layer, after drying and reducing, were purified by p.l.c. (eluant benzene) to afford the natural product (17 mg, 60%). This was sublimed at 100-110° (bath)/2.7 mm Hg, m.p. 119°, mixed m.p. 119-120° (lit[68], 120-122°). (Found: C, 69.45; H, 5.60 $C_{15}H_{14}O_4$ requires C, 69.75; H, 5.45%). The synthetic and natural materials had the same R_f values, and an H^1n.m.r. spectrum consistent with that reported.

(b) In an initial experiment designed to afford the above product, the quinone (193) was treated with an excess (3 molar equivalents) of boron tribromide at room temperature in methylene chloride, and the solution heated under reflux for 20 mins. Workup and p.l.c. as above, yielded in addition to (192), a preponderance of <u>8-bromo-3,4-dihydro-9-hydroxy-2,2-dimethylnaptha [2,3-b]pyran-5,10-quinone</u> (222)

which had the higher $R_f$value. This was sublimed at 145-150° (bath)/ 4 mm Hg, m.p. 180-181. (Found: C, 54.0; H, 4.2 $C_{15}H_{13}BrO_4$ requires C, 53.45; H, 3.9%) τ -2.48 (1H, s, OH), 2.16 (1H, d J 8Hz, 6-H), 2.53 (1H, d J 8Hz, 7-H), 7.38 (2H, t J 7Hz, 4-CH_2), 8.18 (2H, t J 7Hz, 3-CH_2) and 8.56 (6H, s, CH_3).

9-Methoxy-2,2-dimethylnaptha [2,3-b]pyran-5,10-quinone: (211)

The quinone (193) (175 mg) and DDQ (215 mg) were stirred together in dry benzene (100 ml) at room temperature for 5 h. The precipitate (H_2DDQ) was filtered off and washed with benzene. The solution was evaporated and the residue chromatographed over silica (eluant methylene chloride) to afford starting material (10 mg), followed by quinone (211) (60 mg), identical with that obtained from compound (210). A final band gave rise to the *ortho*-quinone (213) which could be converted to quinone (211) as described earlier.

2-Bromo-1,4-napthaquinone: (226)

This was prepared from napthaquinone by the method of McElvain[86] who quote m.p. 130-131°C (found 131°C)

2-Bromo-3-pentyl-1,4-napthaquinone: (229)

The aforementioned quinone (550 mg) was treated with silver nitrate (400 mg), hexanoic acid (400 mg) and ammonium peroxodisulphate (800 mg) in a water-acetonitrile mixture (12 ml - 12 ml) as described earlier for compound (219). Workup as before gave a crude orange crystalline residue. Column chromatography (eluant, 5% ethyl acetate/light petroleum) of this residue afforded the product as yellow needles, m.p. 90-91°C (methylene chloride/light petroleum) (640 mg, 90%). (Found: C, 58.4; H, 4.85 $C_{15}H_{15}BrO_2$ requires C, 58.64; H, 4.92%), ν_{max} (CCl_4) 1670, 1596 and 1470 cm^{-1}, τ 1.78-2.00 (2H, m, 5- and 8 -H), 2.16-2.36 (2H, m, 6- and 7 -H), 7.15 (2H, t J 7Hz, 1ʹ-CH_2). 8.20-8.84 (4H, m, 2 x CH_2) and 9.08 (3H, t J 6Hz, CH_3).

Quinone: (228)

2-Bromo-1,4-napthaquinone (1.00g) was treated as above with silver nitrate (1.00g), ammonium peroxodisulphate (2.6g), and glutaric acid monomethylester (1.3g) (in place of hexanoic acid). Workup and chromatography (eluant, 10% ethyl acetate/light petroleum) as above afforded the quinone as yellow needles, m.p. 104-105°C. (1.00g, 70%). (Found: C, 53.43; H, 3.88 $C_{15}H_{13}BrO_4$ requires C, 53.43, H, 3.89%), ν_{max} (CCl_4) 1742, 1681, 1668 and 1596 cm^{-1}, τ 1.80-2.00 (2H, m, 5- and 8 -H), 2.20-2.38 (2H, m, 6- and 7 -H), 6.33 (3H, s, CO_2CH_3), 7.09 (2H, t J 7Hz, 1' -CH_2), 7.54 (2H, t J 7Hz, 3' -CH_2) and 8.08 (2H, quintet J 7Hz, 2' -CH_2).

Bromodiacetate: (230)

The above product (228) (500 mg) in a pyridine (1 ml)-acetic anhydride (6 ml) mixture was treated with zinc dust (280 mg) and the solution was heated on a steam bath. Further additions of zinc were made after 7 and 15 mins (2 x 280 mg). The mixture was then heated under gentle reflux for a further 10 mins, thrown onto ice, and extracted with chloroform. The organic layer was dried and reduced and the oily residue chromatographed over silica (eluant, 10% ethyl acetate/light petroleum) to afford the diacetate as a white solid, m.p. 113-114°C (570 mg, 90%). (Found: C, 54.4; H, 4.6 $C_{19}H_{19}BrO_6$ requires

C, 53.9; H, 4.5%), ν_{max} ($CHCl_3$) 1764, 1724 and 1600 cm^{-1}, τ 2.18-2.58 (4H, m, 5-, 6-, 7- and 8 -H), 6.32 (3H, s, CO_2CH_3), 7.08 (2H, t J 7Hz, 1′-CH_2), 7.48 (3H, s, $COCH_3$), 7.50 (3H, s, $COCH_3$), 7.57 (2H, t J 7Hz, 3′-CH_2) and 8.06 (2H, quintet J 7Hz, 2′-CH_2).

