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A Thesis entitled

Quinone methidesrelated to 1-naphthol

Submitted to the University of
Glasgow
For the Degree of Master of Science
in the Faculty of Science

by

NOURREDDINE BEGHIDJA

Licence - DES (Constantine)

Chemistry Department September 1986

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DEDICATION

This thesis is dedicated to all members of my family, especially my dear mother.

Also to the people of my beloved homeland, Algeria.

ACKNOWLEDGEMENT

I wish to thank my supervisor Dr. J. Carnduff for his constant guidance and the help he has rendered me throughout the period of this reserach.

I also would like to thank Professor G. W. Kirby for the opportunity of carrying out this work.

I also thank Dr. David Rycroft for his perceptive and useful comments concerning the nmr spectral interpretation.

The assistance of the technical staff of the University of Glasgow Chemistry Department is also gratefully acknowledged.

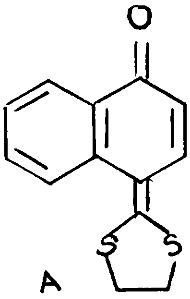
Finally, many thanks are due to the Algerian government for the financial support without which this work could not have been carried out.

SUMMARY

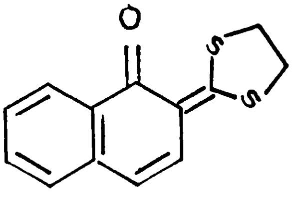
This thesis contains three short reviews as follows:-

1. Reaction of 1-naphthol with electrophiles
2. Formylation of 1-naphthol
3. Preparation methods and different types of reactions of quinone methides.

Repetition of treatment of 1-naphthol with carbon disulphide and then dibromoethane gives the two isomeric quinonemethides (A) and (B) and not, as claimed earlier, exclusively the para isomer.



A



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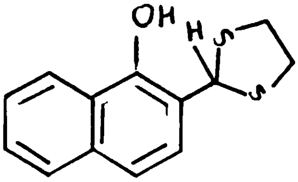

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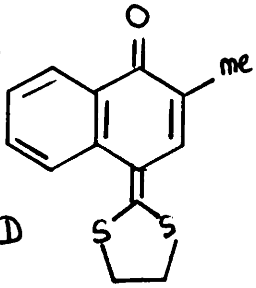


D

The major product of this reaction is proved to be the ortho one by detailed analysis of its spectra and by reduction <u>via</u> a dihydroderivative to 2-methyl-1-naphthol which was prepared independently for comparison. The para isomer is present in very small amount but it can be isolated by chromatography and its structure confirmed spectroscopically.

This thesis describes an investigation of a specific route to the para isomer. Several methods to formylate 1-naphthol were investigated. The Gattermann Adams reaction proved most effective. The dihydrophenol (c)

was made from 4-formyl-1-naphthol but attempts using a wide range of oxidising agents failed to convert it to (A). The 2-bromoderivative also failed to undergo clean oxidation.

2-Methyl-naphthoquinonemethide (D) was prepared by the CS_2 reaction and characterised, but 2-chloro- and 2-bromonaphthols failed to give the corresponding quinone methide.

Changing the solvent of the original reaction of 1-naphthol gave the two isomers in the ratio (1:1). The two isomers were successfully isolated and fully characterised and their spectra is reported. The nmr spectra of (A) were found to be affected by the presence of acid.

CONTENTS

1. INTRODUCTION

1-Naphthalenol (1-naphthol, alpha-naphthol, 1-hydroxy naphthalene) forms colourless crystals which tend to become coloured on exposure to air or light. It can be prepared by three different methods.

i. Pressure hydrolysis of 1-naphthaleneamine with aqueous sulfuric acid at 180°C.

ii. Fusion of sodium 1-naphthalenesulfonate with 50% w/w. aqueous sodium hydroxide at about 290°C followed by neutralization gives 1-naphthalenol in about 90% yield. However, the starting material for this method is not readily available in purity adequate to make high purity 1-naphthol.

iii. Oxidation of tetralin to tetralone which is dehydrogenated in the presence of transition metals as catalyst.

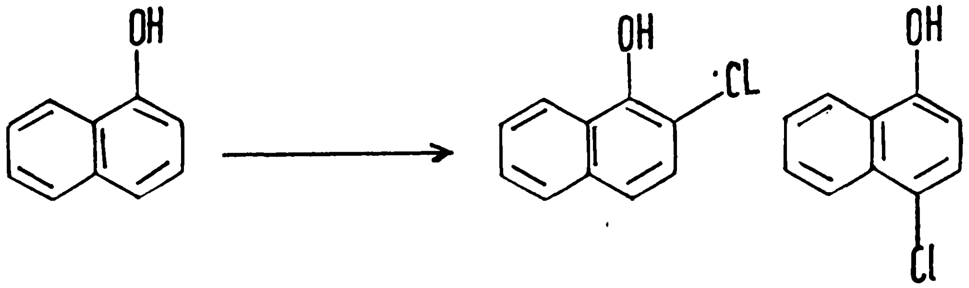
1-Naphthol is a moderately toxic and highly irritating chemical. It has an important use in making several agricultural chemicals and drugs. It is used in the preparation of azo, indigoid- and nitro-dyes, and making dye intermediates, e.g. naphtholsulfonic acids, 4-chloro-1-naphthalenol and 1-hydroxy-2-naphthonic acid. It is an antioxidant for gasoline and some of its alkylated derivates are stabilizers for plastics and rubber.

2. REACTION OF 1-NAPHTHOL WITH ELECTROPHILES

Because of electron release from the phenolic hydroxy group 1-naphthol is expected to react with electrophiles at positions 2 and 4, i.e. ortho and para to the hydroxyl group. A review of the literature was made and it confirms this prediction but also shows that there is little to chose between the two sites and that small changes in the solvent, for example, can change the reaction site. It is also possible that some of the older assignments of structure are wrong. Some seem to have been assumed by analogy, some are confirmed by interconversions. Only recently has proton NMR allowed fairly certain proof.

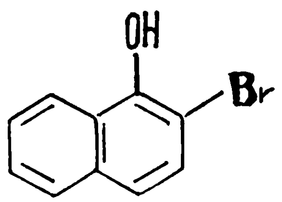
2.1 Halogenation

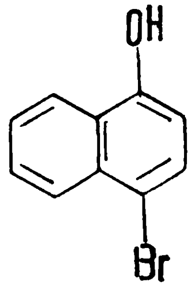
When 1-naphthol is treated with SO_2Cl_2 in hot chloroform 4-chloro-1-naphthol and 2-chloro-1-naphthol are formed(1).

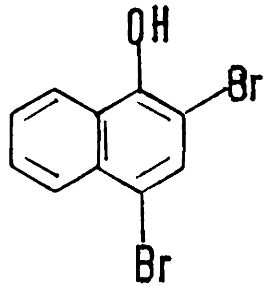


Only 4-chloro-1-naphthol is obtained by the reaction in ether in the presence of $BiCl_3$ as catalyst(2). Treatment of sodium 1-naphthoxide with aqueous sodium hypochlorite gives exclusively 2-chloro-1-naphthol in about 70% yield(3).

On treatment of 1-naphthol with bromine and quinoline sulfate in glacial acetic acid 4-bromo-1-naphthol was formed(4), whereas treatment with bromine and t-butylamine gave 2-bromo-1-naphthol in 61% yield(5).



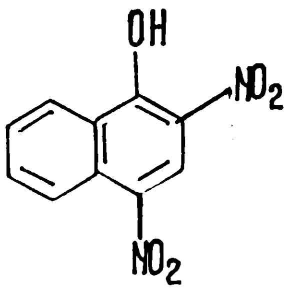


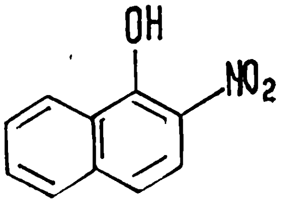


Treatment of 1-naphthol with bromine in glacial acetic acid with cooling or in carbon disulphide gives 2,4-dibromo-1-naphthol.

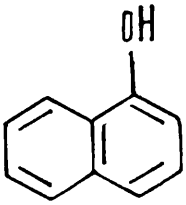
2.2 Nitration and Nitrosation

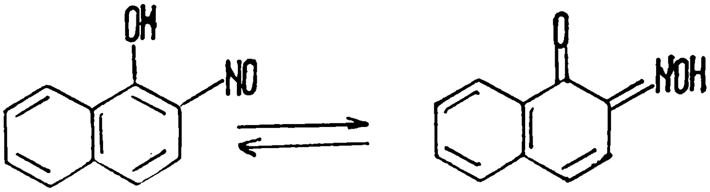
Treatment of 1-naphthol with diacetylorthonitric acid in the cold gives 2-nitro-1-naphthol(6). NO_2 in a cooled mixture of benzene and petroleum ether cooled down in a freezing mixture gave 2-nitro-1-naphthol and 2,4-dinitro 1-naphthol(7).

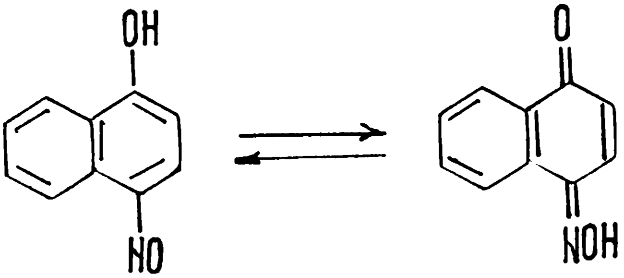




The old literature describes many procedures for nitrosation of 1-naphthol giving 2-nitroso-1-naphthol, tautomeric with 1,2-naphthoquinone-2-oxime and a small amount of 4-nitroso-1-naphthol, tautomeric with 1,4-naphthoquinone oxime.



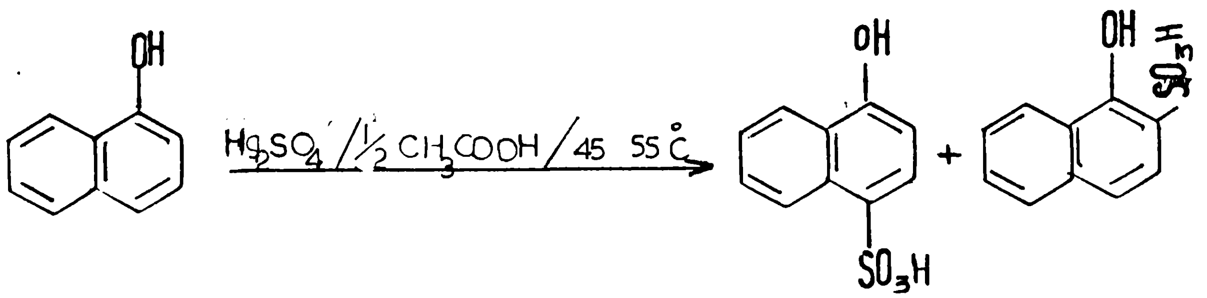




More recently it was found that treatment with sodium nitrite and 2M-hydrochloric acid solution in acetone and water as solvent gives exclusively 4-nitroso-1-naphthol(8). Whereas treatment of 1-naphthol with sodium nitrite and aluminium sulfate in water gives the ortho and the para isomers in the ratio of 31% and 41% respectively(9).

2.3 Sulfonation

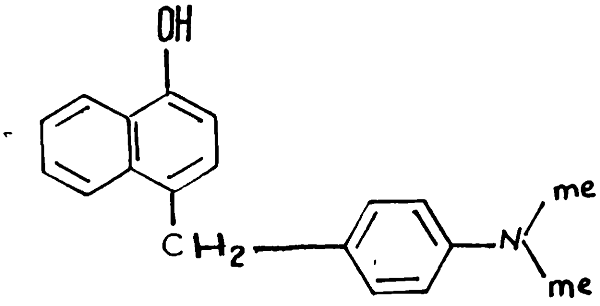
On treatment of 1-naphthol with an equal amount of sulfuric acid at 60°-70°C for a short time 1-naphthol-2-sulphonic acid and some of the 1-naphthol-4-sulphonic acid are formed. These acids are also obtained in the presence of Hg_2SO_4 with an equal amount of sulfuric acid plus half amount of glacial acetic acid(10). On further sulfonation the disulfonic acid appears instead.



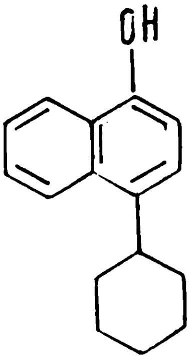
Under various conditions 1-naphthol reacts with chlorosulfonic acid to yield mixtures of both isomers(11).

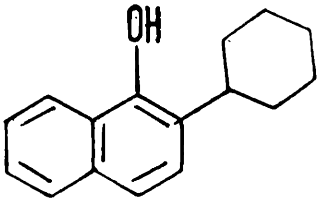
2.4 Reactions with Alcohols

1-naphthol reacts with triphenyl carbinol in acetic acid in the presence of concentrated sulfuric acid at 18°C for 16 hours yielding 4-triphenylmethyl-1-naphthol in 44% yield(12). On boiling with p-dimethylaminobenzyl alcohol in dilute hydrochloric acid it gives 4-(p-dimethylaminobenzyl)-1-naphthol(13).



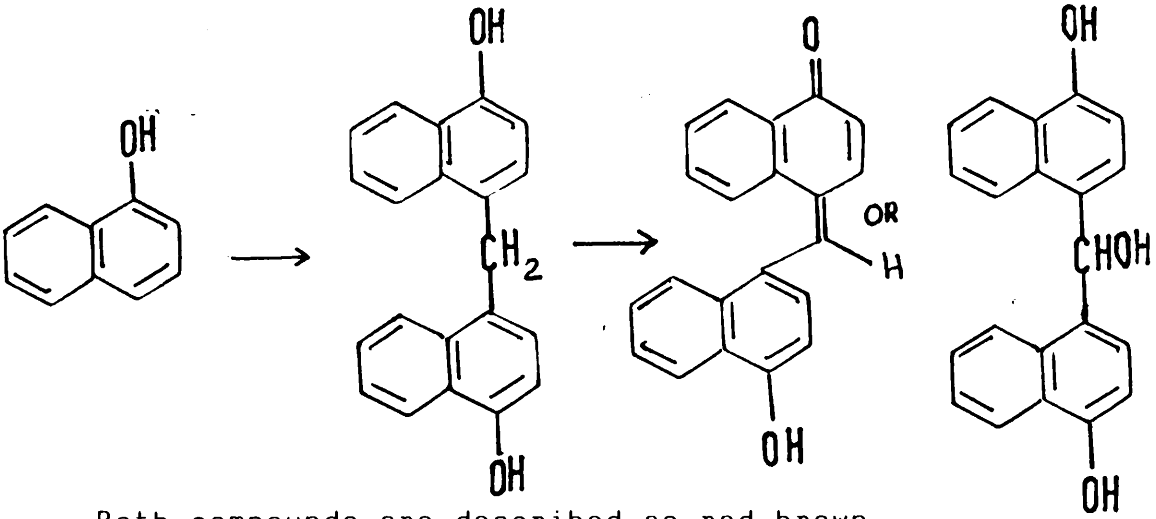
Heating 1-naphthol with cyclohexanol and zinc chloride at 150-170°C gives 2- and 4-cyclohexyl-1-naphthols(14).





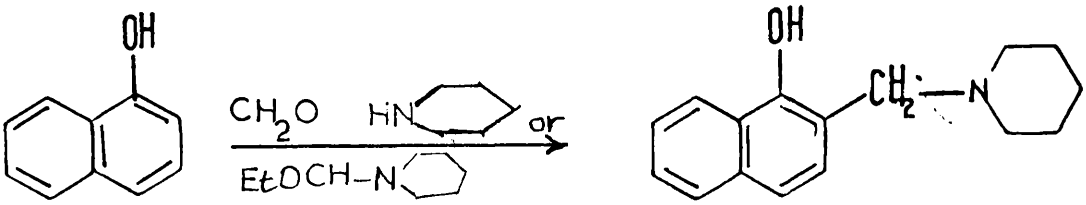
2.5 Reactions with aliphatic keto compounds and derivatives

Warming 1-naphthol and aqueous formaldehyde in alcohol and concentrated hydrochloric acid probably forms bis-(4-hydroxy-1-naphthyl)-methane which according to Zamparo(15) is subsequently oxidised by air to a quinone methide, but according to Castiglioni(16) the product is bis (4-hydroxy-1-naphthyl) carbinol.

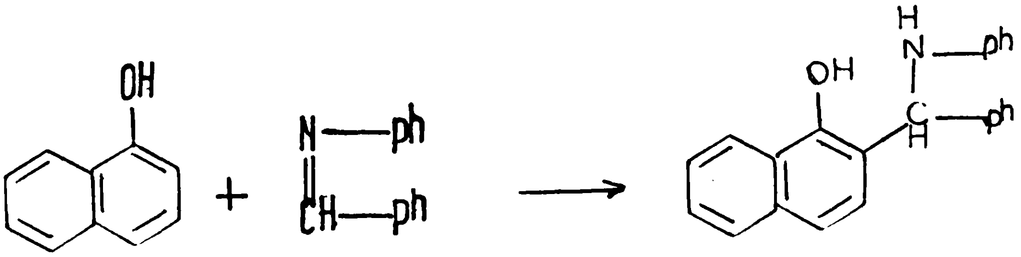


Both compounds are described as red brown products soluble in alkali with a blue colour.

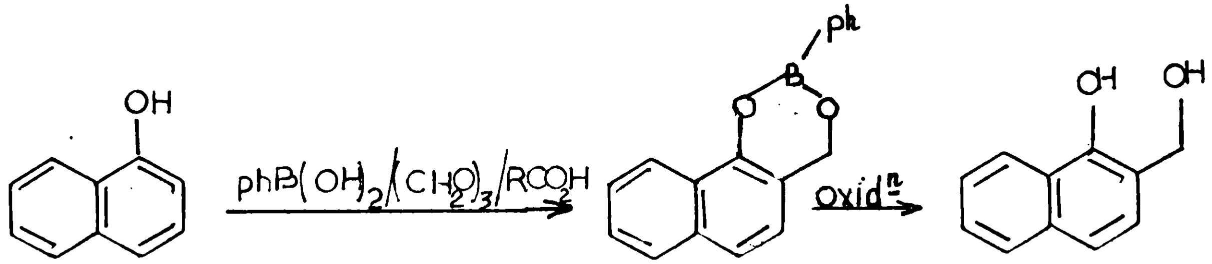
In the older literature the position of the attack on the aromatic nucleus was sometimes assumed without proof. For instance, it was believed(17) that treatment of 1-naphthol with formaldehyde and piperidine gives 4-piperidinomethyl-1-naphthol, but it has been proved(18) later on that the product from this reaction is the ortho isomer. This was done by hydrogenolysis to 2-methyl-1-naphthol.



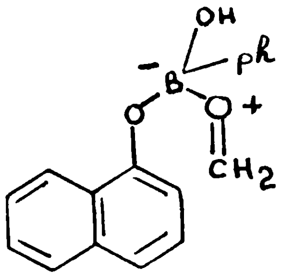
Treatment of 1-naphthol with N-benzylidenaniline in benzene gives 2-(α-anilino benzyl)-1-naphthol(19).



With benzaldehyde and piperidine or with phenyldipiperidino-methane, 2-piperidinobenzyl-1-naphthol is formed(20). Treatment of 1-naphthol with a large excess of paraformaldehyde and slight excess of benzeneboronic acid in refluxing benzene in the presence of 0.3 mole equivalent of propionic acid gave the boronate ester in 90% yield which could be converted via an oxidation process to 2-hydroxymethyl-1-naphthol(21).



The regioselectivity of this reaction is almost certainly due to formation of a complex as is shown below which, by a stepwise electrophilic aromatic substitution or by a pericyclic rearrangement, gives the

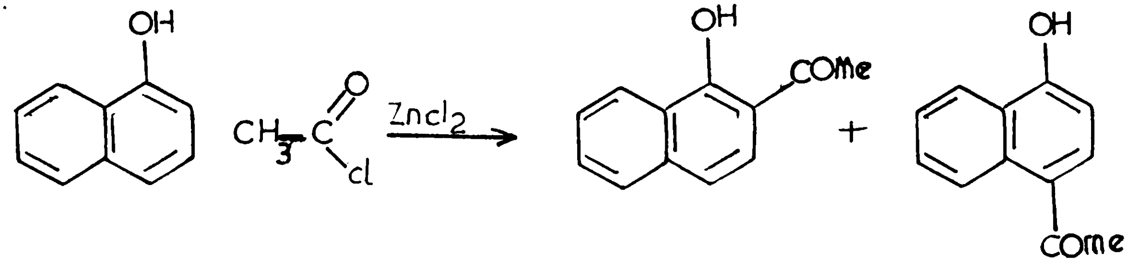


ortho substituted naphthol as its cyclic boronate.

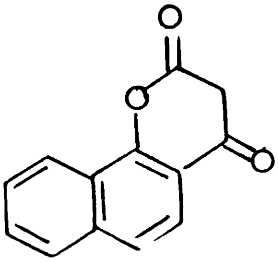
2.6 Reactions with carboxylic acids and their derivates

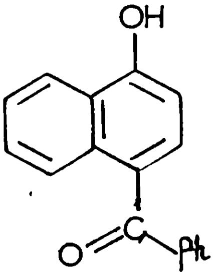
Reactions with formic acid derivates are discussed in the next section, page 13

Treatment of 1-naphthol with acetyl chloride in the presence of zinc chloride in nitro benzene at room temperature gave a mixture of the 2-acetyl and the 4-acetyl derivatives in the ratio of (1:2). The two isomers interconvert when heated with zinc chloride in glacial acetic acid$^{(22)}$.



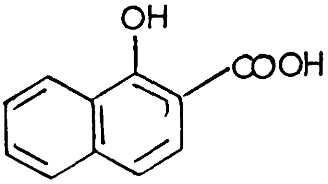
On treatment with acetic acid and boronfluoride the same isomers were obtained in the ratio of (5:95) respectively. But with higher acids such as propionic acid and boron trifluoride as catalyst the 2-acyl-naphthol was obtained as the major isomer [23]. On heating with malonic acid and anhydrous $ZnCl_2$ the lactone of 1-hydroxy-2-naphthoylacetic acid and 2-acetyl-1-naphthol are produced[24]. On heating with benzoyl chloride and zinc chloride 1-naphthol gives 4-benzoyl-1-naphthol[25].



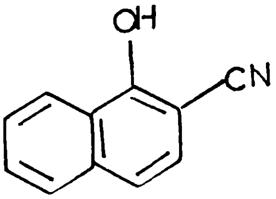


2.7 Reactions with carbon dioxide and carbonic acid derivatives

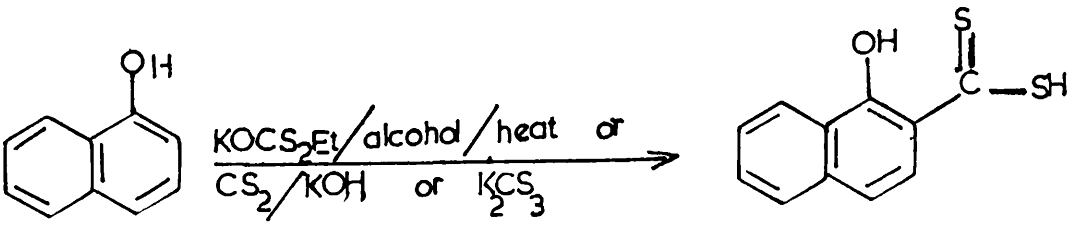
On heating sodium 1-naphthoxide and dry carbon dioxide 1-hydroxy-2-naphthoic acid is formed[26]. The same compound is obtained by heating dry sodium naphthoxide with carbon dioxide at 130°C under pressure or by passing carbon dioxide into a boiling solution of 1-naphthol in toluene which contains sodium.

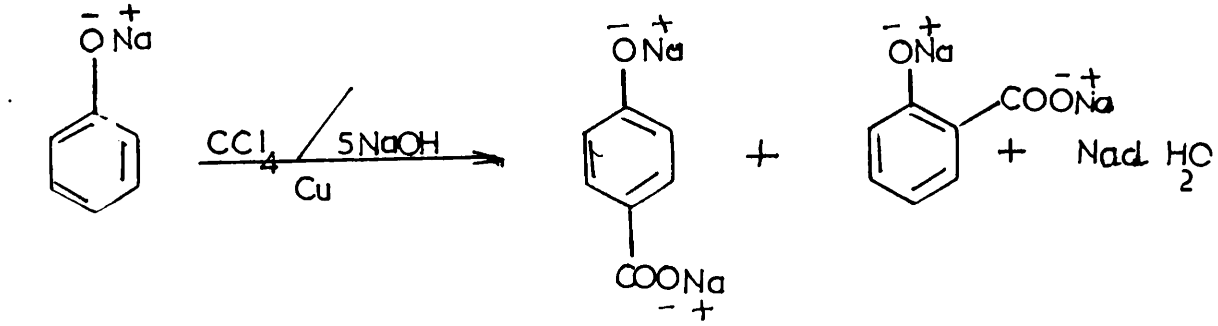


On boiling 1-naphthol with mercury fulminate and Potassium cyanide in aqueous alcohol 1-hydroxy-2-cyano-naphthalene is formed(27).

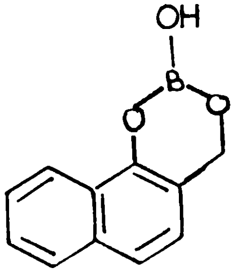


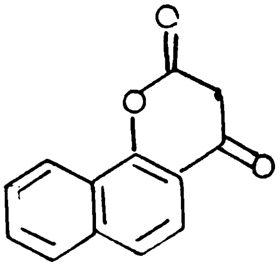
1-naphthol reacts with K_2CS_3, at 130°C or potassium xanthate and alcohol, and potassium naphthoxide reacts with carbon disulfide on a water bath, to yield in each case 1-hydroxy-naphthalene-2-carbodithioic acid(28).





Recently it has been shown that reaction of phenols with carbon tetrachloride and sodium hydroxide catalysed by coppermetal, and involving the CCl_3^+ ion, gives mixtures of 2- and 4-hydroxybenzoic acids. The reaction can be made to give the para isomer almost exclusively by adding certain cyclodextrins(29) or by adjusting the concentration, and so the viscosity, of the sodium hydroxide(30). This reaction of 1-naphthol has not been reported.





In some of the older references given above the structure assignments and the ratio of isomers are sometimes not certain. It is clear that the site of attack by electrophiles is very sensitive to changes in the reaction conditions. Attack sometimes happens only at C-2 and sometimes only at C-4 and the reasons for this are not clear.

The only cases where there is a clear explanation for selectivity are those where an intramolecular mechanism leads uniquely to the 2-substituted-1-naphthol such as: ... those on the previous page.

3. FORMYLATION OF 1-NAPHTHOL

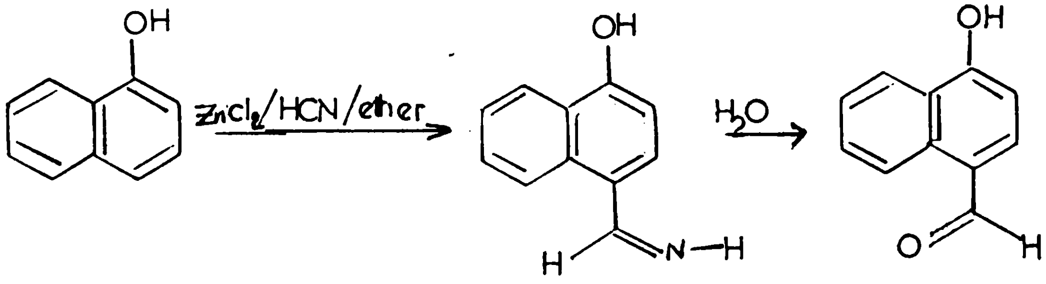
The introduction of a formyl moiety onto an aromatic nucleus has been known for a long time and there has been a series of developments of formylating procedures.

Almost all of these involve substitution by an electrophile reagent. Carbon monoxide, hydrogen cyanide, chloroform, formamides, formamidines and orthoformates or thioformates have been used as the source of the formyl group. There is no clear control over the site of attack and formylation of a phenol can occur ortho or para to the hydroxyl group.

The following review is in roughly historical order and concentrates on methods that have been used for formylating phenols.

3.1 Gattermann reaction

On treating benzene and its substitution products with carbon monoxide and hydrogen chloride in the presence of aluminium chloride as catalyst benzaldehydes are formed in less than 40% yield(31). This process has been altered by Gattermann himself in 1906 who found that certain types of phenols condense with hydrogen cyanide in the presence of zinc chloride to form an intermediate compound which can be hydrolysed very easily to form a hydroxyaldehyde.



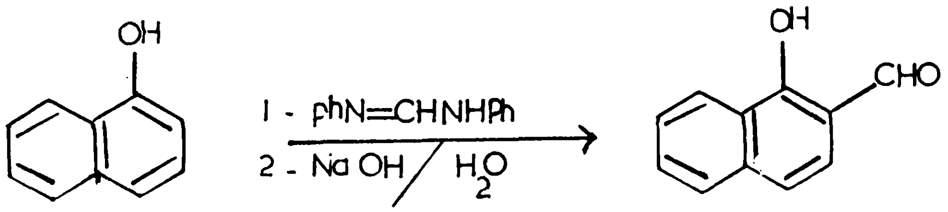
This procedure has been extended to mono and dihydronaphthalene(32).

3.2 Adams Reaction(33)

This procedure is a version of the Gattermann reaction to make it more convenient and more safe. It uses zinc cyanide and dry hydrogen chloride gas in place of the hydrogen cyanide and zinc chloride. Very satisfactory yields have been obtained with resorcinol, 1-naphthol, 2-naphthol, orcinol and pyrogallol under these conditions.

$$\mathrm{Ar{-}H} \xrightarrow{\substack{\text{i - HCl / Zn(CN)}_2 \\ \text{ii - } H_2O}} \mathrm{Ar{-}CHO}$$

The mechanistic pathway involves the production of the hydrogen cyanide in the reaction vessel. Protonated hydrogen cyanide is probably the actual electrophile. In the case of 1-naphthol about 75% of yield of the 4-aldehyde is reported. In contrast heating 1-naphthol with N,N-diphenylformamidine at 95°C followed by hydrolysis with sodium hydroxide gives 20% of 1-hydroxy-2-naphthaldehyde after steam distillation(34).

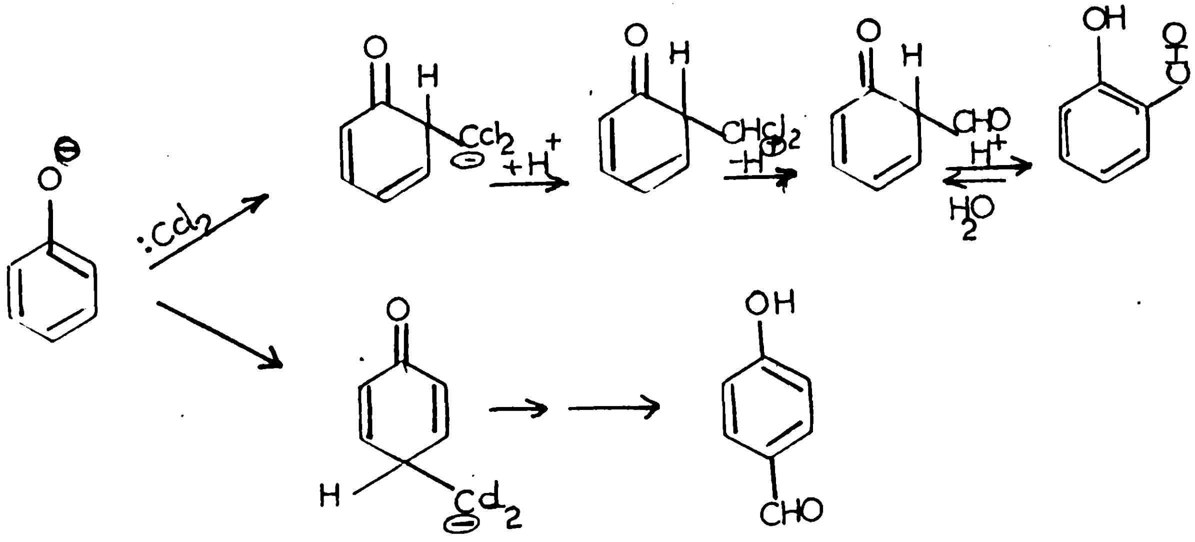


3.3 Reimer Tiemann reaction(35)

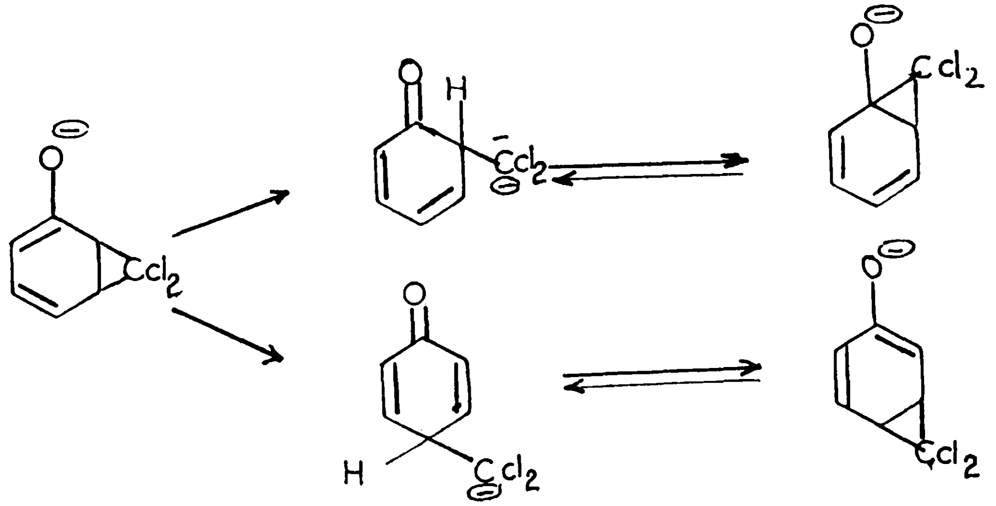
On warming phenol with chloroform in alkaline solution the hydroxy aldehyde can be produced and the substitution occurs generally ortho as well as para to the phenolic hydroxyl. The ortho/para ratio appears to depend upon the solvent, the haloform used, and the nature of the cation.

The mechanism might involve the formation of an alkylated intermediate which can be stabilized with a proton transfer process as follows.

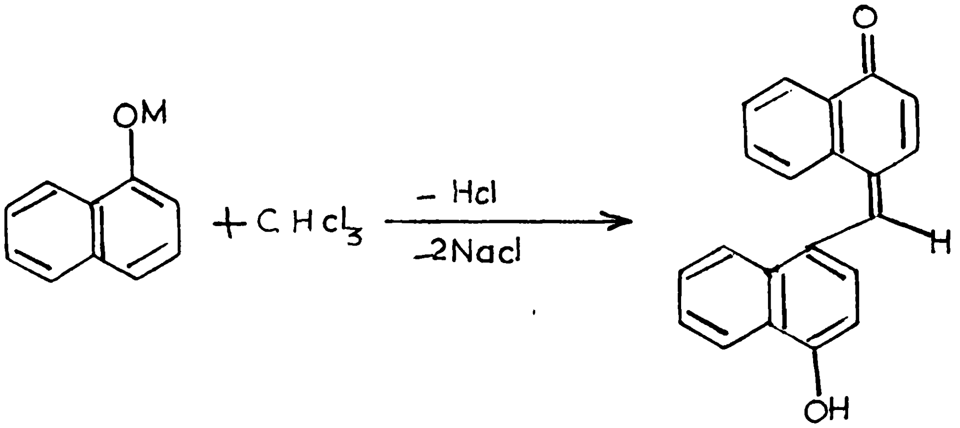
$$CHCl_3 + KOH \longrightarrow :CCl_2 + KOH + H_2O$$



The intermediate carbanions may be in equilibrium with dichloro-cyclopropanes with the charge on the oxygen. The opening of the cyclopropane ring of any of the bicyclic structures could only give the ortho and para but not meta orientation.



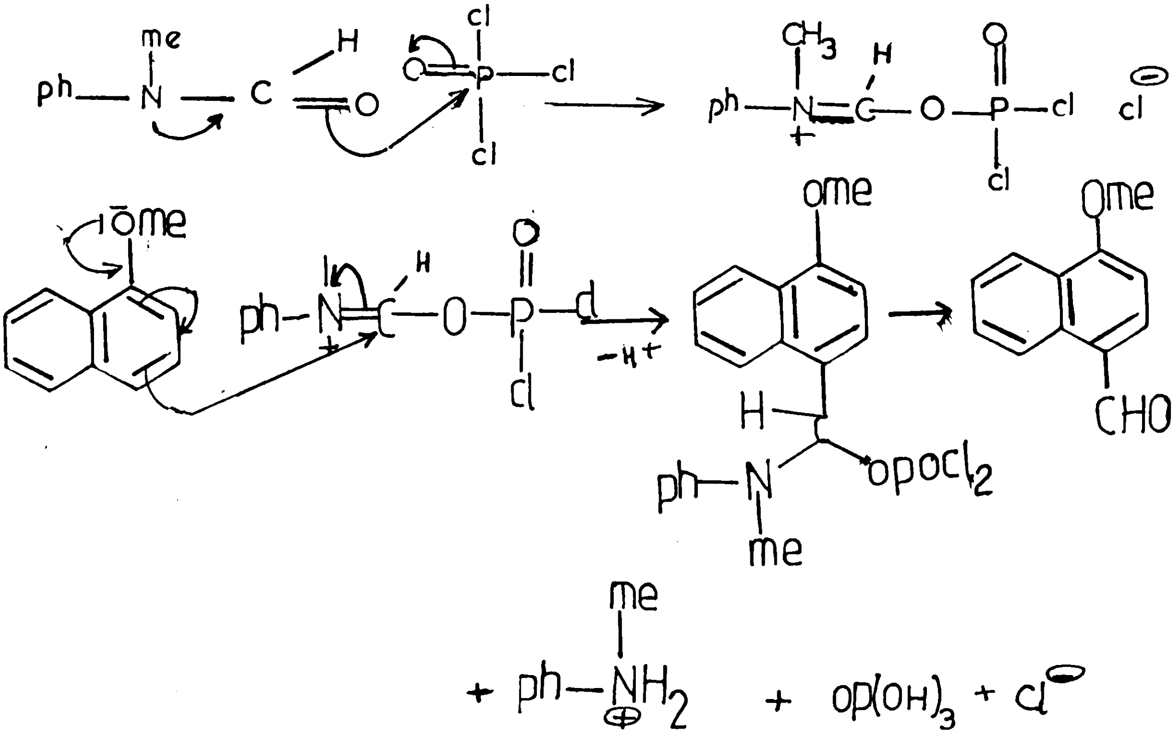
The yield of aldehyde with 1-naphthol is very low probably because two moles of naphthol react with one mole of chloroform as follows[(36)]



M: Metal: Na,K, ...etc.

3.4 Vielsmeier reaction(37)

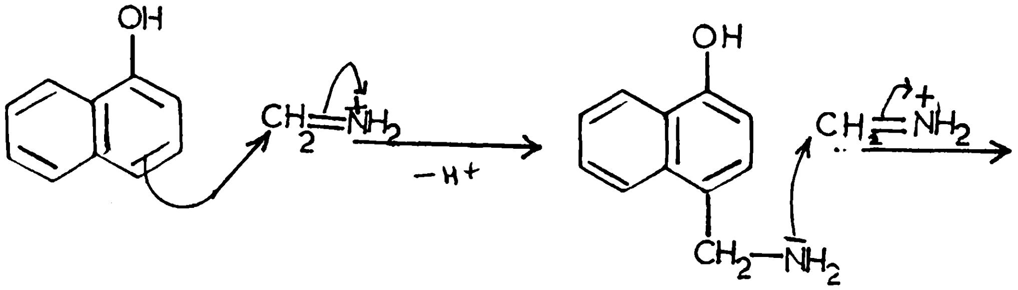
Formamides such as N-methylformanilide react with phosphorus oxychloride to produce an ion which reacts with nucleophilic benzenes to give benzaldehydes after hydrolysis. 1-Naphthol(38) and its methyl ether(37) are reported to give the para-aldehydes.



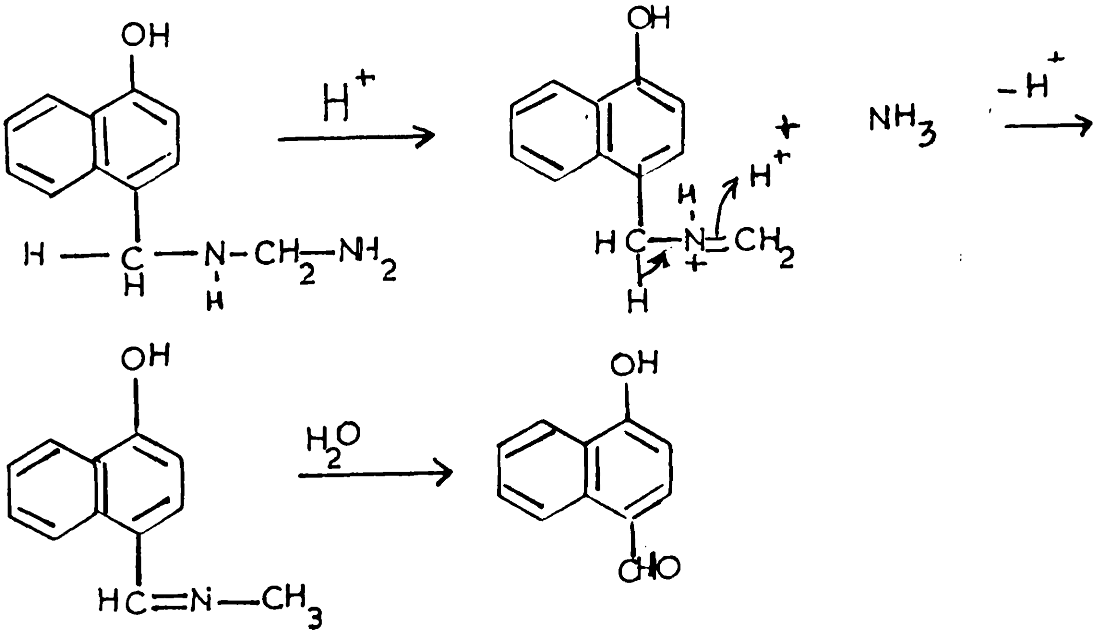
3.5 Duff reaction

This consists of the formylation of an aromatic nucleus via a facile but complex process employing hexamethylene tetramine (HMT.) and acids. When hexamethylenetetramine is used with glyceroboric acid to convert highly activated aromatic compounds to their formyl derivatives the reaction occurs specifically at the position ortho to the phenolic hydroxyl group in low yield(38). By the use of hexamethylenetetramine in conjunction with trifluoracetic acid(39) (stronger acid) a variety of aromatic compounds including simple aromatic hydrocarbons can be formylated. The reaction involves the formation of an imine which is easily hydrolysed to give the corresponding aldehydes. The reaction occurs mainly at the para position.