Diacetate: (233)

The bromodiacetate (230) (300 mg), in glacial acetic acid (5 ml) containing palladium/carbon catalyst (10% Pd/C; 100 mg) and anhydrous sodium acetate (100 mg), was hydrogenolysed over 4 h at 65-70°C and ambient pressure. The mixture was then cooled, filtered, and the solvent removed. The white oily residue was taken up in chloroform (25 ml) and washed with water (2 x 10 ml). The organic layer was dried and evaporated to afford the product as a clear oil (230 mg, 95%). An analytical sample was prepared by p.l.c. (eluant, 20% ethyl acetate/light petroleum). (Found: C, 66.06; H, 5.90 $C_{19}H_{20}O_6$ requires C, 66.27; H, 5.85%), ν_{max} (CCl_4) 1788, 1770, 1740 and 1605 cm^{-1}. τ 2.13-2.39 (2H, m, 5- and 8 -H), 2.40-2.60 (2H, m, 6- and 7 -H), 2.85 (1H, s, 3 -H), 6.33 (3H, s, CO_2CH_3), 7.29 (2H, t J 7Hz, 1′-CH_2), 7.52 (3H, s, $COCH_3$), 7.54 (3H, s, $COCH_3$), 7.63 (2H, t J 7Hz, 3′-CH_2) and 8.03 (2H, quintet J 7Hz, 2′-CH_2).

Bromination of diacetate: (233)

The above product (130 mg) was heated under gentle reflux in dry carbon tetrachloride (15 ml) containing N-bromosuccinimide (81 mg, 1.2 mole equivalents) and a catalytic amount of benzoyl peroxide. The reaction was halted when t.l.c. indicated the total consumption of starting material (ca. 0.5 h). The solution was cooled, filtered and the solvent removed. The oily residue was chromatographed over silica (eluant, 20% ethyl acetate/light petroleum) to afford the bromo-product (235) as a white crystalline material, m.p. 94-95^{o}C (130 mg, 81%). (Found: C, 54.1; H, 4.6 $C_{19}H_{19}BrO_6$ requires C, 53.9; H, 4.5%), ν_{max} ($CHCl_3$) 1764, 1735 and 1608 cm^{-1}, τ 2.08-2.62 (4H, m, 5-, 6-, 7-, 8 -H), 2.58 (1H, s, 3 -H), 4.54 (1H, m, 1′-H), 6.36 (3H, s, CO_2CH_3), 7.20-7.70 (4H, m, 2 x CH_2), 7.48 (3H, s, $COCH_3$) and 7.56 (3H, s, $COCH_3$).

Formation of the olefinic ester: (241)

The bromo-product (235) (460 mg) was heated under gentle reflux in dry 2,6-lutidine (30 ml) for 5 h. The dark mixture was then cooled, the lutidine hydrobromide precipitate filtered off, and the solvent removed. The dark oily residue was chromatographed over silica (eluant, 20% ethyl acetate/light petroleum) to afford the olefin (220 mg, 69%) and starting material (50 mg). τ 2.15-2.65 (4H, m, 5-, 6-, 7- and 8 -H), 2.58 (1H, s, 3 -H), 3.38 (1H, d J 16Hz, 1′-H), 3.64 (1H, d x t J 16 and 6Hz, 2′-H), 6.28 (3H, s, OCH_3), 6.69 (2H, d J 6Hz, CH_2), 7.50 (3H, s, $COCH_3$) and 7.54 (3H, s, $COCH_3$).

Epoxidation of the olefinic ester: (241)

The above olefin (100 mg) and *m*-chloroperbenzoic acid (200 mg, 2 mole equivalents) were stirred together at room temperature in dry methylene chloride (10 ml) for 0.75 h. The mixture was washed successively with a sodium sulphate solution (10 ml, 10%), a sodium bicarbonate solution (30 ml, 5%) and water. The organic layer was then dried and evaporated to afford the epoxide (247) as an off-white solid.

No further purification was attempted. τ 1.95-2.45 (4H, m, 5-,6-, 7- and 8 -H), 2.90 (1H, s, 3 -H), 6.07 (1H, d J 2Hz, 1´-H), 6.26 (3H, s, CO_2CH_3), 6.67 (1H, d x t J 2 and 6Hz, 2´-H), 7.25 (2H, d J 6Hz, CH_2), 7.50 (3H, s, $COCH_3$) and 7.56 (3H, s, $COCH_3$).

Reductive methylation of quinone: (228)

The quinone (228) (1.50g) in diethyl ether (30 ml) was shaken with a solution of sodium dithionite (2.40g; 3 mole equivalents) in water (30 ml) until the organic layer had lost its yellow colour. The ether layer was then dried and evaporated to give the hydroquinone (231) as an off-white solid. This residue was immediately dissolved in dry acetone (50 ml) and treated with anhydrous potassium carbonate (3g, 5 mole equivalents) and dimethylsulphate (3g, 6 mole equivalents) under anhydrous conditions. The mixture was stirred vigorously and heated under gentle reflux for 5 h. The pale solution was then cooled, filtered and reduced. The oily residue was taken up in diethyl ether and washed successively with a concentrated aqueous ammonia solution (10 ml), water, 2N hydrochloric acid (20 ml) and finally with water. The organic layer was dried and evaporated to yield the dimethyl ether (232), m.p. 80-81°C (methylene chloride/light petroleum) (1.57g, 96%). (Found: C, 55.4; H, 5.2 $C_{17}H_{19}BrO_4$ requires C, 55.6; H, 5.2%), ν_{max} ($CHCl_3$) 1727, 1581 and 1456 cm^{-1}. τ 1.82-2.06 (2H, m, 5- and 8 -H), 2.38-2.60 (2H, m, 6- and 7 -H), 6.04 (3H, s, OCH_3), 6.10 (3H, s, OCH_3), 6.34 (3H, s, CO_2CH_3), 6.96 (2H, t J 7Hz, 1´-CH_2), 7.55 (2H, t J 7Hz, 3´-CH_2) and 8.00 (2H, quintet J 7Hz, 2´-CH_2).

Hydrogenolysis of bromo-dimethyl ether: (232)

The dimethyl ether (232) (500 mg) was hydrogenolysed at 35°C as described earlier for compound (230). Workup as before gave the required product (234) as a clear oil (390 mg, 100%). (Found: C, 70.5; H, 6.9 $C_{17}H_{20}O_4$ requires C, 70.8; H, 6.9%), ν_{max} (neat) 1740,1630 and 1600 cm^{-1}, τ 1.72-1.90 and 1.91-2.08 (1H each, 2 x m, 5- and 8 -H), 2.40-2.65 (2H, m, 6- and 7 -H), 3.41 (1H, s, 3 -H), 6.04 (3H, s, OCH_3), 6.14(3H,s, OCH_3),6.34 (3H, s, CO_2CH_3), 7.16 (2H, t J 7Hz, 1′-CH_2), 7.58 (2H, t J 7Hz, 3′-CH_2) and 7.96 (2H, quintet J 7Hz, 2′-CH_2).

Bromination of the dimethyl ether: (234) and its conversion to the olefinic ester: (242)

The above product (300 mg) was brominated with N-bromosuccinimide as described earlier for compound (233). Workup of the reaction mixture in this case was limited to cooling, filtration and the removal of the solvent. No chromatography was carried out for the reason outlined in Section 3.3 and described below. The bromide (236) was hence reacted further in this state. τ 1.70-2.06 (2H, m, 5- and 8 -H), 2.36-2.62 (2H, m, 6- and 7 -H), 3.19 (1H, s, 3 -H), 4.24 (1H, m, 1′-H), 6.02 (3H, s, OCH_3), 6.07 (3H, s, OCH_3), 6.36 (3H, s, CO_2CH_3) and 7.16-7.66 (4H, m, CH_2CH_2).

The crude bromide (236) (150 mg) was heated under reflux in dry 2,6-lutidine for 1.5 h. The solution was then cooled and the lutidine hydrobromide filtered off. Removal of the solvent gave a dark solid residue which yielded the olefin (242) on recrystallisation from methylene chloride/light petroleum, m.p. 61.5-62°C (130 mg, 90%)

(Found: C, 71.35, H, 6.50 $C_{17}H_{18}O_4$ requires C, 71.31; H, 6.34%), ν_{max} ($CHCl_3$) 1739 and 1600 cm^{-1}, τ 1.72-1.9 and 1.91-2.06 (1H each, 2 x m, 5- and 8 -H), 2.42-2.70 (2H, m, 6- and 7 -H), 3.00 (1H, d J 16Hz, 1´-H), 3.16 (1H, s, 3 -H), 3.66 (1H, d x t J 16 and 7Hz, 2´-H), 6.06 (3H, s, OCH_3), 6.16 (3H, s, OCH_3), 6.30 (3H, s, CO_2CH_3) and 6.66 (2H, d J 7Hz, CH_2).

Investigation of the rearrangement undergone by the bromide (236) on chromatography. The generation of the hydroxy ester (237) and the lactone (238).

Two further brominations were carried out as described above, and the residues from the workups were investigated by p.l.c. (eluant, 20% ethyl acetate/light petroleum). In both instances, 100 mg of the dimethoxy bromide (236)was prepared , and on chromatography two new products were observed to form from the bromide. viz Figure 10

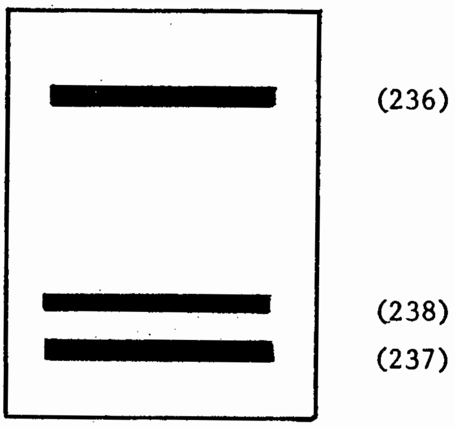


Figure 10

(a) After one elution, the two newly formed products were collected as a mixture. The approximate ratio of the products (237) and (238) in the mixture was calculated from the ^1H n.m.r. spectrum as 1 : 1. The mixture was then rechromatographed as before and eluted a further four times. Recollection and spectroscopy of the mixture then showed the ratio of (238):(237) to be 3:1.