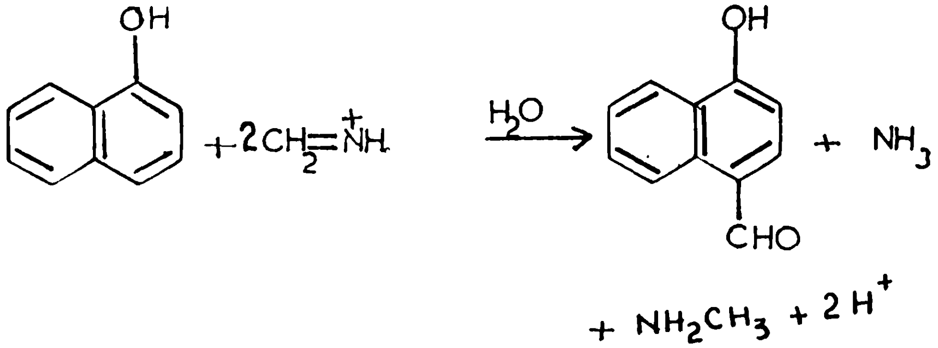
Hexamethylene tetramine might be considered to be in equilibrium with formaldehyde and ammonia and therefore with formaldiminium ion which can act as an electrophile reacting with the phenol.



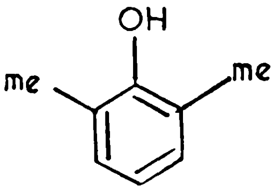
A redox process involving a second formaldimine unit leads, perhaps as follows, to an N-methylimine which is hydrolysed on work-up.

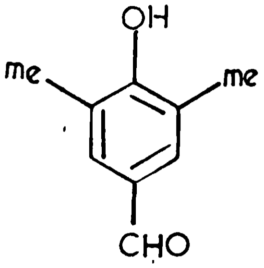


overall



ie. One unit of $CH_2 = \overset{+}{N}H_2$ provides the aldehyde carbon. One unit of $CH_2 = \overset{+}{N}H_2$ oxidises the initial adduct and is reduced to methylamine. As an example, 2,6-xylenol gives 95% of the aldehyde. The reaction of 1-naphthol has not been investigated.





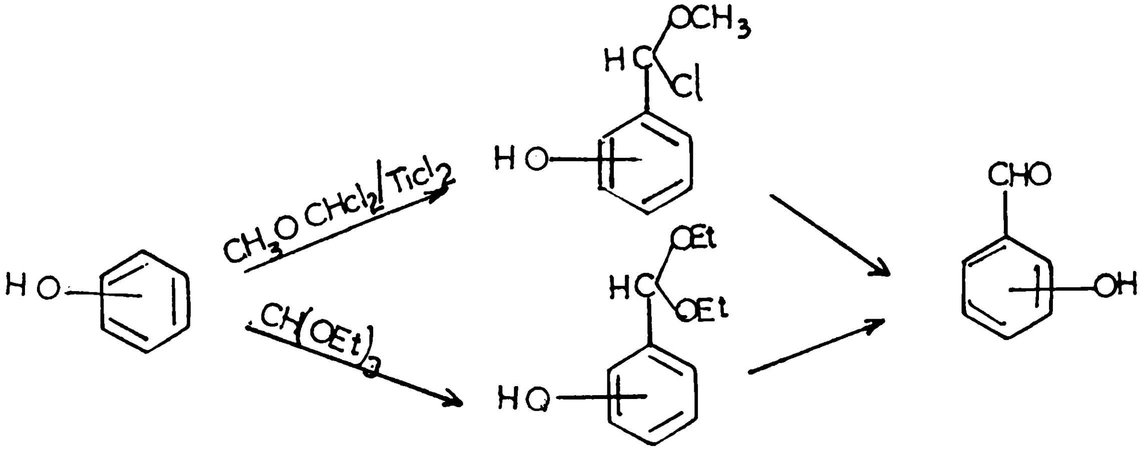
3.6 Orthoformates

Recently a group of formylating agents has been developed which use trisubstituted methanes as the formyl group source. In the presence of Lewis acids they give rise to electrophiles which react with the aromatic ring either by an S_N1 or S_N2 pathways.

$$H\text{—}CX_3 \longrightarrow H\overset{+}{C}X_2 \longrightarrow ArCHX_2 \longrightarrow ArCHO$$

3.6.1 Use of triethyl orthoformate

Phenols can be converted into phenolic aldehydes using dichloromethyl methyl ethers and titanium chloride or by the use of triethyl orthoformate and aluminium chloride.

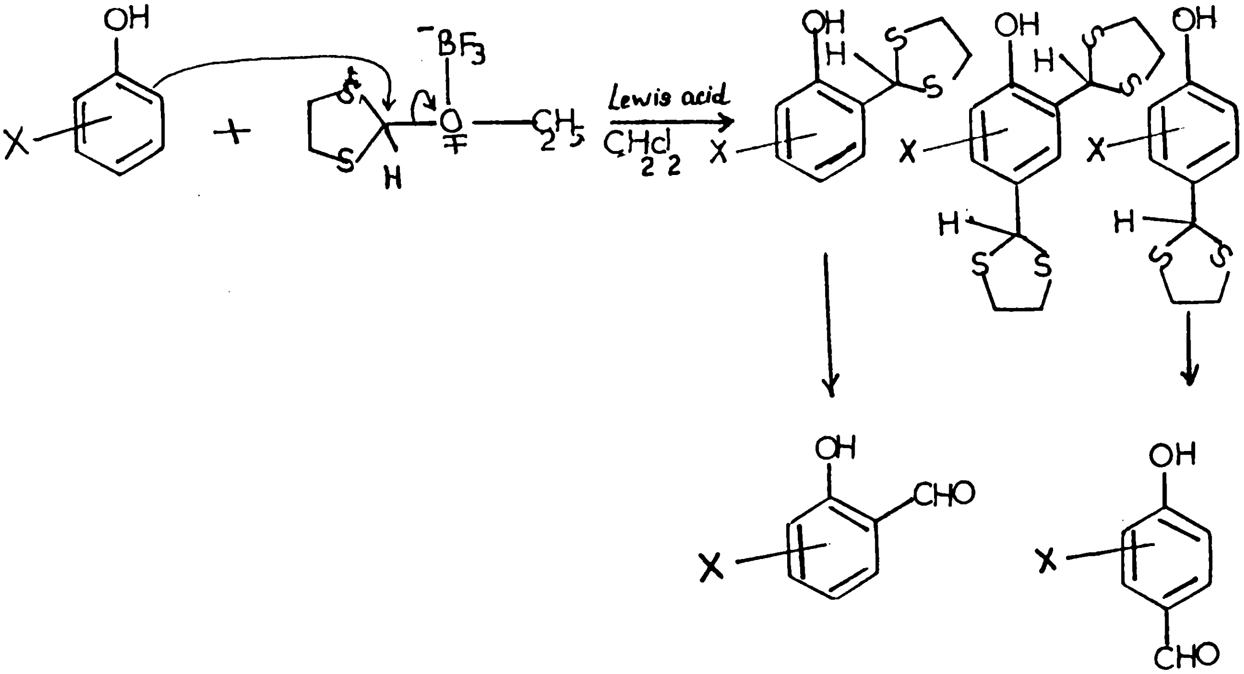


The former procedure works well with monohydroxy benzenes and gives a mixture of para and ortho regioselectivity; whereas the latter gives mainly the para isomer.

When 1-naphthol is treated under the conditions mentioned above it gives both isomers with the first procedure in yields of 10% ortho and 60% of the para one; but under the second conditions mainly the para isomer is produced and isolated, as its DNP, in 97% yield.

3.6.2 The use of 2-ethoxy-1,3-dithiolane

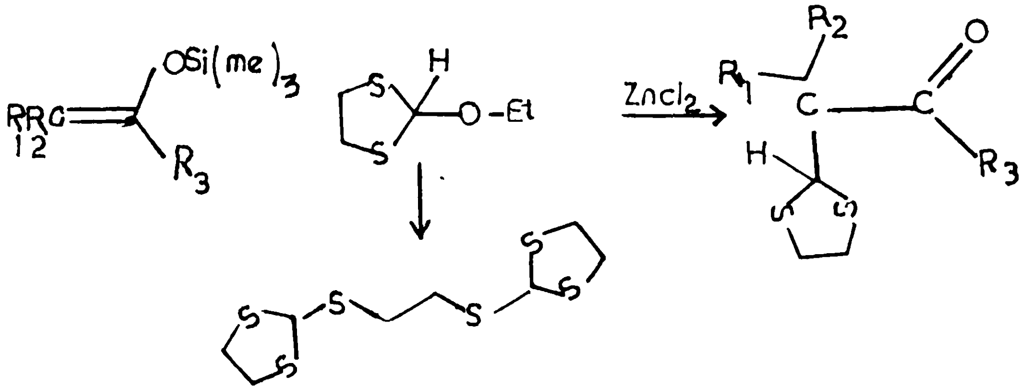
Recently it was found that 2-ethoxy-1,3-dithiolane in dichloro methane with Lewis acid as catalyst is an efficient agent for the introduction of the 1,3-dithiolan-2-yl group into some phenols and that the resulting protected formylated phenols are easily hydrolysed to the corresponding aldehyde. This process of formylation could be extended also to N, N-dimethylaniline and indole.



It seems as if the reaction path involves co-ordination of boron trifluoride with 2-ethoxy-1,3-dithiolane to give the 1,3-dithiolan-2-ium ion followed by a subsequent attack on the aromatic ring. 2-Ethoxy-1,3-dithiolane has been chosen as a suitable formyl cation equivalent because its stability to Lewis acids is more than its corresponding oxygenated analogs. This reagent can be prepared easily from 1,2-ethanedithiol and triethyl orthoformate(42). 2-Ethoxy-1,3-dithiolane can also react with the following nucleophiles, to introduce a protected formyl group.

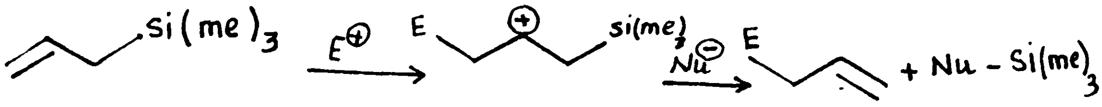
i. enol silyl ethers:-(43)

Enolizable aldehydesor ketones can be converted into half protected 1,3-dicarbonyl compounds by reaction of their enol silyl ethers (1-alkenyl-silyl ethers) with 2-ethoxy-1,3-dithiolane. This reaction can proceed very smoothly and efficiently in the presence of zinc chloride as catalyst, and the formation of 2,2-[1,2-ethandiyl-bis (thio)] bis-1,3-dithiolane as by-product can be avoided in this reaction, in contrast to the use of aluminium chloride, titanium IV chloride and boron trifluoride etherate.

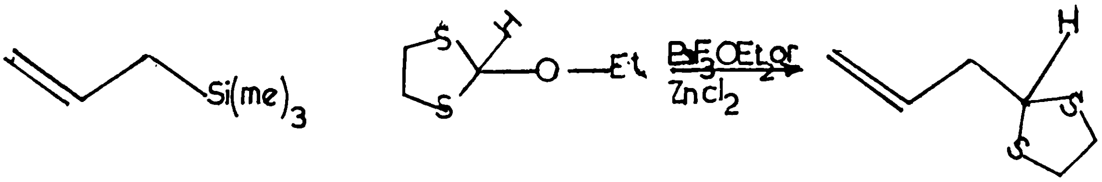


ii. allyl-silanes(44)

Allyl-silanes react specifically with electrophiles with rearrangement as the chart shows.

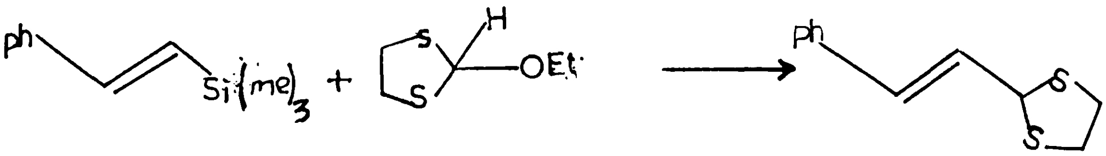


They react with the ethoxy dithiolane to yield thioacetals of butenals as shown in low yield.



iii. Vinyl silanes$^{(45)}$

Treatment of vinyl silanes with 2-ethoxy-1,3-dithiolane in the presence of Lewis acid also affords the protected aldehyde in 20% yield.



The most recent example of this kind of formylating agent consists in the use of

3.6.3 Tris (phenylthio) methane$^{(46)}$

Treatment of the carbocationic species produced from the reaction between soft, thiophilic Lewis acids ($MeS—\overset{+}{S}Me_2$) and tris [phenylthio] methane followed by an electrophilic aromatic substitution gives the aldehyde as is shown in the scheme below.

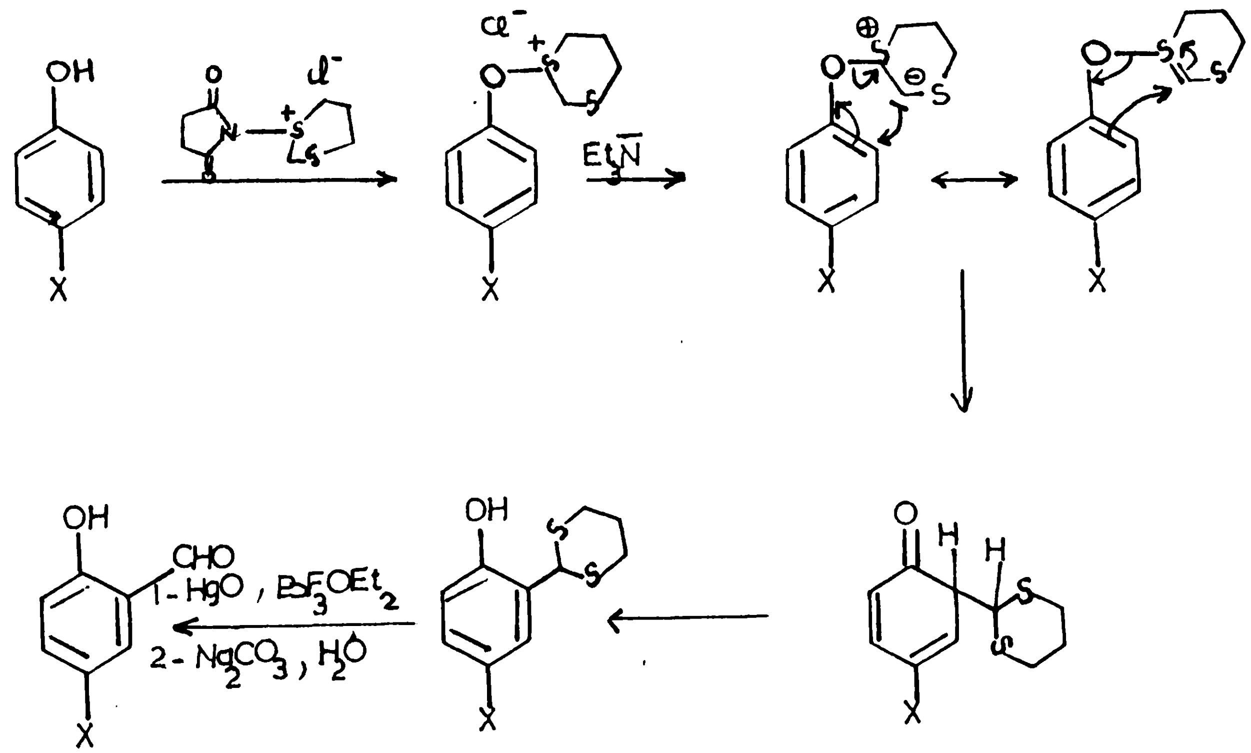
$$(PhS)_3\ CH + Me\ \overset{+}{SS}\ Me_2 \longrightarrow (PhS)_2{}^+CH \xrightarrow{ArH} Ar\text{-}CH(SPh)_2$$

$$\xrightarrow[H_2O]{MeSS^+Me_2} Ar\text{-}CHO$$

In the case of 1-naphthol, 4-formyl-1-naphthol is afforded in the 70% yield.

Gassmann Reaction(37)

All the methods so far involve an electrophilic reagent which can formylate the phenol either ortho or para although there was often high site selectivity. Gassmann in 1974 reported a method for selective ortho formylation of anilines and(47), later of phenols(48) which uses a dithiane as the formyl equivalent and a pericyclic rearrangement to control the site of attack. Treatment of dithiane with chlorine or N-chlorosuccinimide gives the sulphonium ions shown which can react with phenols in the presence of base as follows.



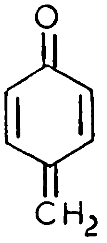
Reaction of the initially formed oxosulfonium salt with base leads to the formation of an ylide which undergoes a pericyclic rearrangement to give the cyclohexadienone. Hydrogen transfer and rearomatization of the ring gives the protected orthoaldehyde which could be subjected to treatment with mercury oxide, boron trifluoride etherate, and sodium carbonate and water to yield the aldehyde in 20-35% overall yield.

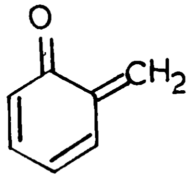
The most recent review on the synthesis of aldehydes is in Houben-Weyl(49).

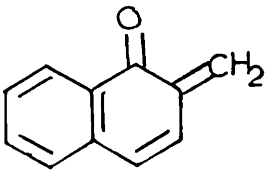
4. QUINONE METHIDES

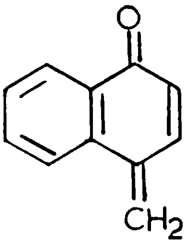
4.1 Generalities

The name quinone methide is derived from a structural analogy between this class of compounds and the quinones. If one oxygen atom of a quinone is replaced by a methylene group, the quinone methide results.

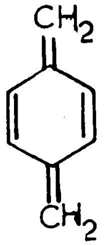


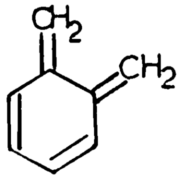


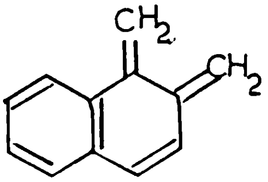


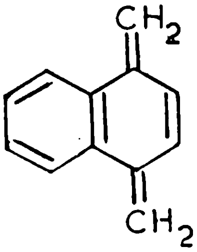


Such compounds have also been called quinomethanes[50] and methylene quinones. If both oxygen atoms of a quinone are replaced by methylene groups the so-called quinodimethanes result.





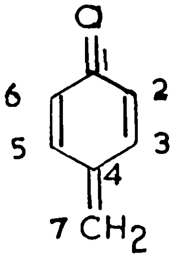




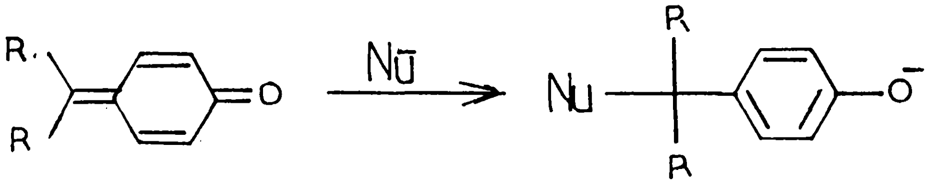
Quinone methides are listed as cyclohexadienone derivatives in the subject index of the Chemical Abstracts.

The chemistry of quinone methides has attracted considerable attention in recent years because of their intriguing chemical and physical properties and there are two recent reviews[51,52].

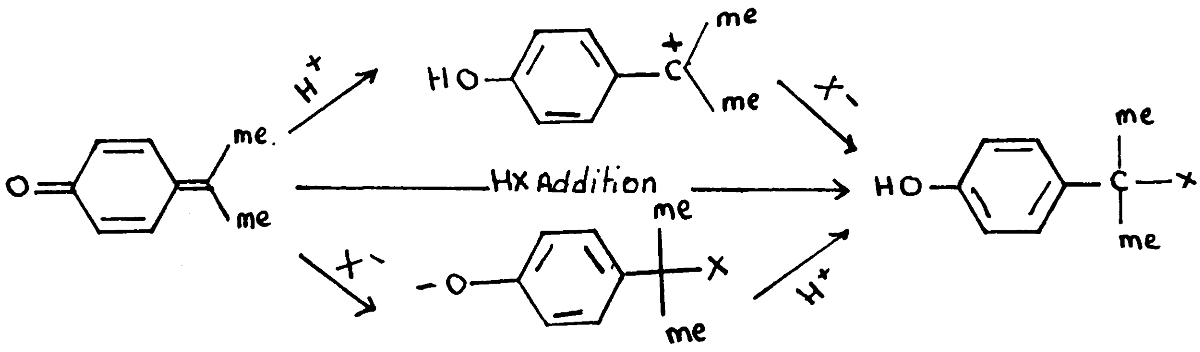
Due to their vinylogous carbonyl systems they behave as ambifunctional electrophilic reagents in addition to the usual electrophilic reactivity of the carbonyl group.