(b) In this case, the newly formed compounds were isolated separately after one elution to afford, from Band 2, the lactone (238) m.p. 128-129°C (35 mg, 33%) (Found: C, 70.35; H, 5.85. $C_{16}H_{16}O_4$ requires C, 70.57; H, 5.92%), ν_{max} ($CHCl_3$) 1765, 1630 and 1600 cm^{-1}, τ 1.65-1.86 and 1.90-2.07 (1H each, 2 x m, 5- and 8 -H), 2.35-2.60 (2H, m, 6- and 7 -H), 3.31 (1H, s, 3 -H), 4.03 (1H, dd J 3 and 5Hz, Ar-<u>CH</u>-CH_2), 6.01 (3H, s, OCH_3), 6.08 (3H, s, OCH_3) and 7.11-7.90 (4H, m, lactone CH_2CH_2); and from Band 3, the hydroxy compound (237) (40 mg, 42%), ν_{max} ($CHCl_3$) 3450(br), 1720(br), 1633 and 1599 cm^{-1}, τ 1.70-1.90 and 1.91-2.08 (1H each, 2 x m, 5- and 8 -H), 2.38-2.62 (2H, m, 6- and 7 -H), 3.17 (1H, s, 3 -H), 4,72 (1H, t. J 6Hz, 1'-H), 6.02 (3H, s, OCH_3), 6.11 (3H, s, OCH_3), 6.34 (3H, s, CO_2CH_3) and 7.22-8.00 (4H, m, CH_2CH_2). No further purification of this latter product was carried out. Instead, the hydroxy compound (237) was stirred overnight in a mixture of tetrahydrofuran (5 ml) and dilute hydrochloric acid (5 ml). The solution was then extracted with chloroform (2 x 20 ml) and the organic layer dried and evaporated. ^1H n.m.r. spectroscopy of the residue indicated the conversion of the hydroxy compound into the lactone (238) (3:1 ratio of lactone to OH starting material). This conversion agrees with that observed in (a) and served as a characterisation of compound (237).

<u>Butoxide treatment of the bromide: (236)</u>

The bromo-compound (236) (100 mg) and potassium *t*-butoxide (60 mg, 1.5 mole equivalents) were heated under reflux in dry tetrahydrofuran for

1h. The mixture was cooled, thrown into water and extracted with ether. The organic layer was dried and evaporated and the residue purified on p.l.c. (eluant 1% ethyl acetate/light petroleum). After three elutions, the major band afforded the cyclopropyl product (244) as a clear oil (55 mg, 73%). (Found: C, 71.2; H, 6.5 $C_{17}H_{18}O_4$ requires C, 71.3; H, 6.3%), ν_{max} ($CHCl_3$) 1720, 1632 and 1598 cm^{-1}, τ 1.75-2.05 (2H, m, 5- and 8 -H), 2.20-2.63 (2H, m, 6- and 7 -H), 2.79 (1H, s, 3 -H), 6.07 (3H, s, OCH_3), 6.09 (3H, s, OCH_3), 6.25 (3H, s, CO_2CH_3), 6.87-7.11 (1H, m, Ar-$\underline{CH}$-CH_2), 7.83-8.65 (3H, m, $\underline{CH_2CH}CO_2CH_3$).

Oxidative demethylation of the lactone: (238)

The lactone (238) (50 mg), in dry dioxane (5 ml), was oxidised with silver (II) oxide (100 mg) and 6N nitric acid (0.3 ml) as described in Chapter 1. Workup as before afforded a yellow solid which was purified by p.l.c. (eluant 20% ethyl acetate/light petroleum). This gave the pale yellow quinone (240), m.p. 152-154°C (dec) (methylene chloride/light petroleum) (32 mg, 72%). (Found: C, 69.3; H, 4.1 $C_{14}H_{10}O_4$ requires C, 69.4; H, 4.1%), ν_{max} ($CHCl_3$) 1787, 1670 and 1600 cm^{-1}, τ 1.80-2.0 (2H, m, 5- and 8 -H), 2.10-2.32 (2H, m, 6- and 7 -H), 2.98 (1H, d J 2Hz, 3 -H), 4.40 (1H, apparent triplet J 7Hz, lactone $\underline{CH}CH_2CH_2$) and 6.94-8.06 (4H, m, lactone CH_2CH_2).

Cis hydroxylation of the olefinic ester: (242)

The olefin (242) (65 mg), in dry pyridine (2 ml), was treated at room temperature with osmium tetroxide (70 mg, 1.1 mole equivalents) in dry ether (3 ml). The solution was stirred for 0.75 h and then treated with a mixture of sodium bisulphite (250 mg) in water (5 ml) and pyridine (5 ml). This mixture was stirred until a homogenous orange colour was attained (ca. 0.5 h). The solution was extracted with chloroform (3 x 15 ml), and the organic layer dried and evaporated. This gave the diol (263) as a clear oil (72 mg, 73%). ν_{max} (neat) 3460, 1737, 1635 and 1602 cm^{-1}, τ 1.70-1.88 and 1.96-2.10 (1H each, 2 x m, 5- and 8 -H), 2.40-2.62 (2H, m, 6- and 7 -H), 3.16 (1H, s, 3 -H), 4.91 (1H, d J 7Hz, 1′-H), 5.65-5.90 (1H, m, 2′-H), 6.04 (3H, s, OCH_3), 6.12 (3H, s, OCH_3), 6.32 br (2H, s, 2 x OH), 6.42 (3H, s, OCH_3) and 7.26-7.78 (2H, m, CH_2).

Acid-catalysed lactonisation of the *cis* diol: (263)

Without further purification, the above diol (62 mg) in tetrahydrofuran (10 ml) was treated with concentrated hydrochloric acid (4-5 drops) and the solution set to stir for 4 h. The mixture was partitioned between water and methylene chloride. The organic layer was dried and evaporated and the residue purified by p.l.c. (eluant, methylene chloride). This afforded starting diol (263) and the product lactone (265), m.p. 145.5-146.5°C (methylene chloride/light petroleum) (40 mg, 85% based on unrecovered starting material). (Found: M^+ 288; C, 65.55; H, 5.55 $C_{16}H_{16}O_5$ requires M^+ 288; C, 66.50; H, 5.60%), ν_{max} ($CHCl_3$) 1780 cm^{-1}, τ See Figure 6.

Oxidative demethylation of the lactone: (265)

The above lactone (40 mg) was oxidatively demethylated with silver (II) oxide (100 mg) and 6N nitric acid (0.3 ml) as for compound (238). Workup as before gave a crude yellow product which, on recrystallisation, afforded the pale yellow quinone (225), m.p. 201-203°C (dec) (ethyl acetate/light petroleum) (31 mg, 86%). (Found: M^+ 258; C, 63.60; H, 3.85 $C_{14}H_{10}O_5$ requires M^+ 258; C, 65.10; H, 3.90%), ν_{max} 3460, 1775, 1728 and 1664 cm^{-1}, τ See Figure 8.

Formation of the olefinic acid: (252)

The olefin (242) (90 mg) was heated under reflux in 5% aqueous potassium hydroxide for 3 h. The cooled solution was washed with ether to remove any starting material (10 mg recovered from ether layer), and then acidified with dilute hydrochloric acid. This solution was extracted with chloroform and the organic layer dried and evaporated. The oily residue was purified by p.l.c. (eluant, 2% ethanol/methylene chloride) to afford the acid (252) as white needles, m.p. 139-140°C (methylene chloride/light petroleum) (70 mg, 92%). (Found: C,69.55 ; H, 5.85. $C_{16}H_{16}O_4$ requires C, 70.57; H, 5.92%). ν_{max} ($CHCl_3$) 3540-2600, 1712 and 1598 cm^{-1}, τ 1.72-2.06 (2H, m, 5- and 8 -H), 2.40-2.64 (2H, m, 6- and 7 -H), 2.98 (1H, d J 16Hz, 1'-H), 3.16 (1H, s, 3 -H), 3.62 (1H, d x t J 16 and 7Hz, 2'-H), 6.04 (3H, s, OCH_3), 6.14 (3H, s, OCH_3) and 6.60 (2H, d J 7Hz, CH_2).

Epoxidation of the olefinic ester: (242)

The ester (100 mg) in methylene chloride (10 ml) and aqueous sodium bicarbonate (0.5 M, 10 ml) was treated with *m*-chloroperbenzoic acid (100 mg, 85% peracid), in small portions, over 20 mins. The solution was stirred at room temperature for 3 h, after which time the organic phase was separated. This layer was washed with aqueous sodium hydroxide (1M, 5 ml) and then with water (10 ml). Subsequent drying and evaporation of the organic phase gave the epoxide (254) as a semi-crystalline residue, (95 mg, 90%). This product was shown to be sensitive to chromatography, and was hence reacted further without final purification. τ 1.70-2.10 (2H, m, 5- and 8 -H), 2.26-2.70 (2H, m, 6- and 7 -H), 3.50 (1H, s, 3 -H), 5.73 (1H, d J 2Hz, 1´-H), 6.06 (6H, s, 2 x OCH_3), 6.27 (3H, s, CO_2CH_3), 6.64 (1H, d x t J 6 and 2Hz, 2´-H) and 7.19 (2H, d J 6Hz, CH_2)

Formation of lactone : (251) from the olefinic acid: (252)

(a) Under biphasic conditions:

The acid (100 mg) was treated with *m*-chloroperbenzoic acid in the same solvent system used for the preparation of compound (254). The resulting solution was stirred for 10 h at room temperature. Workup as before afforded the lactone (251) (48 mg, 46%). The aqueous phase was retreated with more peracid in an attempt to epoxidise any further starting material present. This, however, proved unsuccessful. The product (251) has resisted all attempts at further purification by recrystallisation. The above crude lactone was purified partially by p.l.c. (eluant, methylene chloride). ν_{max} ($CHCl_3$) 3410, 1780, 1630 and 1597 cm^{-1}. τ See Figure 5.