The conjugated centres C-3, C-5 and C-7 can enter into addition reactions of Michael type.



The LUMO energy of the quinone methide is low, though not as low as that of a quinone. Also the coefficient of the exo-carbon atom in this LUMO is particularly high; and the charge distribution in the quinonemethides is such that C-7 has the highest positive charge. For both of these reasons nucleophiles add at C-7[53].



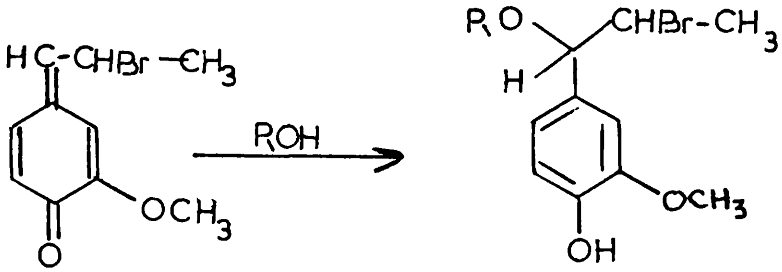
Also, the HOMO energy of the quinonemethides is higher than that of the quinone. The highest coefficient in HOMO is at the oxygen atom which also has a partial negative charge. For both of these reasons electrophiles add at the oxygen atom. Overall the addition occurs stepwise in both cases. i.e. addition of the electrophiles preceeds that of the nucleophile or vice-versa, but in both cases the ring becomes aromatic in the first step as shown in the scheme. This reactivity can be explained on the basis of the change from the initial quinonoid structure to the more benzenoid structure of the transition state or the end product.

4.2 Reactions

There are two main types of reactions of quinone methides both of which lead to formation of aromatic rings and both of which result from the polarity and orbital energies discussed above. Addition of nucleophile/electrophile pairs follows the scheme above. Examples are known where either the proton or the nucleophile adds first (see below). The second major group of reactions are cycloadditions, usually of Diels Alder type, either dimerisations or reactions with other alkenes. There are also some reactions of other types such as polymerisation, isomerisation and radical reactions.

4.2.1 Addition of alcohols

The rate of addition of alcohols to quinone methides depends to a substantial extent on the acid strength of the alcohol component(54). The more easily the proton is removed, the faster is the addition.

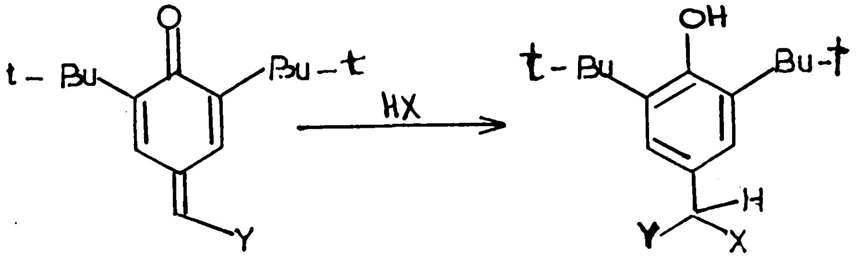


Rate: PhOH $>$ Sugar $>$ H_2O $>$ CH_3OH $>$ C_2H_5OH
pKa 10 pKa 16 pKa 17

This implies that in such cases addition of the proton to the oxygen of the quinonemethide is the important step.

4.2.2 Addition of HX and C-H acidic compounds

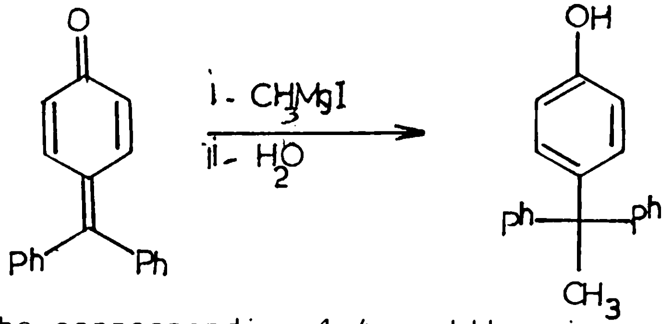
The same dependence on the acid strength of a component HX is found with some of the quinone-methides carring electron donating substituents (Y: NR_2,OR).



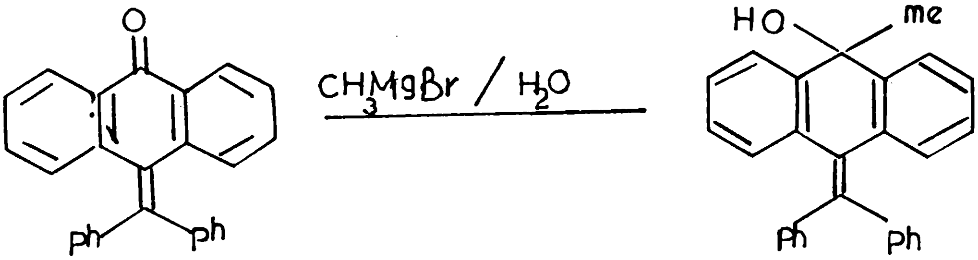
When Y is an electron acceptor such as (CN, CO_2H), the quinone methide reacts only with very strong nucleophiles(55) as shown in scheme (lower path) and then the electrophilicity of the other end of the conjugated system determines the reaction rate.

4.2.3 1,6-Addition

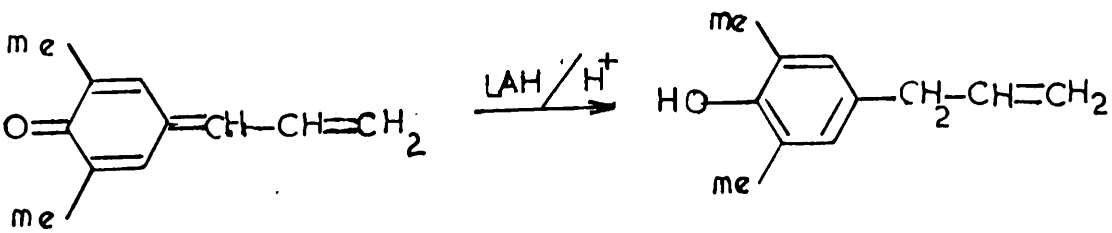
This addition occurs with formation of the phenolic system as exemplified below.



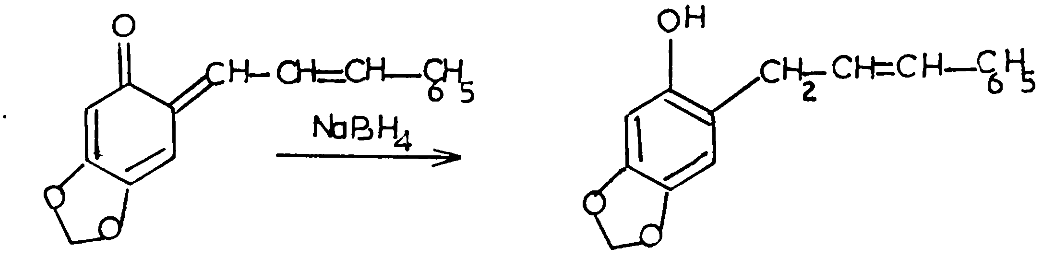
The corresponding 1,4-naphthoquinone methide reacts analogously, but methylmagnesium bromide reacts with the 9,10-anthraquinone methide by 1,2-addition to the carbonyl group(56).



Addition of one molecule of hydrogen to the quinone methide can be done by the reaction of lithium aluminium hydride or sodium borohydride(57).

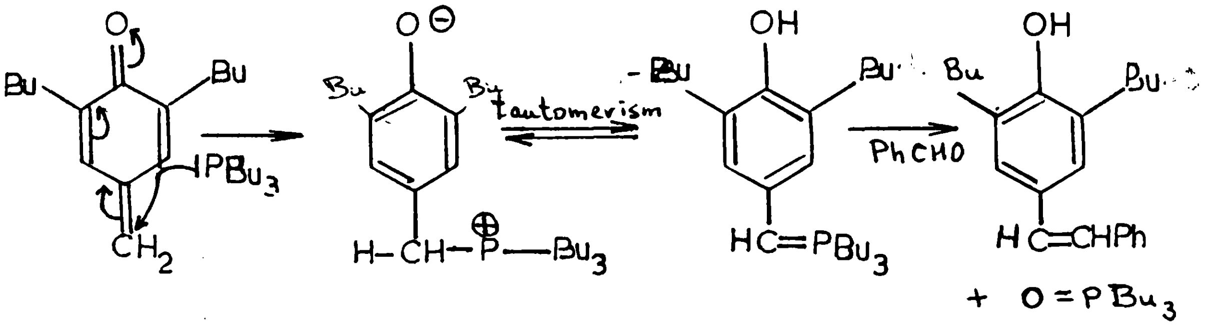


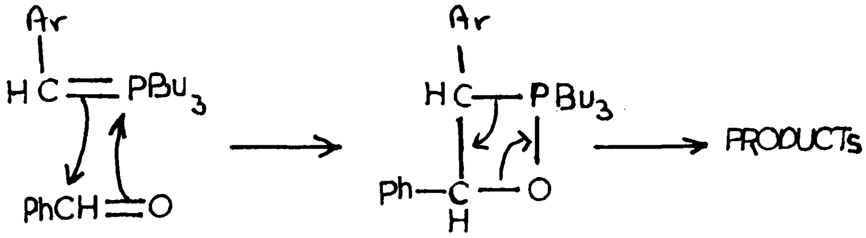
And it is also possible to do similar reduction with acidic reagents such as zinc metal and acetic acid.



4.2.4 Addition of tributylphosphine

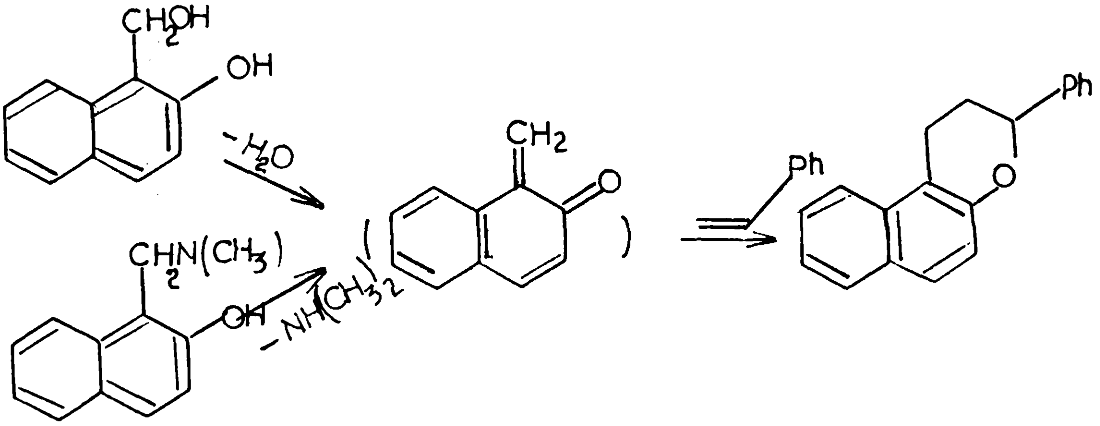
Reaction of tributylphosphine and quinone methide affords a phosphonium betaine in good yield. The latter can be isolated and can be trapped by the Wittig reaction with benzaldehyde[58].



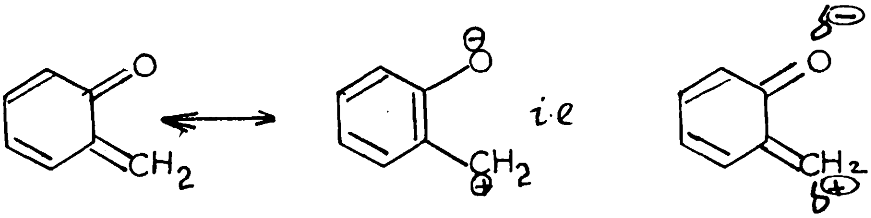


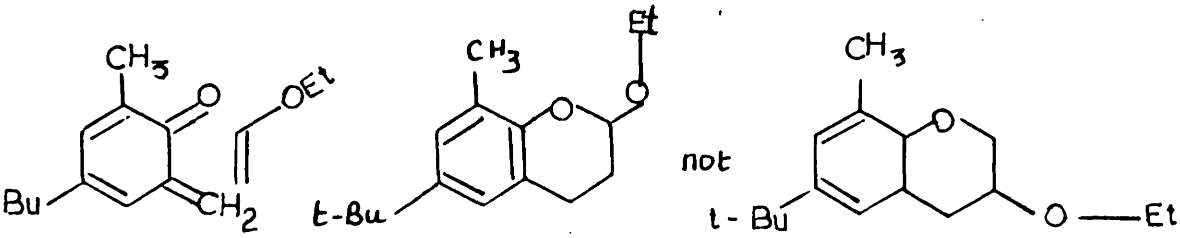
4.2.5 Cycloaddition reactions

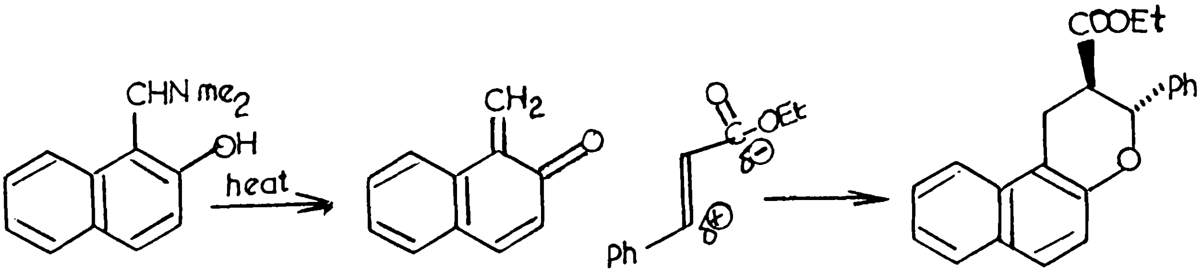
Transition from the quinonoid to the corresponding benzenoid structure can be achieved particularly easily with ortho-quinonoid systems by a bond shift during the course of a Diels Alder reaction and this is the driving force to the great tendency of ortho-quinone methides to dimerize. Dehydration of orthohydroxybenzylalcohols gives the ortho-quinone methide which can undergo addition of olefin yielding a flavan if the olefin[59] is styrene. The same reaction occurs with ortho-naphthoquinone methide obtained from benzylamines.



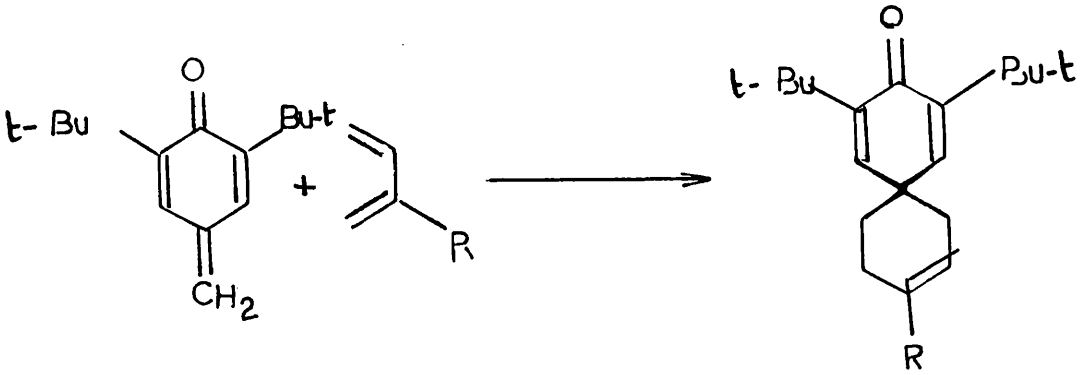
In all cases the ortho-quinonemethide acts as a hetero-diene component and the high regiospecificity corresponds to polarization of the methide in the manner shown as illustrated by addition of vinyl ethers[60] or ethyl cinnamate[61].



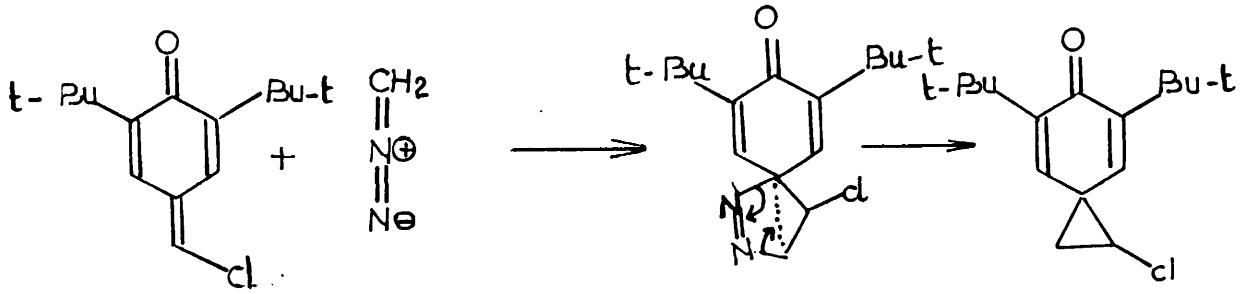




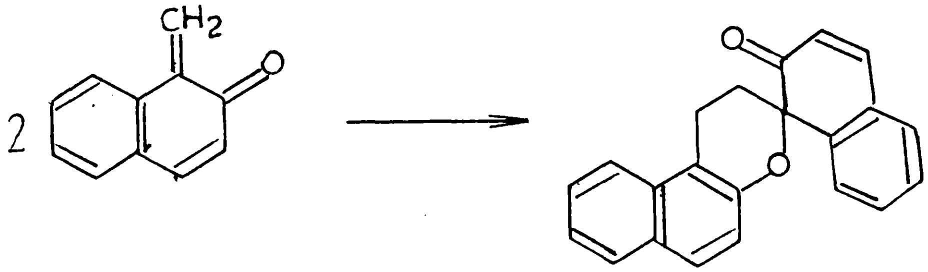
The exo-methylene group in a para-quinone methide can behave as a dienophile. This can be exemplified by the behaviour of 2,6-di-t-butyl-p-benzoquinone methide with substituted butadienes[62].

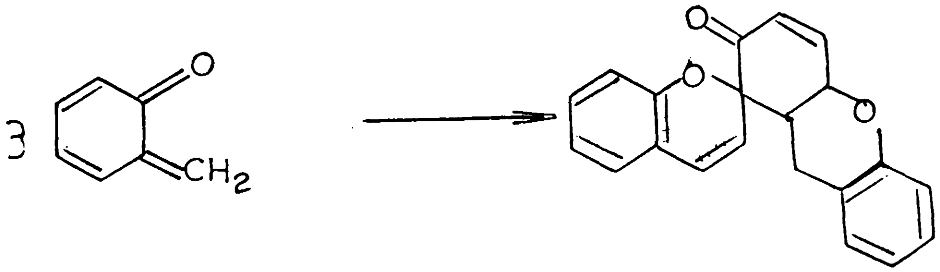


The methylene group undergoes cycloaddition in reaction with diazomethane to give eventually spirocyclopropyl derivatives in very good yield as shown for a 7-chloromethide[63].



In the absence of a suitable alkene the tendency of an ortho-quinone methide to add to a heterodiene system leads to dimerization[64], such as that shown for ortho-naphthoquinone, and trimerization such as in the case of ortho-benzoquinone methide[60]. One molecule acts as dienophile and another as heterodiene.

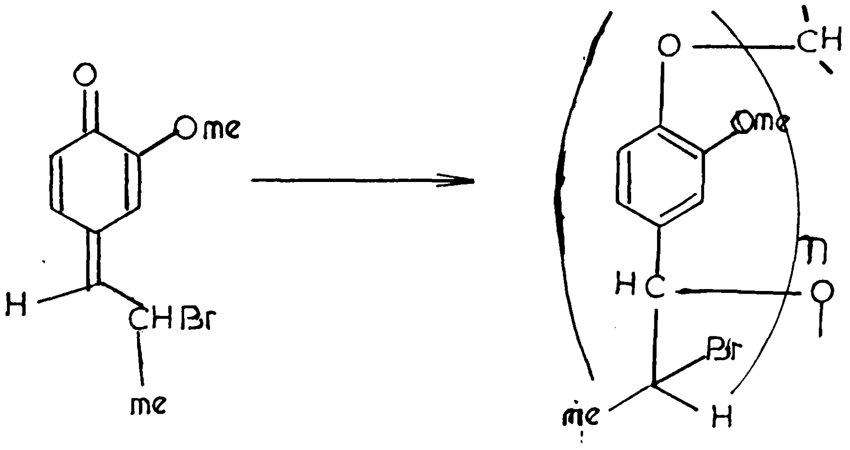




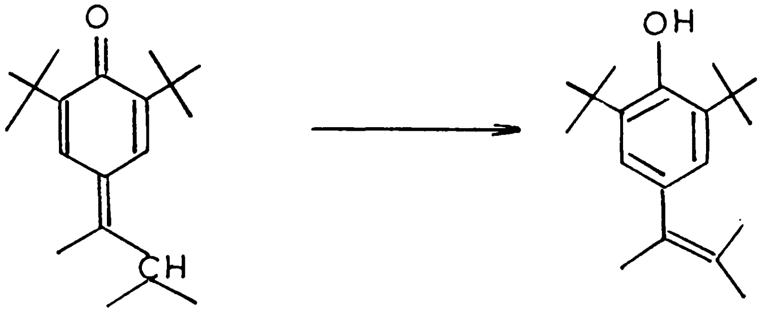
Thermal cracking of the dimer can be a good way of getting the quinonemethide monomer free of impurities.