(b) Under monophasic conditions:

The acid (100 mg), in a mixture of acetonitrile (10 ml) and aqueous sodium bicarbonate)0.5 M, 10 ml), was treated with *m*-chloroperbenzoic acid (3 mole equivalents) in small portions. (Additions of peracid were made when starch-iodide tests indicated consumption of the previous portion). At the completion of additions, the mixture was stirred for a further 4 h, and then partitioned between chloroform and water. The organic layer was dried and reduced to afford the required lactone (54 mg, 50%), identical with the material obtained in (a).

Oxidative demethylation of the lactone: (251)

The above lactone (80 mg) was oxidatively demethylated with silver (II) oxide (150 mg) and 6N nitric acid (0.4 ml) as for its isomer (265). Workup as usual gave the required quinone (224), m.p. 166-168°C (dec) (methylene chloride/light petroleum) (64 mg, 90%). (Found: M^+ 258; C, 63.80; H, 3.80 $C_{14}H_{10}O_5$ requires M^+ 258; C, 65.10; H, 3.90%). ν_{max} ($CHCl_3$) 3325, 1788, 1728, 1667 and 1600 cm^{-1}. τ See Figure 7.

BIBLIOGRAPHY

1. A.G. Anderson and D.M. Forkey, *J. Amer. Chem. Soc.*, 1969, **91**, 924.

2. M.J.S. Dewar, A.J. Harget, N. Trinajstic and S.D. Worley, *Tetrahedron*, 1970, **26**, 4505.

3. (a) R. Mayer, H. Kleinert, S. Richter and K. Gewald, *J. Prakt. Chem.*, 1963, **20**, 244.

   (b) M.P. Cava and N.M. Pollack, *J. Amer. Chem. Soc.*, 1966, **88**, 4112.

4. (a) L.F. Fieser and M.J. Haddadin, *Can. J. Chem.*, 1965, **43**, 1599.

   (b) R. McCulloch, A.R. Rye and D. Wege, *Tet. Lett.*, 1969, 5231.

   (c) W.S. Wilson and R.N. Warrener, *Tet. Lett.*, 1970, 5203.

5. R. Kreher and J. Seubert, *Z. Naturforsch. B.*, 1965, **20**, 75.

6. (a) G.M. Priestley and R.N. Warrener, *Tet. Lett.*, 1972, 4295.

   (b) R.N. Warrener, *J. Amer. Chem. Soc.*, 1971, **93**, 2346.

7. (a) H. Heaney, S.V. Ley, A.P. Price, R.P. Sharma, *Tet. Lett.*, 1972, 3067.

   (b) B. Jaques and R.G. Wallace, *J. Chem. Soc. Chem. Comm.*, 1972, 397.

   (c) R. Bonnett and R.F.C. Brown, *J. Chem. Soc. Chem. Comm.*, 1972, 393.

8. J.F. Geldard and F. Lions, *J. Org. Chem.*, 1965, **30**, 318.

9. (a) K. MacKenzie and W.P. Lay, *Tet.Lett.*, 1970, 3241.

   (b) W.P. Lay and K. MacKenzie, *J. Chem. Soc. Chem. Comm.*, 1970, 398.

10. R.G.F. Giles and I.R. Green, *J. Chem. Soc. Perkin I*, 1974, 228.

11. R.G.F. Giles and G.H.P. Roos, *J. Chem. Soc. Chem. Comm.*, 1975, 260.

12. E. Ghera, Y. Gaoni and D.H. Perry, *J. Chem. Soc. Chem. Comm.*, 1974, 1034

13. S.E. Fumagalli and C.H. Eugster, *Helv. Chim. Acta.*, 1971, **54**, 959.

14. O.C. Musgrave, *Chem. Rev.*, 1969, **69**, 499.

15. L. Syper, *Tet. Lett.*, 1967, 4193.

16. C.D. Snyder, W.E. Bondinell and H. Rapoport, *J. Org. Chem.*, 1971, **36**, 3951.

17. C.D. Snyder and H. Rapoport, J. Amer. Chem. Soc., 1972, 94, 227.

18. C.W. Rees and D.E. West, J. Chem. Soc. (C), 1970, 583.

19. H. Heaney, J.H. Hollinshead, G.W. Kirby, S.V. Ley, R.P. Sharma and K.W. Bentley, J. Chem. Soc. Perkin I, 1973, 1840.

20. P.G. Sammes and T.W. Wallace, J. Chem. Soc. Chem. Comm., 1973, 524.

21. E. Gould and D. Ginsberg, J. Chem. Soc.(C)1967, 15.

22. R.C. Cookson, J.J. Frankel and J. Hudec, J. Chem. Soc. Chem. Comm., 1965, 16.

23. M.V. Sargent and D. O'N. Smith, J. Chem. Soc.(C)1969, 2763.

24. (a) A.W. Hofmann, Proc. Roy. Soc., 1863, 13, 4.
    (b) Fieser and Fieser, "Advanced Organic Chemistry", Reinhold, New York, 1961, 853.
    (c) D.W. Cameron and R.G.F. Giles, J. Chem. Soc. (C), 1968, 1461.

25. F. Fieser, "Organic Experiments", D.C. Heath and Co., Boston, 1964, 250.

26. (a) J.F.W. McOmie, M.L. Watts and D.E. West, Tetrahedron, 1968, 24, 2289.
    (b) J.F.W. McOmie and D.E. West, Org. Syn. Col. Vol. 5, 412.