Several other types of reactions can happen to quinonemethides which lead to aromatic products such as:-

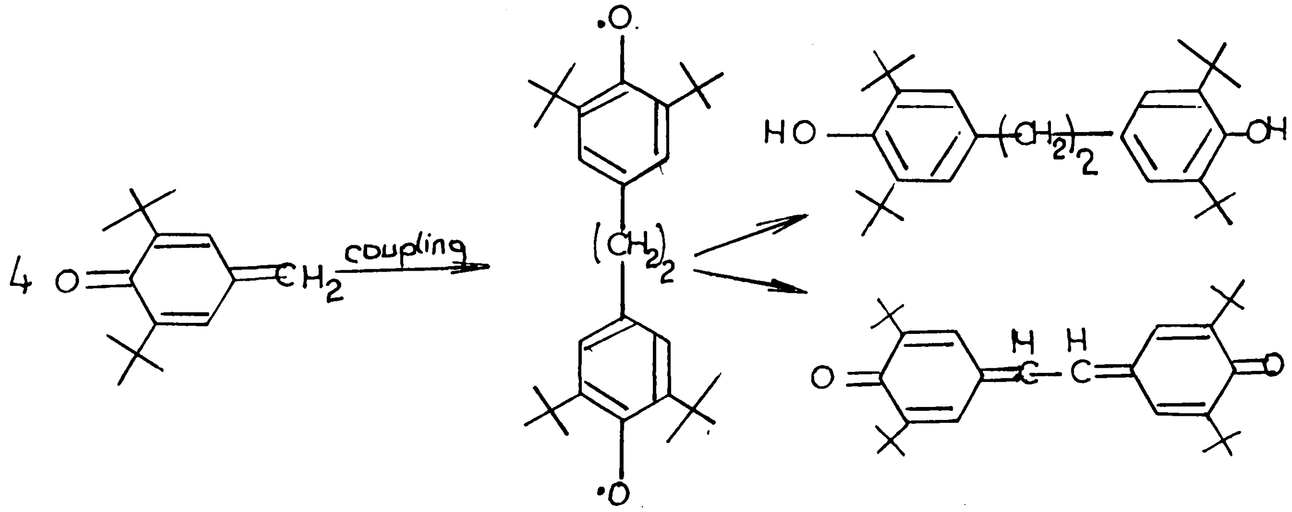
i. Self addition of para-quinonemethides leads to polymeric 1,6-adducts[54].



ii. Isomerization[58] of the quinone methide which is carrying a hydrogen atom on the carbon atom attached to the methylene carbon atom gives the corresponding phenol in the presenceof alumina or NEt_3 or heat or Bu_3P.

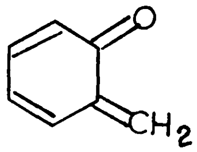
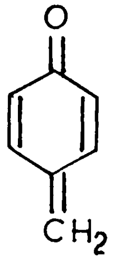
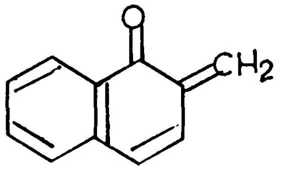
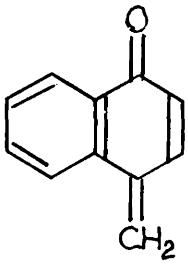


iii. Radical reaction: On evaporating a pure solution of a quinonemethide a dimeric diradical might be formed which, via a disproportionation, gives a quinone methide and a phenol[65].

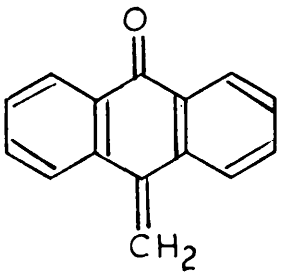


4.2.6 Stability

In general quinone methides are not stable owing to the presence of the quinonoid system which favours them to undergo different types of reactions as illustrated in the previous section. The parent quinone methides shown below have never been isolated.

Their reactivity can be decreased either by attaching alkyl substituents to the parent (the stability increasing according to the bulk of the substituents) or by building up one or two benzene rings onto the ring double bonds or by delocalisation involving substituents which affects the polarity of the compound and makes it more stable. These effects are illustrated by the following examples of quinone methides stable as monomers in the solid state at room temperature.



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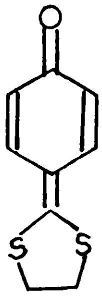

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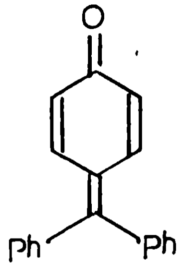

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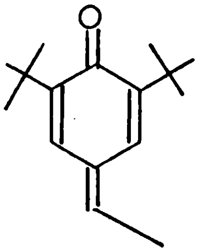

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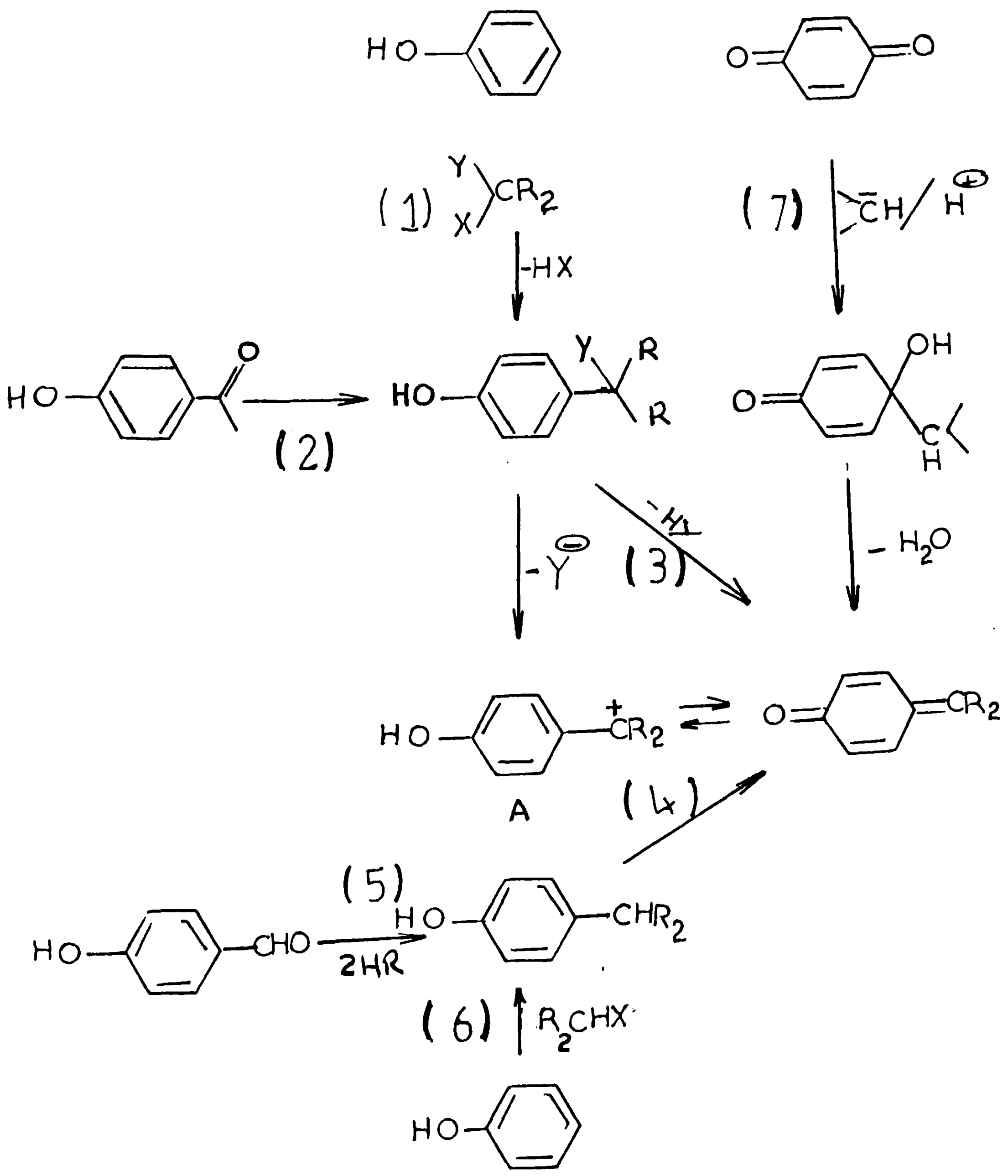
4.3 Preparative Methods

Quinone methides are usually prepared either from the corresponding phenols or substituted phenols or quinones as illustrated in the scheme below.



Scheme

Although the possibilities for synthesis of quinone methides from quinones is greatly limited by the low electrophilicity of the carbonyl carbon atom of the quinone, ways round this problem will be discussed later on. The different synthetic routes described in the scheme for para-benzoquinone methides are representative for all quinone methides and are valid for both para and ortho quinonoid systems in general. Thus, quinone methides can be prepared by an electrophilic aromatic substitution of a phenol (route 1 and route 6) to make an intermediate which is subjected to an elimination (step 3) in the former case or to a dehydrogenation or oxidation (step 4) in the latter case to give the corresponding quinone methide. In both of these cases there is a question about the regioselectivity, ortho or para, of the aromatic substitution.

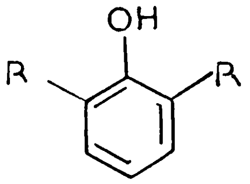
Quinone methides can also be prepared by an addition of HR to the carbonyl group of an aromatic hydroxy-ketone route (2) which leads to the same kind of intermediate as in the previous route (1). In this case RH is often provided by the metallated derivative, e.g.: Grignard reagent.

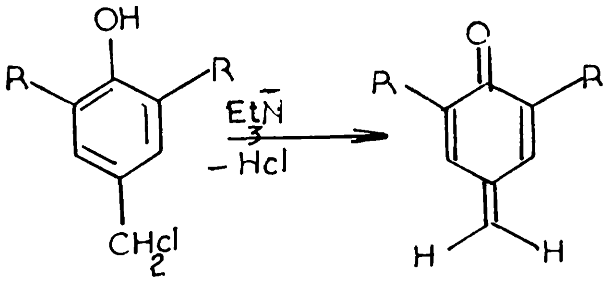
Reaction of type (5) consists in the conversion of an aromatic hydroxy aldehyde into a derivative such as an acetal or thioacetal which is subsequently oxidised in step (4). In these two cases the structure of the quinone methide is determined by the structure of the starting ketone or aldehyde.

The elimination step (3) may occur in two stages. If Y is a good leaving group the ion (6) may be formed and later deprotonated to give the quinone methide. The cation is easily regenerated by protonating the quinone methide.

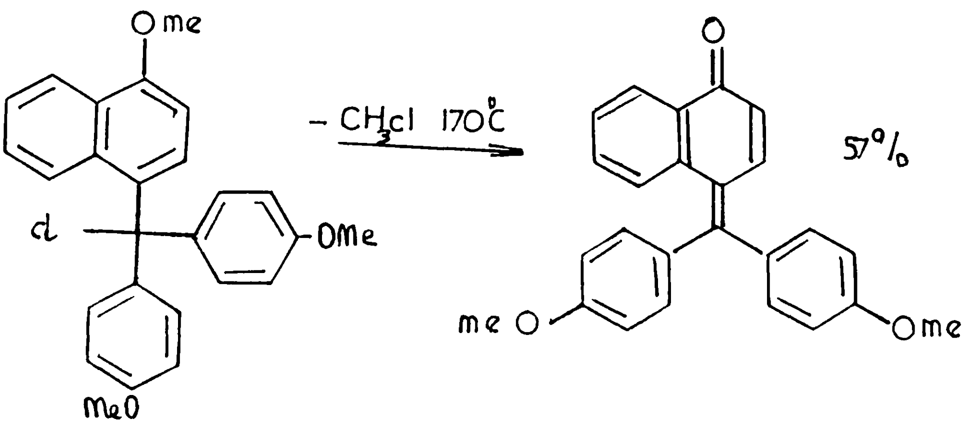
4.3.1 Synthesis by Electrophilic aromatic substitution of phenols and subsequent elimination

Chloromethylation of a phenol and subsequent elimination of hydrogen chloride by triethylamine at -15°C leads to an orange red solution of the quinone methide. In the case of simple phenols, the resulting quinone methide cannot be isolated since dimerization and other reactions occur on concentration of the solution[70]. Also the base used may add (1,6) to the quinone methide or cause tautomerism of the quinone methide to an alkenyl phenol. The alkyl halide can also be prepared from the alcohol with hydrochloric acid gas and then treatment with triethylamine, sodium acetate or sodium bicarbonate.

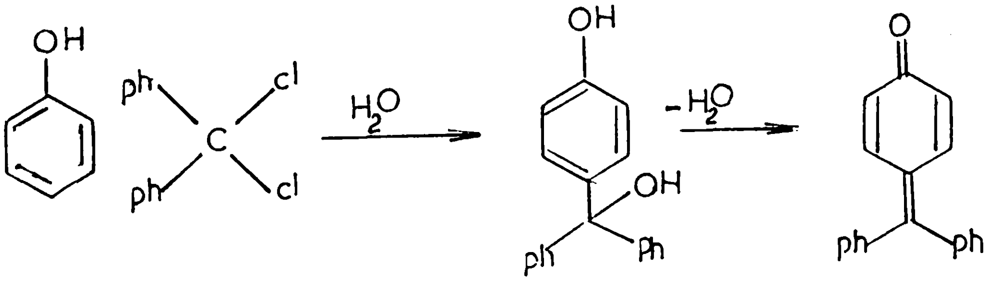




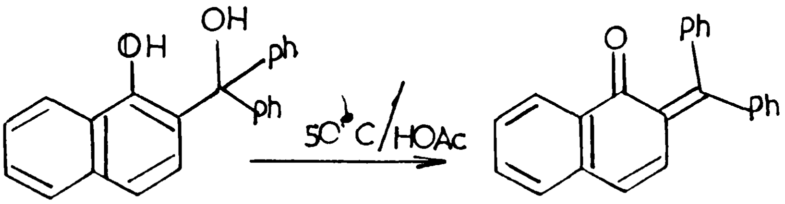
In the fuchsone series alkyl halides can also be removed from alkoxybenzyl halides at elevated temperature for example[71]



Ketones are, as a rule, too feebly electrophilic to be able to attack phenols. However, numerous quinone methides, in particular fuchsone derivatives have been prepared by condensing ketone chlorides with phenols and then eliminating water from the resulting alcohols.

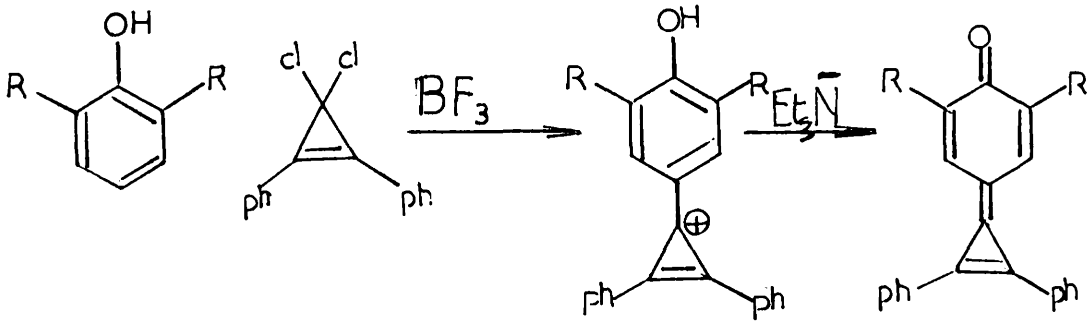


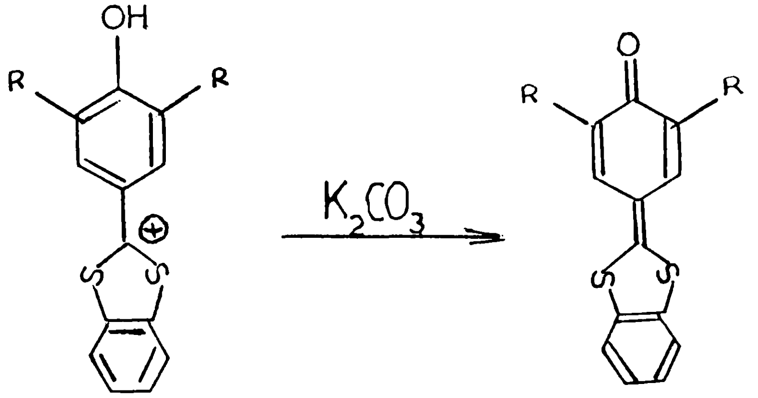
Ortho quinone methides are usually too reactive to be isolated from dehydration of ortho hydroxy benzyl alcohols. However, ortho naphthofuchsones can be made[71,72].



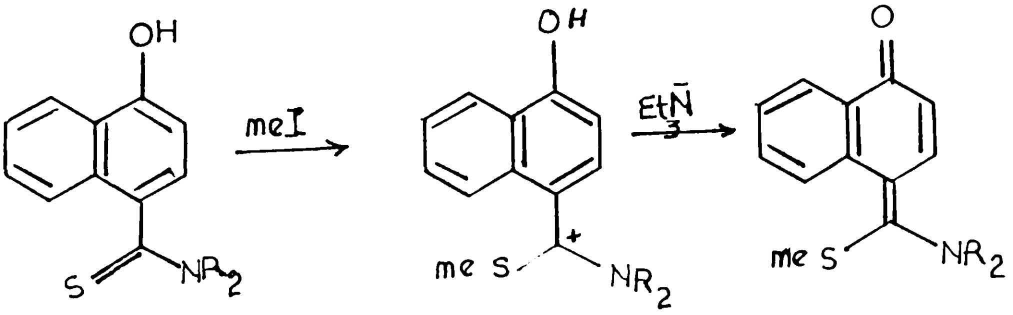
Electrophilic aromatic substitution on phenols with ketones generally needs to be catalysed with Lewis acids[73].

In some cases the aromatic substitution reaction conditions lead also to loss of the group Y and formation of an isolable cation of type (A) (see scheme). This can later be deprotonated by mild base to give a quinone methide[74].

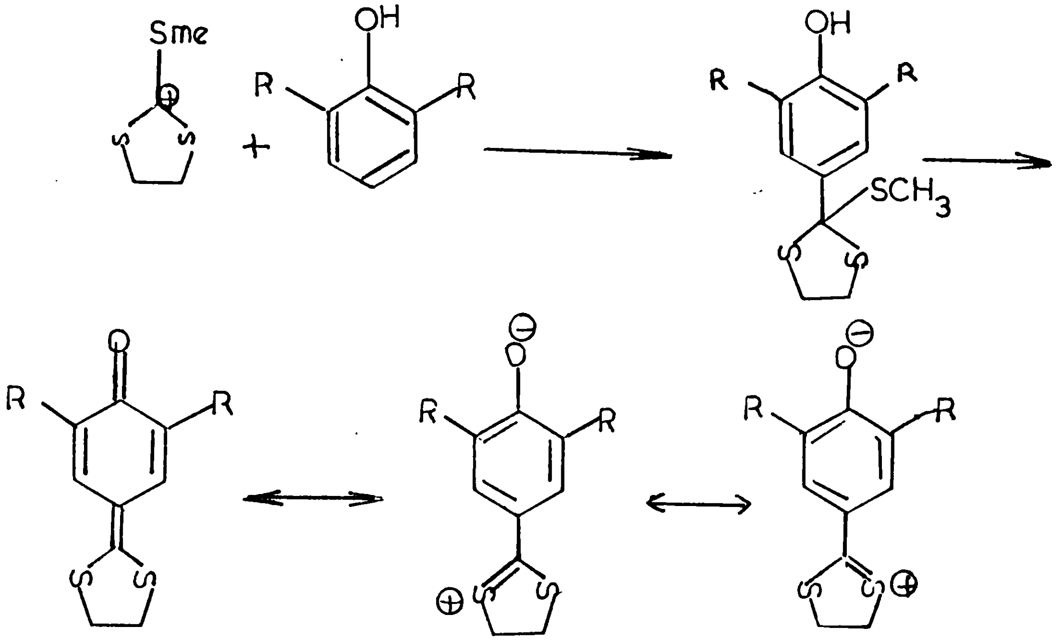




Cations of type (A) can be made by a quite different method if the substituents are heteroatoms. Again deprotonation gives a quinone methide[75].

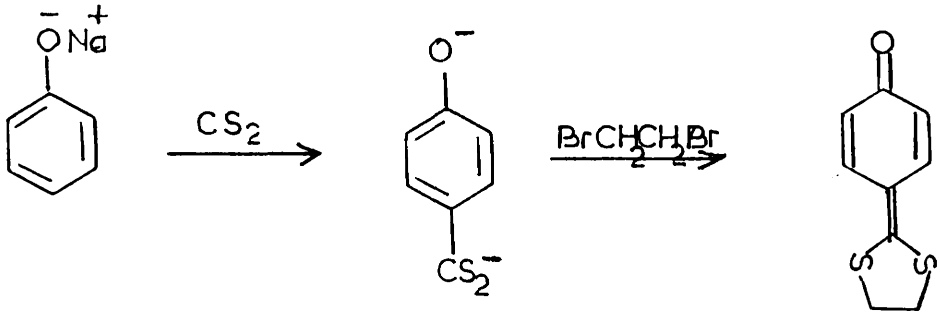


Ring substitution of phenols by resonance - stabilized carbenium ions is very generally applicable. For instance, dithiolanium salts react with 2,6-di-t-butyl phenol to give, after spontaneous loss of methanethiol in a good yield, the very stable quinone methide[76].

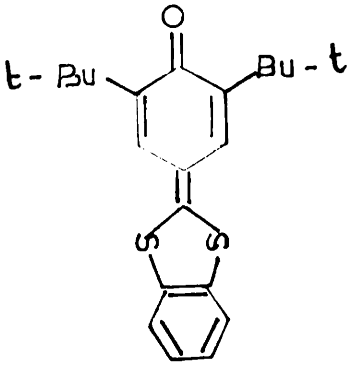


The polar structure of this resonance-stabilized product is reflected in the dipolar resonance structures. (Scheme). This weakens the electrophilicity of the exo carbon atom, decreasing its reactivity, so that the quinone methides of this type are stable and can be isolated.

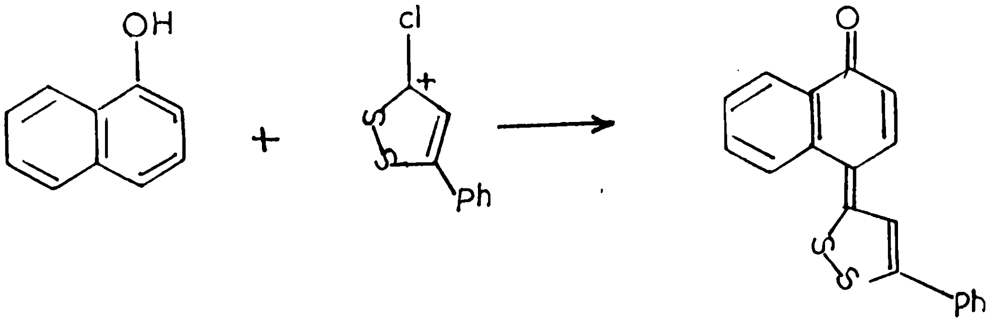
Phenoxides[77] can react with carbon disulphide as electrophiles by a similar aromatic substitution process to produce parahydroxy-dithiobenzoic acids which can be alkylated by e.g.: 1,2-dibromoethane to give the same type of quinone methide as illustrated bellow



Other quinone methides made by substitution by a stable cation procedure include the following[78,79].

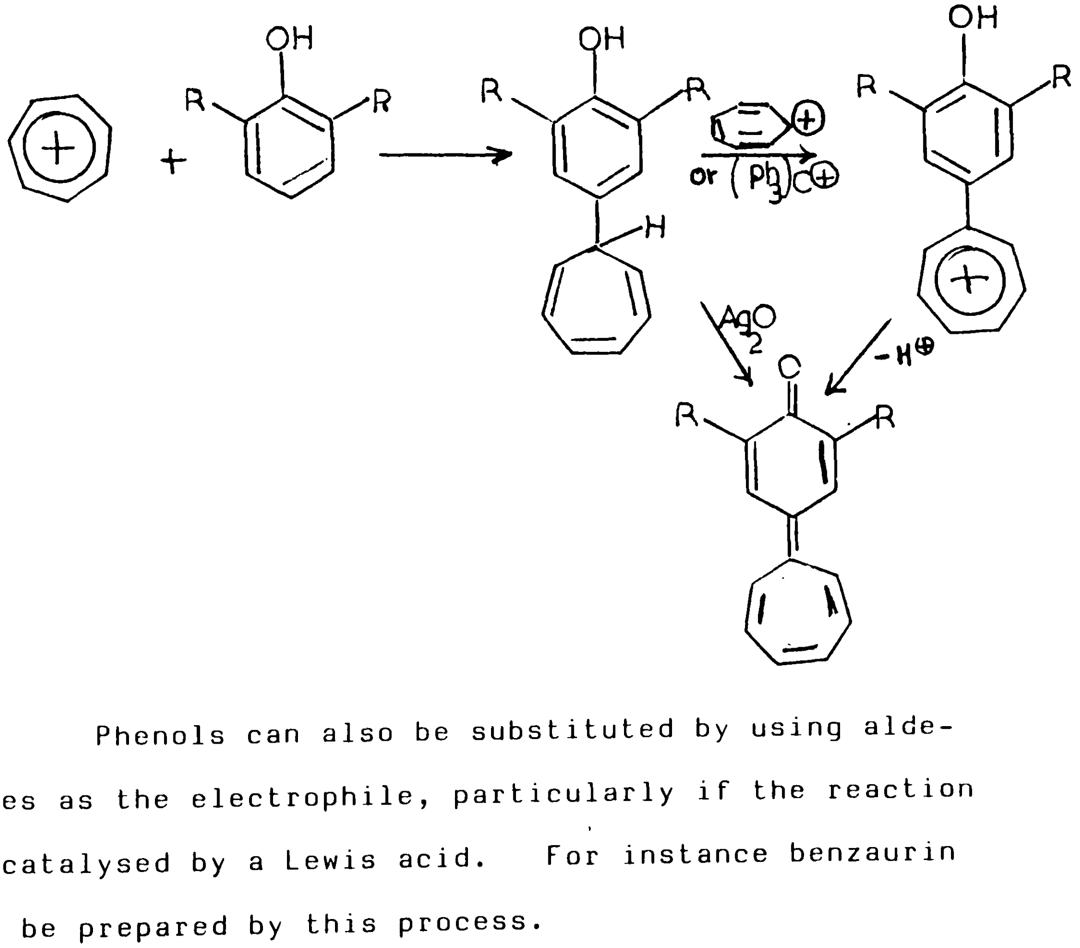


In the case of 1-naphthol the para isomer was isolated in high yield.

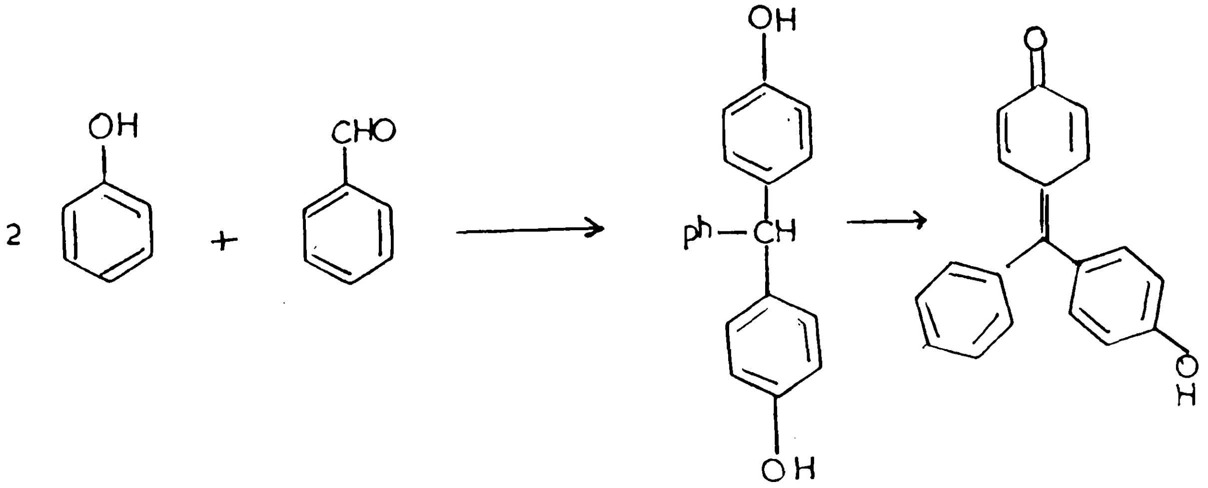


4.3.2 Synthesis by electrophilic aromatic substitution of phenols and subsequent oxidation

Reactions of most 2,6-disubstituted phenols with tropylium salts gives the corresponding alkylphenol as intermediate which can be then subsequently dehydrogenated either by the use of an excess of the salt or by isolating the phenol and treating it with a triphenylcarbenium salt or other oxidising reagent such as silver oxide[80,81].



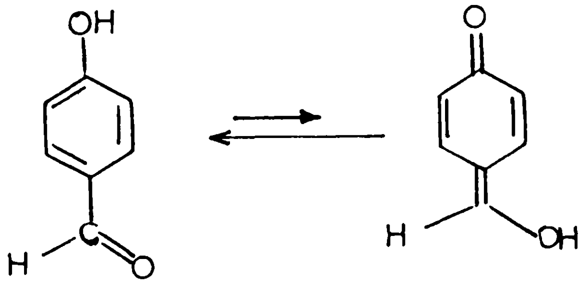
Phenols can also be substituted by using aldehydes as the electrophile, particularly if the reaction is catalysed by a Lewis acid. For instance benzaurin can be prepared by this process.



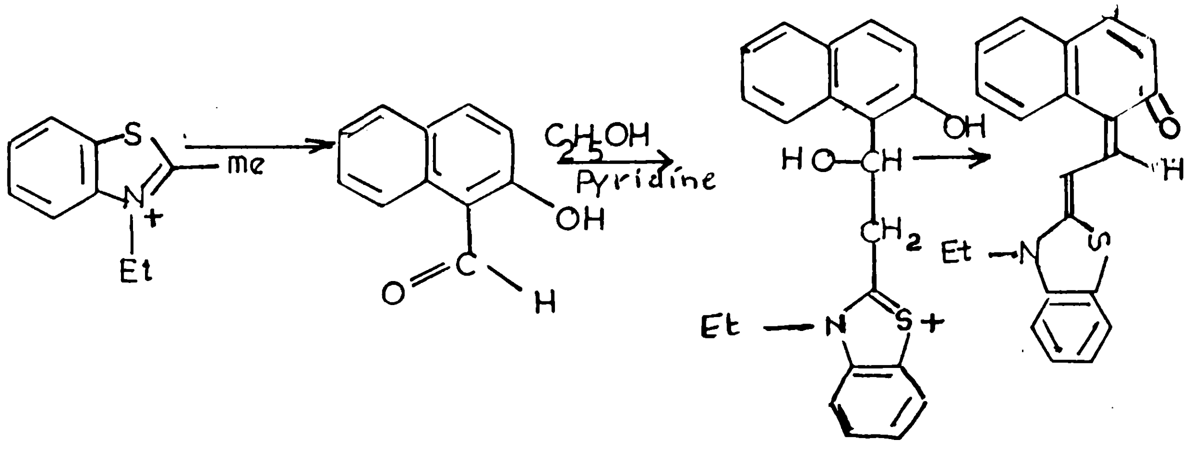
As it is shown from this reaction (scheme), this synthetic route leads to the fuchsone series.

4.3.3 Synthesis from aromatic hydroxy - aldehydes and ketones

Para-hydroxy aldehydes can themselves exist in a tautomeric equilibrium with hydroxy quinone methides but the equilibrium lies to the left.

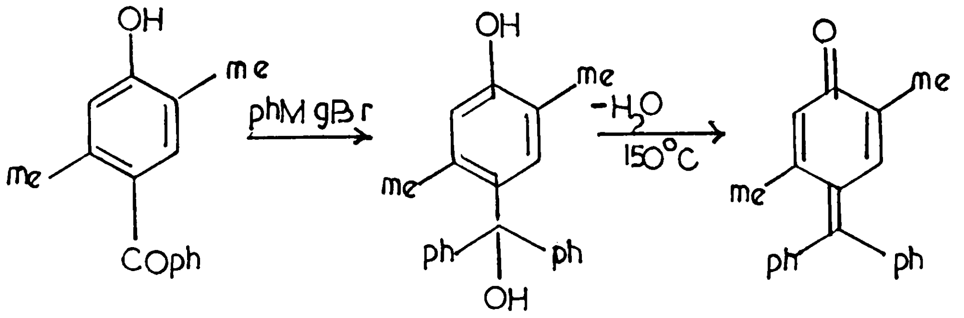


Such aldehydes undergo aldol condensation with C-H acidic components.



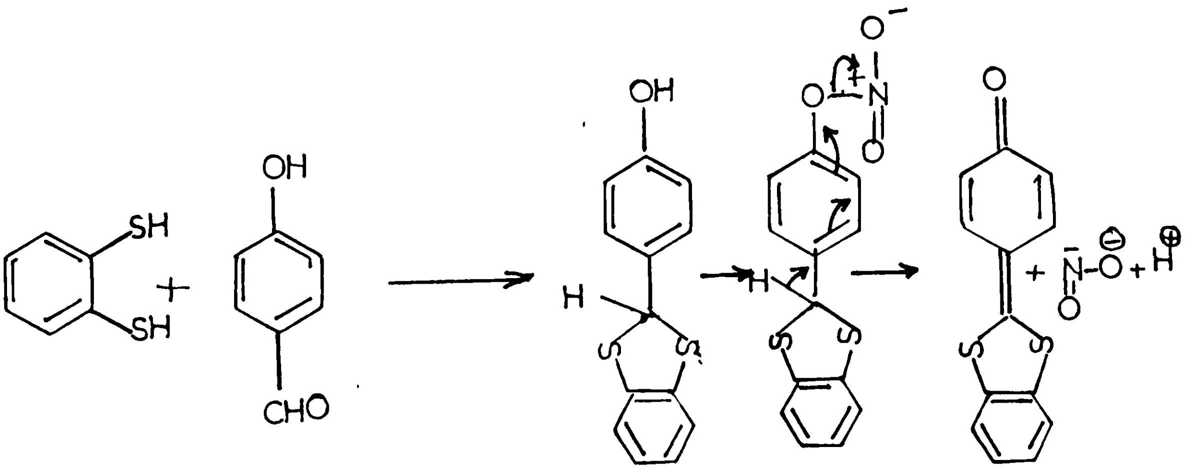
The interaction of aromatic hydroxy ketones with organometallic compounds proceeds by the same type of condensation[73].

Loss of water from the resulting alcohol leads to fuchsone[82].

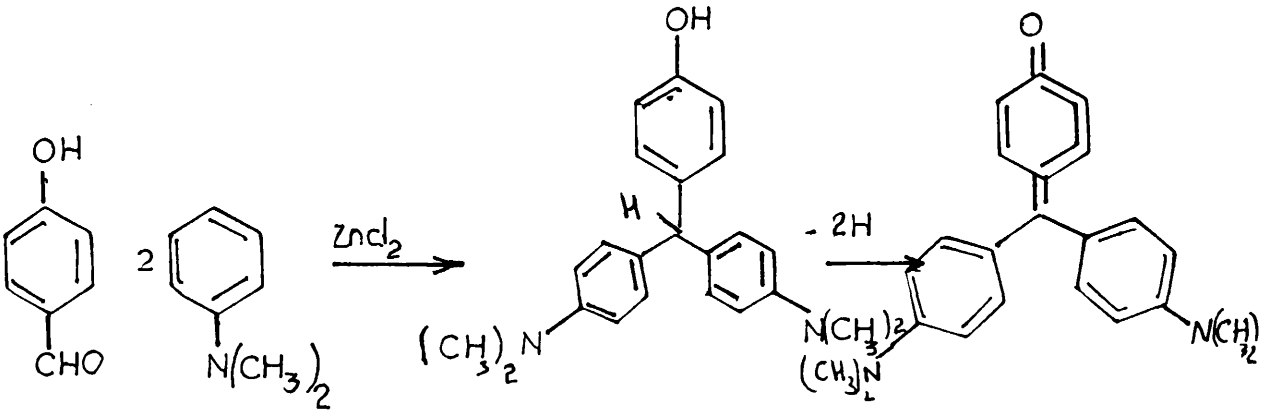


4.3.4 Synthesis from aromatic hydroxy aldehydes by oxidation of their derivatives

Addition to the aldehyde of groups which can stabilise the quinone methide makes oxidation easier. This synthesis is based mainly on the push-pull effect which stabilizes the quinone methide[83]. Oxidation of the mercaptal of the aromatic aldehyde by nitric acid occurs by way of the nitrate.

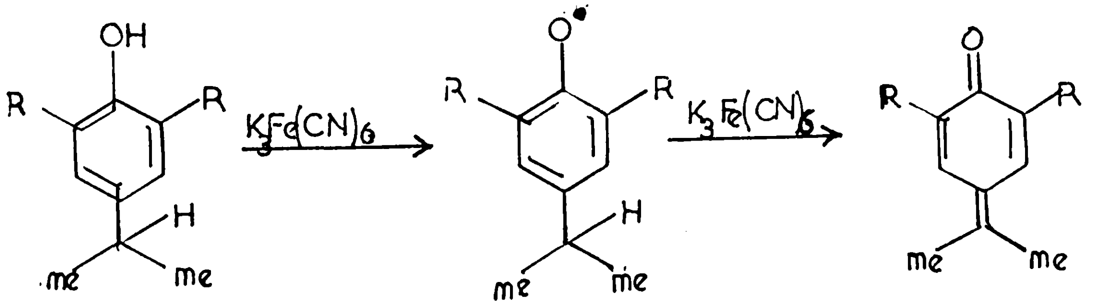


Further, preparation of the fuchsones derivatives and analogous triphenylmethane dyes proceeds through derivatives of aromatic hydroxyaldehydes that are very easily oxidized[84].



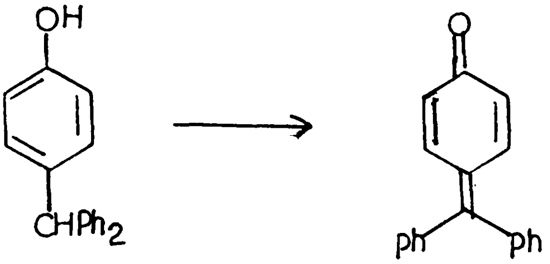
4.3.5 Synthesis by oxidation of alkyl phenols

A variety of oxidising agents has been used to oxidise alkyl phenols. Some of these such as hexacyanoferrate ion[85] involve one electron transfers giving aryloxyl radicals as intermediates.

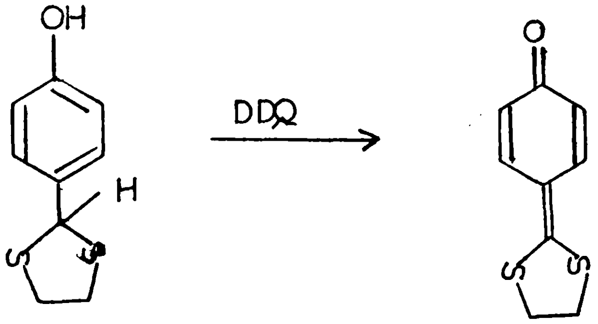


Similar oxidations can be effected by very many other oxidizing agents, including silver oxide[86,87] lead oxide[88,89] and chloranil[90] though here the mechanisms are not clear.

To make fuchsones a wide variety of agents can be used. The best yields (~90%) are given using DDQ in methanol[91] or nickel peroxide or manganese dioxide in benzene[92].

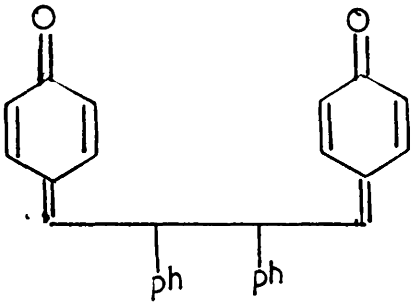


Sulfur-stabilized quinone methides can be made in the same way in good yields[93].



DDQ can, however, give rise to other types of product[94].

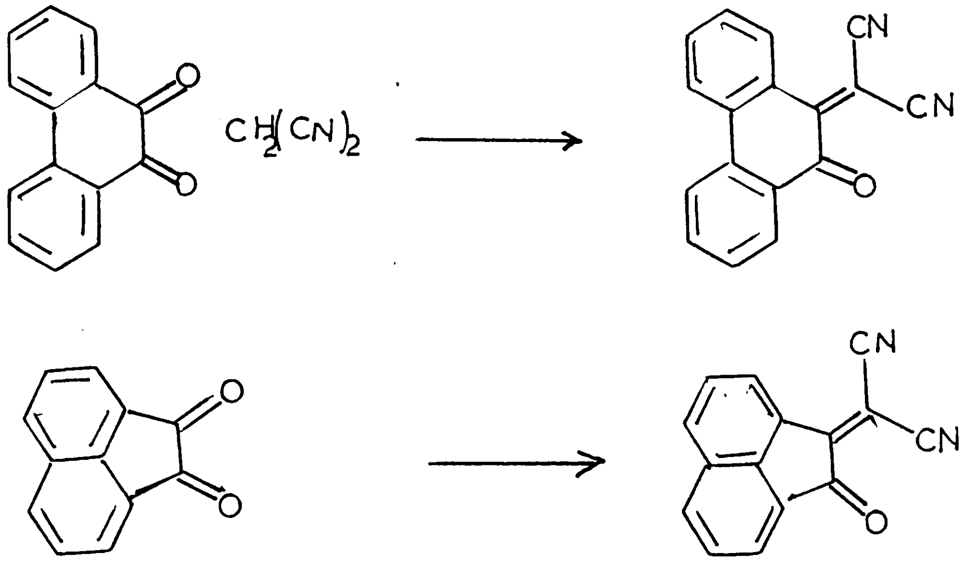
e.g.