27. S. Hakamori, J. Biochem.,(Tokyo), 1964, 55, 205.

28. R.M. Lukes, G.I. Poos, R.E. Beyler, W.F. Johns and L.H. Sarett, J. Amer. Chem. Soc., 1953, 75, 1707.

29. J.D. Roberts and M.C. Caserio, "Basic Principles of Organic Chemistry", W.A. Benjamin, Inc. New York, 1964, 981.

30. J.L. Melles and H.J. Backer, Rec. Trav. Chim., 1953, 72, 491.

31. W. Davies and F.C. James, J. Chem. Soc., 1954, 15.

32. (a) W.J. Bailey and E.W. Cummins, J. Amer. Chem. Soc., 1954, 76, 1932.
    (b) W.J. Bailey and E.W. Cummins, J. Amer. Chem. Soc., 1954, 76, 1936.
    (c) W.J. Bailey and E.W. Cummins, J. Amer. Chem. Soc., 1954, 76, 1940.

33. M. Procházka, Coll. Czech. Chem. Com., 1965, 30, 1158.

34. G. Haberman, Chem. Ber., 1898, 11, 1034.

35. G.I. Feutrill and R.N. Mirrington, Aust. J. Chem., 1972, 25, 1719.

36. H. Zimmer, D.C. Lankin and S.W. Horgan, Chem Rev., 1971, 71, 229.

37. F.G. Pope and A.S. Wood, J. Chem. Soc., 1912, 101, 1823.

38. I. Fleming and T. Mah, J. Chem. Soc., Perkin I, 1975, 964.

39. K.L. Shepard, Tet. Lett., 1975, 3371.

40. G.L.Ciamician and M. Dennstedt, Chem. Ber., 1882, 15, 2579.

41. R.H. Thomson, "Naturally Occurring Quinones", Academic Press, 2nd Ed., London and New York, 1971.

42. P.M. Brown, V. Krishnamoorthy, J.W. Mathieson and R.H. Thomson, J. Chem. Soc. (C), 1970, 109.

43. A.C. Baillie and R.H. Thomson, J. Chem. Soc. (C), 1966, 2184.

44. (a) R.G. Coombe, Aust. J. Chem., 1972, 881, 25.

    (b) R.G. Coombe, Aust. J. Chem., 1974, 1327, 27.

45. J.E. Davies, F.E. King and J.C. Roberts, J. Chem. Soc., 1955, 2782.

46. (a) A.J. Birch, E.M.A. Shoukry and F. Stansfield, J. Chem. Soc., 1961, 5376.

    (b) A.J. Birch, D.N. Butler and J.B. Siddall, J. Chem. Soc., 1964, 2932.

    (c) A.J. Birch, D.N. Butler and J.B. Siddall, J. Chem. Soc., 1964, 2941.

    (d) A.J. Birch and G. Subba Rao, Adv. Org. Chem., 1972, 8, 1.

47. K. Alder and H.F. Rickert, Chem. Ber., 1937, 70, 1354.

48. A.J. Birch and V.H. Powell, Tet. Lett., 1970, 3467.

49. A.J. Birch and J.S. Hill, J. Chem. Soc. (C), 1966, 419.

50. M.F. Ansell and A.H. Clements, J. Chem. Soc. (C), 1971, 269.

51. eg: L.F. Fieser and H. Fieser, "Advanced Organic Chemistry", Reinhold, New York, 1961, 853.

52. F. Benington, R.D. Morin and L.C. Clark, J. Org. Chem., 1955, 20, 102.

53. (a) D. Leupold and S. Dähne, Theor. Chem. Acta., 1965, 3, 1.
    (b) S. Dähne, J. Ranft and H. Paul, Tet. Lett., 1964, 3355.
    (c) S. Kulpe, D. Leupold and S. Dähne, Ang. Chem. (Int. Ed.), 1966, 5, 599.
    (d) S. Dähne and D. Leupold, Ang. Chem. (Int. Ed.), 1966, 5, 984.

54. J.A.D. Jeffreys, J. Chem. Soc., 1959, 2153.

55. (a) A.J. Birch, Quart. Rev., 1950, 4, 69.
    (b) A.J. Birch, J. Chem. Soc., 1944, 430.
    (c) A.J. Birch and K.P. Dastur, J. Chem. Soc. Perkin I, 1973, 1650.

56. R.H. Thomson, J. Org. Chem., 1948, 13, 870.

57. J. Wolinsky and R.B. Login, J. Org. Chem., 1970, 35, 1986.

58. (a) K. Yoshihira, M. Tezuka, C. Takahashi and S. Natori, Chem. Pharm. Bull., (Tokyo), 1971, 19, 851.
    (b) M. Tezuka, M. Kuroyanagi, K. Yoshihira and S. Natori, Chem. Pharm. Bull., (Tokyo), 1972, 20, 2029.