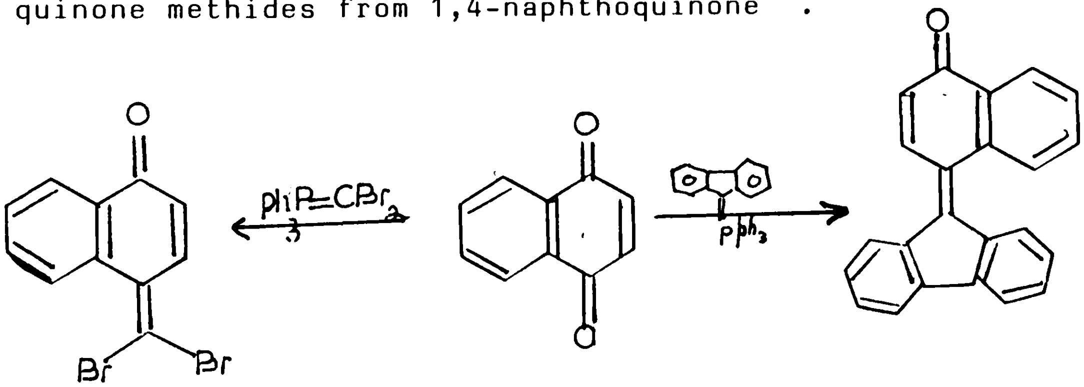
4.3.6 Synthesis from quinones

Owing to low electrophilicity of the carbonyl group in the quinones, the possibilities for synthesis of quinone methides from them are greatly limited.

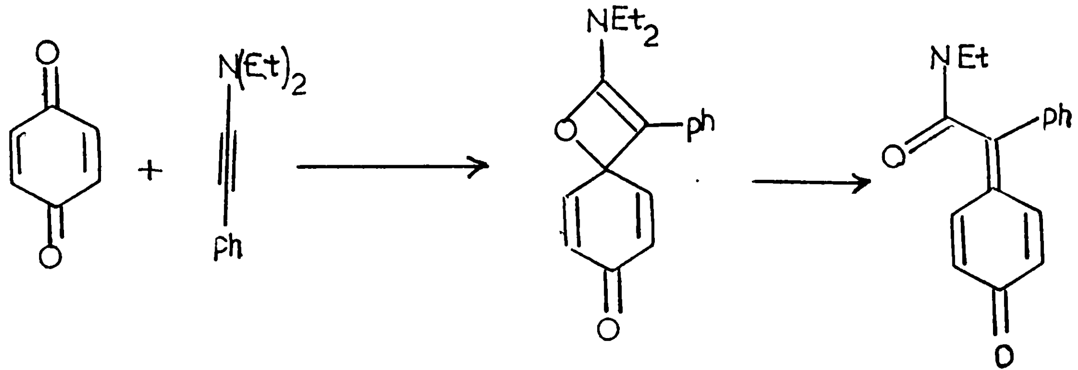
Even the condensation of C-H acidic components which is often used for synthesis of methylene groups in other series of compounds rarely succeeds. However in special cases, such as phenanthraquinone and 1,2-acenaphthenequinone, reaction with malonodinitrile gives quinonemethides as is shown below[95].



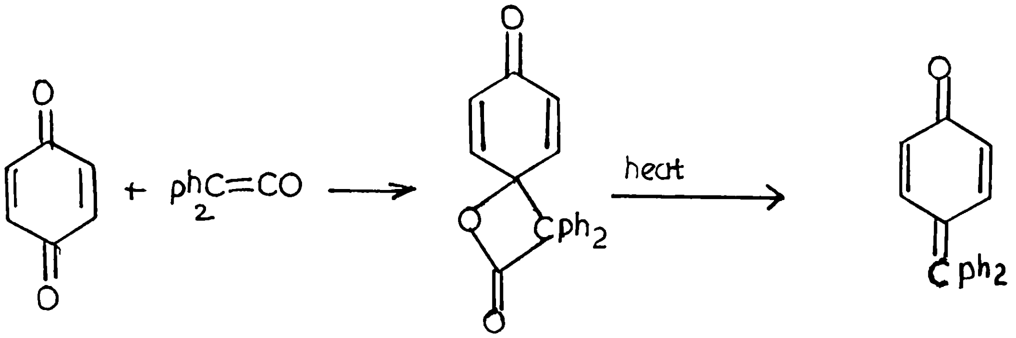
Synthesis of methylene derivatives from carbonyl compounds by the Wittig reaction can be carried out to give quinone methides from 1,4-naphthoquinone[96].



Reaction between the carbonyl group of quinones and very reactive ynamines affords quinone methides. For instance, para-benzoquinone and N,N-diethyl-2-phenylethynylamine give the corresponding quinone methide, whose formation is most simply formulated as occurring through the four membered cycloaddition product followed by a subsequent ring opening[97].

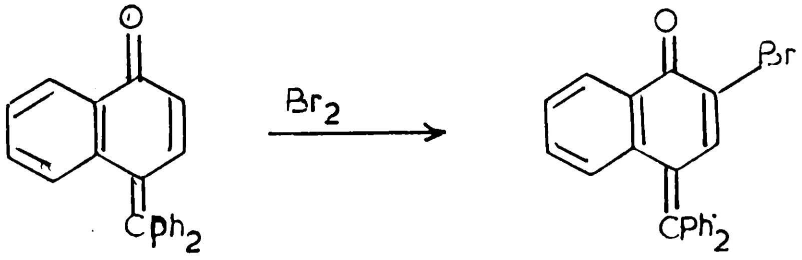


A similar reaction occurs with ketenes[98].



4.3.7 Synthesis from Quinone methides

There are a few examples of substitution of an intact quinonemethide. 1,4-Naphthofuchsone can be brominated in the quinonoid ring[99].



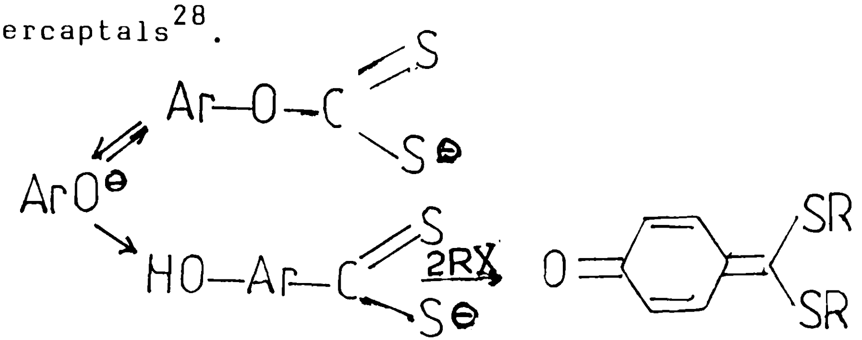
2. DISCUSSION

The following contractions have been used throughout this section.

S	Singlet
b	broad
d	doublet
m	multiplet
mp	melting point
ir	infra red
uv	ultra violet
^{1}Hnmr	nuclear magnetic resonance
^{13}Cnmr	nuclear magnetic resonance
tlc	thin layer chromatography
lit	literature
DMSO	dimethyl sulfoxide
THF	Tetrahydrofuran
PDC	Pyridinium dichromate

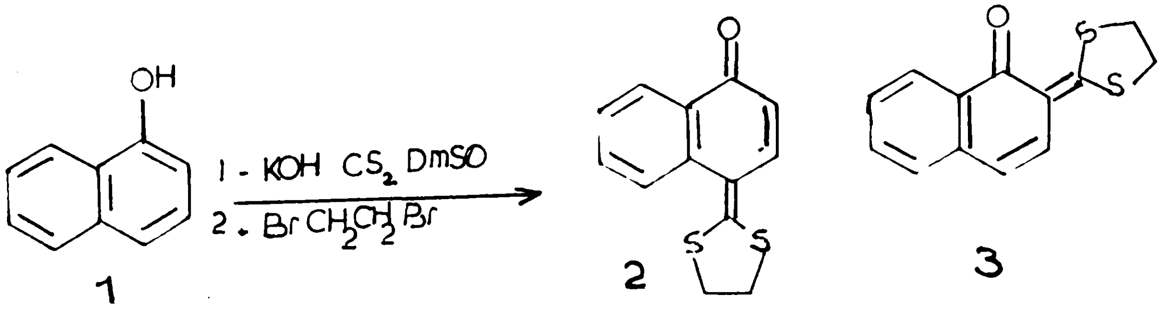
2.1 Introduction

It is known that treatment of phenol with carbon disulfide as electrophile in alkaline solution affords the salts of dithioacids and their alkylation leads to ketene mercaptals[28].

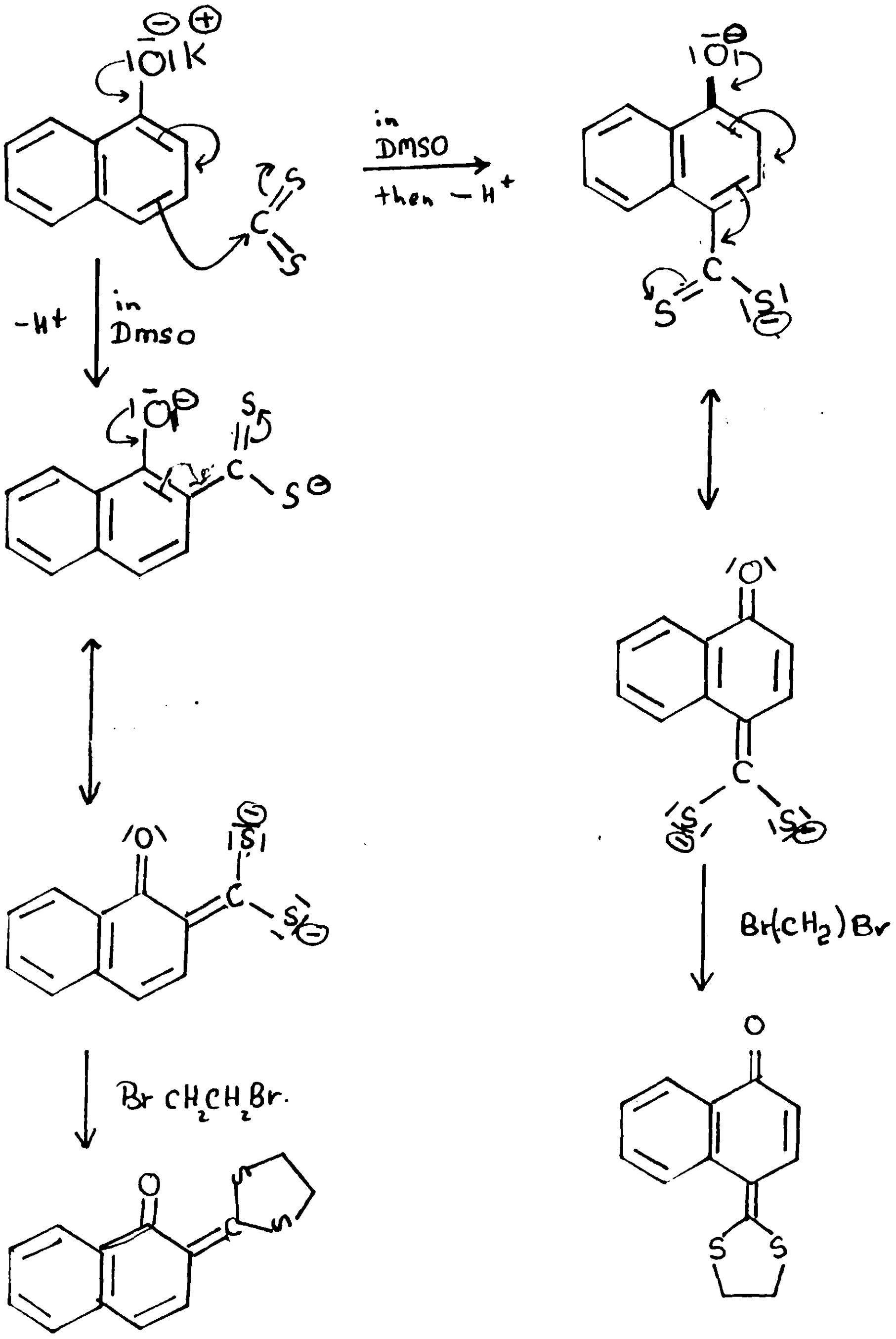


It has been stated that reaction with carbon disulphide is not only to be expected on the ring, but also on the oxygen atom, because the phenoxide ion is delocalised and is an ambident nucleophile. The xanthate ester resulting from attack at oxygen might be formed first and then rearranged to the more stable dithiocarboxylate. With some phenols more than one dithiocarboxylate isomer is possible. The outcome of the reaction might also be dependent on the solvent, base and temperature.

It has been reported that treatment of 1-naphthol with K_2CS_3 at 130°C or potassium xanthate and alcohol or treatment of potassium naphthoxide with carbon disulphide on a water bath gives in each case 1-hydroxynaphthalene--2-carbodithioic acid. Whereas Gompper in 1965 stated that treatment of 1-naphthol with carbon disulphide in alkaline solution in DMSO gave 1-hydroxy naphthalene-4-carbodithioic acid which could be alkylated with dibromoethane to give the stable quinone methide (2) as deep orange



crystals melting at 177°C (from methanol) in 25% yield. uv spectra has been reported (see table). The alternative structure (3) for this product was not considered. The reaction path was thought to be as illustrated below.



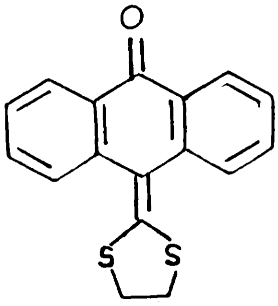
On the purpose to study the spectral properties of the quinonemethide (2), this reaction was repeated by Koutek in 1982 when he reported each of the ir, ^{1}Hnmr and the dipolemoment of the para isomer apparently got by Gommper's procedure.

This reaction provoked our interest due to the following matters.

i. The reported para-regioselectivity which suggested that it would be a suitable procedure for making 4-methyl-1-naphthol (which was needed for other synthetic purposes) <u>via</u> Raney-nickel reduction of the quinone methide (2).

ii. The formation of 1-hydroxy-naphthalene-2-carbodithioic acid which was observed by K_2CS_3 procedure (discussed in section 2.7). Gompper in 1965, however, reported that treatment of 1-naphthoxide with CS_2 in dimethylsulphoxide gives exclusively the 1-hydroxy-naphthalene-4-carbo-dithioic acid which when treated with dibromoethane gave para-quinone methide (2) as orange crystals. No sign of the ortho isomer was mentioned.

iii. The orange colour of the compound obtained by Gompper is in disagreement with his observation of the benzene (4) and anthracene (5) analogs which are



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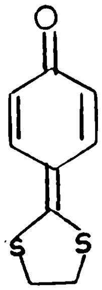

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pale yellow in colour. There is no reason why the para-naphthaquinone should absorb at longer wave length than either of these analogs.

Having stated these matters a doubt has arisen regarding the regioselectivity. It was felt that this reaction needs to be reinvestigated.

2.2 Attempted preparation of the para-quinone methide(2)

In an attempt to prepare the title compound starting from 1-naphthol Gompper's procedure was repeated as reported[28]. Tlc (20% EtOAc/Pet. ether) indicated two main spots (Rf 0.25, Rf 0.20) showing as orange and yellow respectively in the daylight, along with the starting material (Rf: 0.85) as a colourless spot showing under the uv lamp.

The structure of the two components were identified from the ^{1}Hnmr spectrum of the mixture. By subtracting the set of signals corresponding to the starting material, two different sets of signals appeared. From the integral comparison, it was immediately possible to identify the major component as the ortho isomer. Whereas the minor component was identified as the para isomer on the basis of the presence of a widely separated AB system at δ 6.45 (H2) and 7.95 (H3) with a coupling constant of the order of 10.0 Hz. Crystalisation from methanol yielded orange crystals melting at 127°C identified by the elemental analysis as a quinone methide. Its uv data in methanol fit properly with those previously reported by Gompper. Its ^{1}Hnmr, ^{13}Cnmr data are in disagreement with those previously reported by Koutek.

Therefore, there is no doubt from the analysis and uv that the major orange product is that isolated by Gompper and that his melting point (127°C) is probably a misprint. There is also no doubt that this orange product is the ortho quinonemethide (3) from its ^{1}Hnmr spectrum δ ($CDCl_3$) 8.40, bd, 1H (H8); 7.3-7.4 ,m, 3ArH (H5, H6, H7); 7.15, d, 1H (H3); 6.70, d, 1H (H4), 3.58, S, 4H (CH_2CH_2). It has one low field proton (H8) and two alkene protons (H3 and H4) with similar chemical shifts coupled to one another. A double irradiation experiment proved that H4 couples to all of H3, H5 and H8 with the following values of the coupling constant respectively. (JH_4, H_3 9.50 Hz., JH4, H5 0.35 Hz., JH4, H8 0.75 Hz.) and H3 is coupled to H7 (0.30 Hz).

2.3 Separation of reaction mixture by chromatography

The mixture obtained (1.5g) was chromatographed on a preparative silica gel column with chloroform as eluent. 1-Naphthol (900 mg.) was eluted first followed by the orange quinone methide (3) (320 mg.) and then the yellow quinonemethide (20 mg). The latter fraction was purified by means of tlc plates to give about 15mg. of a pure sample of the yellow component. This could not be crystallised, but it was possible to obtain a 100 MHz ^{1}Hnmr ($CDCl_3$) which showed the presence of a widely separated AB system at 6.45 and 7.95 which corresponds to H2 and H3 respectively, coupled to one another with a coupling constant of 10.0 Hz. and two superposed broad multiplets at low field (δ 8.35) which must be H5 and H8, peri to the carbonyl and exo methylene groups and deshielded because of the anisotropy or steric congestion. This ^{1}Hnmr data is compatible with the proposed structure of the para-quinone methide. It was unfortunate a full comparison of the two isomers was not possible since the yellow compound has not been obtained in sufficient amount.

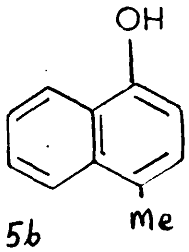
Repeated attempts to alter the ortho/para ratio by changing the reaction conditions such as the reagent quantities, temperature and reagent addition procedure were unsuccessful.

2.4 Reduction of the orange quinone methide (3)

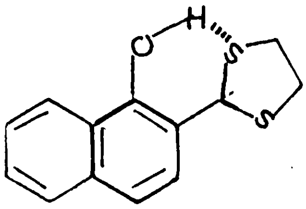
It was thought that it would be possible to confirm the structure of the orange quinonemethide by converting it to a methylnaphthol and comparing it with 4-methyl-1-naphthol (5b), a sample of which was available for comparison.

Raney-nickel seemed to be a likely reducing agent to convert the orange quinonemethide (3) to its corresponding methyl naphthol.

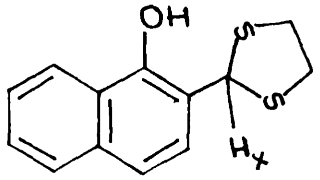
Direct reduction with washed Raney-nickel in ethanol at room temperature gave a mixture of a phenol and two other components. ^{1}Hnmr was unable to identify them. This reaction was not clean.



5b



6a



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An alternative method of reduction of the compound (3) to the corresponding phenol with sodium borohydride in THF met with failure and no reaction occurred at all.

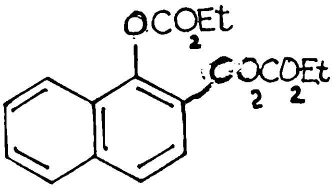
Eventually, it was found that treatment with an excess of lithium aluminium hydride rapidly changed the orange colour of the solution into a pale green solution. Tlc showed no starting material remained. The reaction was then worked up, by filtering off the lithium aluminium hydride and destroying it with ethanol before disposal. The solution was evaporated to give a new phenol in 95% yield identified as the thioacetal (6) from its ^{1}Hnmr ($CDCl_3$) which shows a new singlet at δ 5.90 (H_x). A change also happened at δ 3.50 by which the singlet due to ($-CH_2-CH_2-$) in the quinone methide structure split into a complex symmetrical AA′BB′ system. This change might be due to hydrogen bonding in (6a) which restricts the free rotation about the exo bond, and also makes H_A and $H_{A'}$ (and H_B, H_B') different from one another. This was proved by the infrared spectrum which shows that the hydroxyl groups are almost all hydrogen bonded in solution in CCl_4 (broad band with maxima at 3400 and 3300 cm^{-1} and no change occurs on dilution.

Further treatment of compound(6) with Raney nickel in methanol reduced it cleanly to a methylnaphthol.

Tlc and ^{1}Hnmr comparison with authentic 4-methyl-1-naphthol showed them to be different. Therefore, this confirms that the starting material is clearly not the para isomer. The spectrum of this new phenol suggested it might be 2-methyl-1-naphthol but no sample of this was available for comparison. Also it was concluded that preliminary treatment of the quinone methide (3) with lithium aluminium hydride in THF afforded the phenol (6), which can be reduced to 2-methyl-1-naphthol in an excellent overall yield without isolating the intermediate.