59. R.G.F. Giles and G.H.P. Roos, Tet. Lett., 1975, 4159.

60. R.G. Coombe, Aust. J. Chem., 1974, 27, 1327.

61. R.H. Thomson, J. Chem. Soc., 1949, 1277.

62. R.H. Thomson, J. Org. Chem., 1948, 13, 377.

63. M. Asano and J. Hase, J. Pharm. Soc. Japan, 1943, 63, 83 and 90; Chem Abs., 1952, 46, 92.

64. G.R. Birchall and A.H. Rees, Can. J. Chem., 1974, 52, 610.

65. J.W. MacLeod and R.H. Thomson, J. Org. Chem., 1960, 25, 36.

66. A. Rashid and G. Read, J. Chem. Soc. (C), 1967, 1323.

67. T. Matsumoto, C. Mayer and C.H. Eugster, Helv. Chim. Acta., 1969, 52, 808.

68. H. Inouye, T. Okuda and T. Hayashi, Chem. Pharm. Bull.(Tokyo), 1975, 23, 384.

69. S.C. Hooker, J. Amer. Chem. Soc., 1936, 58, 1163.

70. (a) L.F. Fieser, M.T. Leffler, *et al.*, J. Amer. Chem. Soc., 1948, 70, 3151.

(b) L.F. Fieser, S. Archer, *et al.*, J. Med. Chem., 1967, 10, 513, 517.

71. (a) P.K. Nayak, D. Molins, F.J. Carelton and R.K. Morrison, Federation Proc., 1968, 27, 532.

(b) K.V. Rao, T.J. McBride and J.J. Oleson, Cancer Research, 1968, 28, 1952.

72. N. Tanaka, H. Ogata, K. Ushiyama and H. Ono, Jap. J. Antibiotics, 1971, 24, 222.

73. M.E. Bergy, J. Antibiotics, (Tokyo), 1968, 21, 454.

74. " The Constitution and Properties of Lapachol, Lomatiol and Other Hydroxynapthaquinone Derivatives ", 1937. Memorial Volume to S.C. Hooker (1864-1935). ed. L.F. Fieser.

75. L.F. Fieser, J. Amer. Chem. Soc., 1926, 48, 3201.

76. L.F. Fieser, J.Amer. Chem. Soc., 1927, 49, 857.

77. A.R. Burnett and R.H. Thomson, Chem. Ind. (London), 1968, 1771.

78. (a) L.F. Fieser, J. Amer. Chem. Soc., 1939, 61, 3467.

(b) O. Isler and K. Doebel, Helv. Chim. Acta., 1954, 37, 225.

(c) H. Noll, R. Rüegg, U. Gloor, G. Ryser and O. Isler, Helv. Chim. Acta., 1960, 43, 433.

(d) L.M. Jackman, R. Rüegg, G. Ryser, C. von Planta, U. Gloor, H. Mayer, P.Schudel, M. Kofler and O. Isler, Helv. Chim. Acta, 1965, 48, 1332.

79. K.L. Stevens, L. Jurd and G. Manners, Tetrahedron, 1972, 28, 1939.

80. M. Gates and D.L. Moesta, J. Amer. Chem. Soc., 1948, 70, 614.

81. K.H. Dudley and R.W. Chiang, J. Org. Chem., 1969, 34, 120.

82. (a) S.C. Hooker, J. Chem. Soc., 1892, 61, 611.

(b) S.C. Hooker, J. Chem. Soc., 1896, 69, 1355.

83. M.G. Ettlinger, J. Amer. Chem. Soc., 1950, 72, 3090.

84. (a) N. Jacobsen and K. Torssell, Ann., 1972, 763, 135.

(b) N. Jacobsen and K. Torssell, Acta. Chem. Scand., 1973, 27, 3211.

85. A.R. Burnett and R.H. Thomson, J. Chem. Soc. (C), 1967, 1261.

86. S.M. McElvain and E.L. Engelhardt, J. Amer. Chem. Soc., 1944, 66, 1077.

87. eg: L.F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol I, 1967, Wiley, 80.

88. R.G.F. Giles and I.R. Green, J.Chem Soc.(Perkin I), 1974, 228.

89. L.F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol I, 1967, Wiley, 135.

90. L.F.Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol I, 1967, Wiley, 457.

91. W.K. Anderson and T. Veysoglu, J.Org. Chem., 1973, 38, 2267.

92. Y. Ogata and Y. Sawaki, Tetrahedron, 1964, 20, 2065.

93. eg: R. Criegee, B. Marchand and H. Wanqowius, Ann., 1941, 550, 99.
L.H.Sarett, J. Amer. Chem. Soc., 1948, 70, 1454.
D.H.R.Barton and D. Elad, J. Chem. Soc., 1956, 2090.

94. J.S. Baran, J. Org. Chem., 1960, 25, 257.

ACKNOWLEDGEMENTS

The author wishes to thank his supervisor Dr. R.G.F. Giles for his guidance and continual encouragement whilst supervising this project, and Professor A.M. Stephen for the facilities of his department.

The author also wishes to thank Professor R.H. Thomson, Department of Chemistry, University of Aberdeen, Scotland for stimulating discussions during a visit to this Department.

The author is also grateful to Mr. W.T. Hemsted for the microanalyses performed, to Dr. Bartel, University of Stellenbosch, for the high resolution mass spectrometric data, and Mr. I. Finter and the University of Cape Town n.m.r. unit for running the ^{1}H n.m.r. spectra.

Financial support received from the Council of the University of Cape Town and the Council for Scientific and Industrial Research is gratefully acknowledged.

Finally, the author wishes to thank his wife for her patience and for the typing of the thesis.