2.5 Preparation of 2-methyl-1-naphthol

An attempt was made to hydrogenolyse 2-piperidinomethyl-1-naphthol (7) (which was prepared with success in a good yield by treating 1-naphthol with 40% formaldehyde in 75% methanol and piperidine at room temperature[18]) with 20% palladium charcoal in anhydrous methanol, but there was no uptake of hydrogen, even on adding a few drops of glacial acetic acid to catalyse the reaction. they had brought about this hydrogenolysis over copper chromite under pressure and other amino-methyl-naphthols had been hydrogenolysed with Pd/C at 1 atm.



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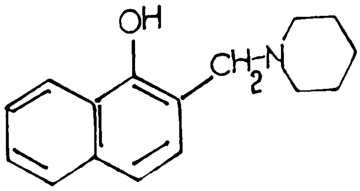

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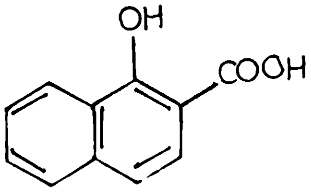

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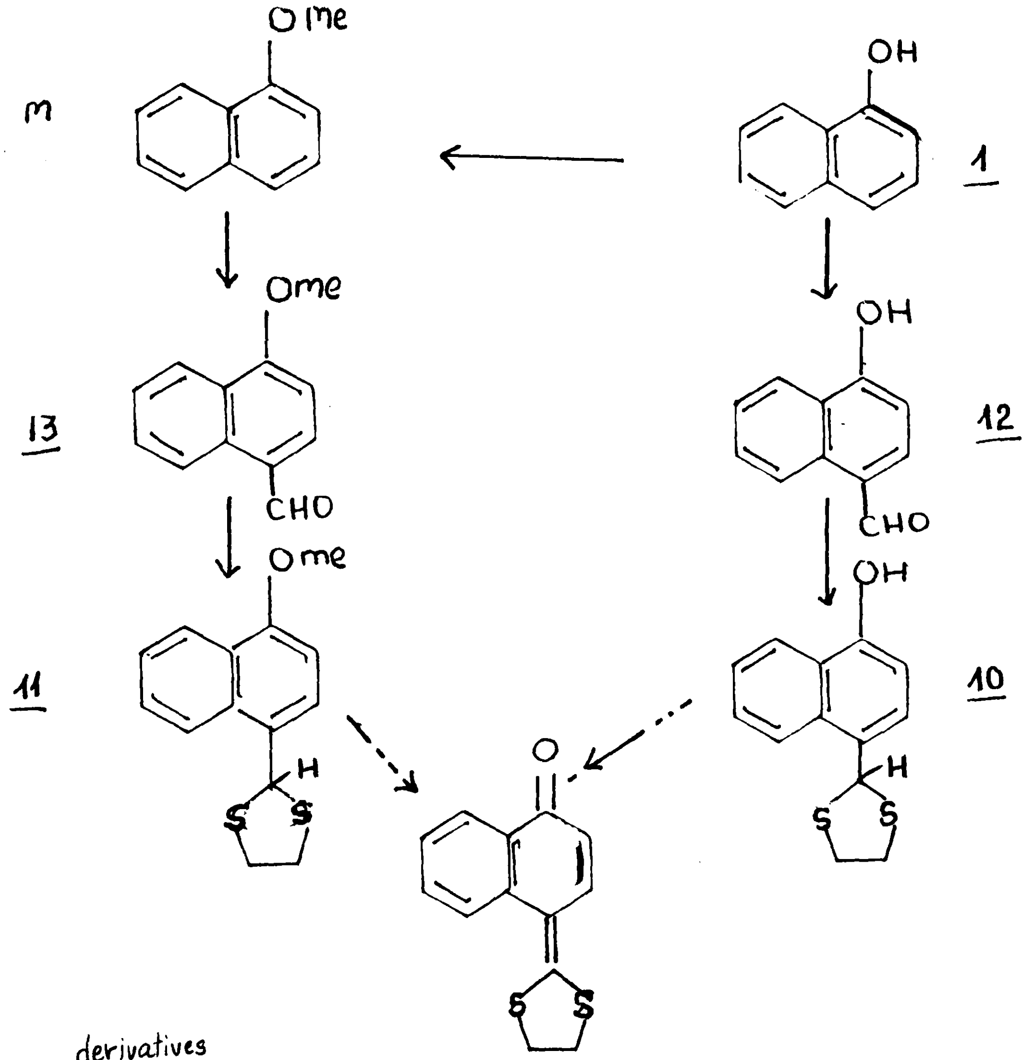
An alternative route to the phenol (6) which involves the reduction of 1-hydroxy-2-naphthoic acid (8) in the form of its double ethoxy - carbonyl derivative (9)[100] was found in the literature. Following this procedure the acid was treated with ethyl chloroformate and then excess sodium borohydride yielded the phenol (6) whose structure was confirmed by ^{1}Hnmr in chloroform, in a yield of 55 % (lit. 62.2%). Tlc plate and ^{1}H nmr comparison of the phenol obtained this way and the material obtained from the reduction of compound (3) showed them to be identical, confirming the orange quinone methide has the ortho structure (3).

Regarding the previous comparison, there is a confusion, in the literature, concerning the assignment of the site of the attack in the reaction of 1-naphthol with carbondisulphide. It was clear that Gompper obtained the ortho isomer, whereas he thoought he obtained the para-isomer. This error might have been due to the limited availability of ^{1}Hnmr which is indispensible. The preference for ortho attack in DMSO is in line with the old literature work in other solvents and with the ortho attack by carbon dioxide.

6. Approaches to the para-quinonemethide via 4-hydroxy-1-naphthaldehyde

The para isomer was present in small amounts but I had not beenable to obtain it pure; it was therefore decided, to investigate an unambiguous synthetic route to the para isomer by means of dehydrogenation of the

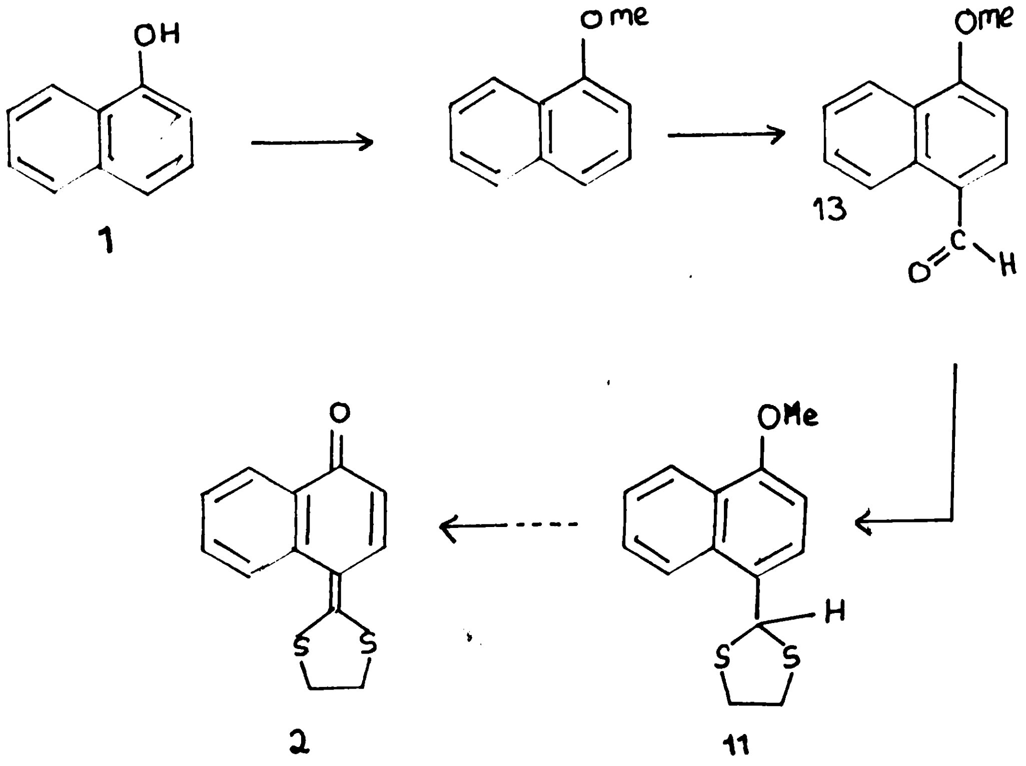


phenol~~s~~ derivatives (10 or 11) which might be obtained by the formation of 1,2-dithiolane rings from 4-hydroxy-1-naphthaldehyde (12) or 1-methoxy-4-naphthaldehyde (13) (see scheme above).

In order to carry out this investigation in a systematic manner, it was necessary to prepare 4-hydroxy-1-naphthaldehyde which would then be subjected to treatment with ethane dithiol in chloroform; the methoxy aldehyde is commercially available but expensive.

4-Methoxy-1-naphthaldehyde(13) and its dithio acetal (11)

1-Methoxynaphthalene(m) was prepared from 1-naphthol using dimethyl sulphate and formylated using N-methylformanilide and phosphorus oxychloride$^{(101)}$. Fractional distillation separated unreacted methoxynaphtalene from the aldehyde, which was obtained in moderate yield. Treatment of the aldehyde with ethanedithiol and boron fluoride etherate in chloroform at room temperature gave the dithioacetal cleanly whose structure was proved by ^{1}Hnmr ($CDCl_3$). An attempt was made to oxidise the compound (11) using triphenyl carbinol and hydrogen bromide in acetic acid. It was hoped that the triphenylmethyl cation would capture hydride ion and that the bromide ion would remove the methyl group. Unfortunately



the product was a complex mixture in which no yellow spot of the correct Rf for the para quinone methide could be detected and this approach was abandoned.

Some components in the Vilsmeir reaction, perhaps the methoxynaphthalene, caused a severe skin irritation which took several weeks to clear and this also forced a change of approach.

Attempted formylation of 1-naphthol using ethyl orthoformate

It is reported that this gives the 4-aldehyde in good yield[40]. Several attempts to repeat this reaction using different batches of aluminium chloride lead either to very low conversion or to complex mixtures containing some of the required aldehyde. When titanium tetrachloride was used as catalyst the reaction was much slower and still complex. While simple, safe and cheap this literature method seems to require precise conditions whichIwas unable to repeat.

Attempted formylation of 1-naphthol by the use of hexamethylenetetramine in trifluoroacetic acid

It had been reported that a variety of aromatic compounds have been converted into aldehydes regioselectively via a facile formylation process employing hexamethylene-tetramine in conjunction with trifluoroacetic acid[39]. For instance, in the case of toluene a ratio of 50% to 11% of para and orthotolualdehyde was obtained.

$$\text{Ar-H} + C_6H_{12}N_4 \xrightarrow[2.\ H_2O]{1.\ CF_3CO_2H} \text{ArCHO}$$

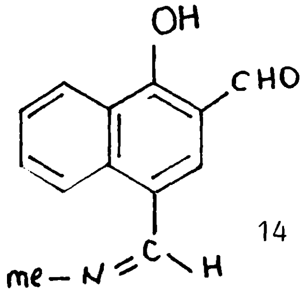
The mechanism has been already discussed in the introduction.

There are no reports of this reaction being applied to 1-naphthol so this was tried.

1-naphthol (1.4g) was treated under the literature conditions and the bulk of the solvent was recovered by distillation and the residue diluted with water and neutralised with sodium carbonate. The aqueous layer was washed with ether. Tlc of the ether layer showed several components (Rf 0.25, Rf 0.35, Rf 0.60) along with the starting material.

The ether layer deposited a yellow solid on standing overnight at room temperature. It was filtered off and dried to give 0.85g of a new compound thought to be an imine m.p., 228-229.9°C from ethyl acetate/light petroleum (60-80°C). Elemental analysis results indicated that it was pure and fits for the formula $C_{13}H_{11}NO_2$. Its ^{1}Hnmr in chloroform showed δ 9.90, s.s1 CHO; 9.15, b.d.., H8; 8.49 b.d., H5; 7.48, S. H3; 7.50-7.80, m, H6, H7 and N=CH; 7.9, b.s., OH; 3.40, S., Me. The last chemical shift corresponds to the chemical shift of a methyl group attached to a nitrogen atom. This suggests an N-methylaldimine group.

The absence of H2 and the presence of two downfield protons suggests that positions 2 and 4 of the phenol ring are occupied. H3 was a fairly sharp singlet. This product must therefore be (14) or (15).



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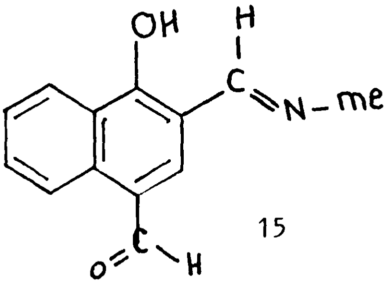

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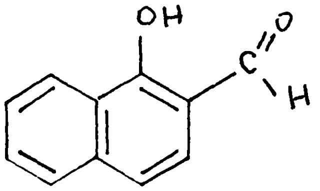
This assignment was supported later on by the ^{13}C spectrum (see table). To confirm this structure deliberate acid hydrolysis of the orange crystals yielded a dialdehyde (17). This same aldehyde was obtained from the original reaction by acidifying the sodium carbonate layer with 2M hydrochloric acid and extraction with ethyl acetate. Concentration gave a yellow solid (350 mg) whose ^1H nmr showed it to be a mixture. Crystalisation gave the dialdehyde mp 151°C. The positions of the two aldehyde groups were clear from its ^1Hnmr spectrum at δ 10.13 and 9.98, two sharp singlets (2 x CHO); 9.2, d, H5; 8.45, d, H8; 7.98, s.s, H3; 7.82, d.t., and 7.6, d.t., H6 and H7.

By subtracting this spectrum from that of the above mixture it was possible to show that the mixture had contained an other aldehyde which has no up-field proton (H2) and which presumably was the orthoaldehyde (16).

The Duff reaction under the conditions used seems therefore to give mainly 2,4-disubstitution in the case of the strongly electron rich 1-naphthol. The isolation of the monoimine must be the result of faster hydrolysis of one of the two imine groups selectively.



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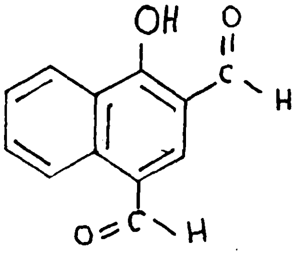

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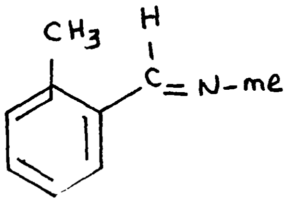
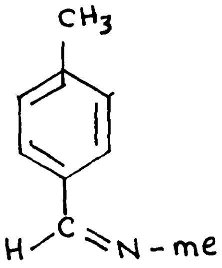
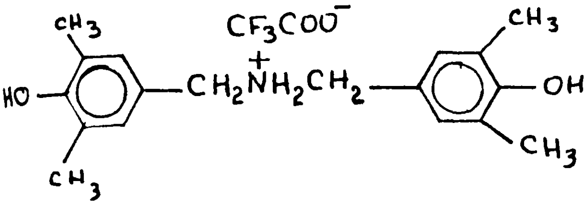
The indications were that the para aldehyde would not be obtained pure even under milder conditions. N-Methylimines have been isolated before. In the case of toluene when the reaction mixture was subjected to brief hydrolytic work-up, the para and orthotolualdimines were obtained in predominance to the carbonyl compounds and

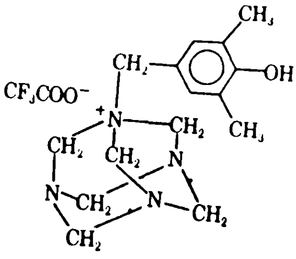




it was thought that they could be formed either by rearrangement of the methyleneimines $ArCH_2N = CH_2$ or arise in exchange reactions involving methylamine. Other kinds of intermediates have been isolated and identified when both heating and hydrolysis are avoided. The dibenzylammonium salt (A) and the hexaminium salt (B) were isoalted from low temperature reaction of hexamethylenetetramine with xylenol.



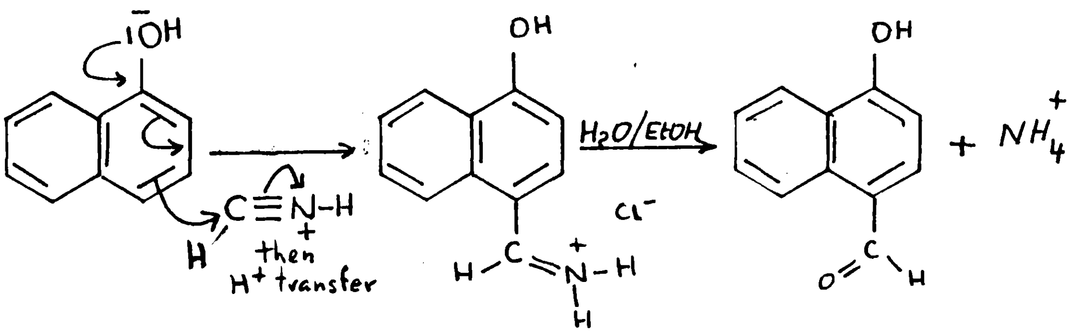
A



B

Formylation of 1-naphthol with zinc cyanide and dry HCl

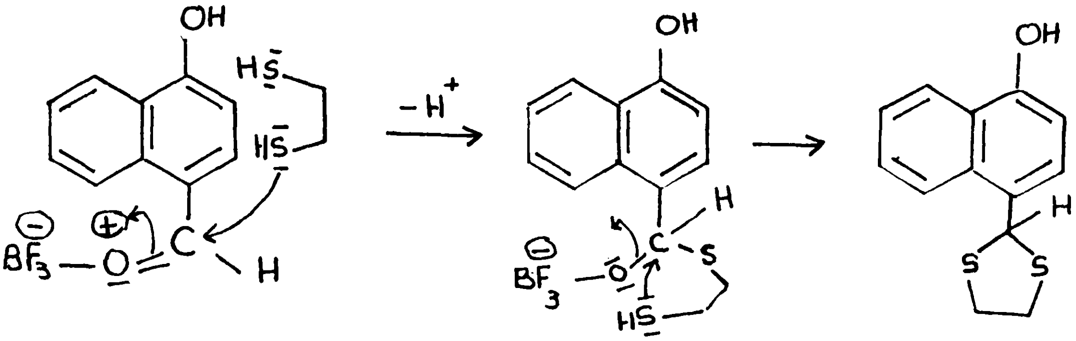
Due to the negative and disappointing results obtained from the previous attempts, it was decided to use the modified procedure of Gattermann. This method was previously avoided in the present work, because it involves the generation of hydrocyanic acid from the reaction of zinc cyanide and hydrogen chloride to be used as the formylating agent. This gas needs serious precautions but a 72% yield is reported[33]. By bubbling hydrogen chloride gas through a solution of 1-naphthol in dry ether containing solid zinc cyanide, the zinc cyanide gradually dissolves and is replaced by a sticky gum which eventually turns to a yellow granular solid. This solid imine hydrochloride was dissolved in aqueous ethanol. The aldehyde gradually precipitates out in



a yield of 60% and the reaction went exclusively in the para position. No sign of the ortho naphthaldehyde was noticed. The structure was confirmed by the ^{1}Hnmr and the purity was confirmed by tlc plate and melting point. The mechanism of this reaction might involve the generation of hydrocyanic acid which condenses with 1-naphthol to yield the imine hydrochloride as a cake and then hydrolysis gives the corresponding aldehyde which showed H2 and H3 as an AB system at δ 7.00 and 7.90; H5 peri to the aldehyde group as a broad doublet at 9.35; H8 as a broad doublet at 8.35 and the aldehyde proton at 10.00.

Conversion of 4-formyl-1-naphthol into its ethane dithiol acetal

The dithioacetal (10) was obtained in about 90% yield by treatment of the freshly prepared aldehyde with ethane dithiol in the presence of boron trifluoride as Lewis acid catalyst in a mixture of chloroform and methylene chloride for 14 hours at room temperature followed by washing with 2M sodium carbonate to destroy the boron trifluoride. A tlc plate indicated only one colourless spot showing under the uv lamp, slightly less polar than the aldehyde. It went green in colour after Ce^{IV} spray and became yellow by heating it up in an oven. There was a tiny spot of the starting material. Crystallisation from ethylacetate/light petroleum (60-80°) gave pink crystals mp 138-140°C. The reaction path may involve the co-ordination of the boron trifluoride to the oxygen atom of the carbonyl group followed by a nucleophilic attack on the carbon atom and then an S_N2 reaction as illustrated below.



This reaction might have been better regarding the yield and the length of time needed if the aldehyde had been entirely in solution from the beginning, but the aldehyde is very insoluble.

The previously unknown dithioacetal (10) was characterised by elemental analysis to be $C_{13}H_{12}OS_2$. Its ^{1}Hnmr in chloroform showed at δ 8.20, m, H8, H7; 7.87, s d (J 10.0 Hz), H3; 7.40-7.70, bm, H6, H7; 6.78, sd, (J 10.0 Hz), H2; 6.40, ss, Hx; 3.50, bq, CH_2CH_2; 5.70-5.30, lump, OH (this disappears by D_2O exchange).

Th appearance of the peak relating to the $-CH_2-CH_2-$ group as a broad singlet is perhaps due to a low barrier to rotation about the C-C single bond. The ^{13}C nmr data are given in the table.

<u>Comparison between two dithioacetals obtained, (6) and (10)</u>

This new acetal should be an isomer of that got by $LiAlH_4$ reduction of the orange quinone methide and it was therefore interesting to contrast them.

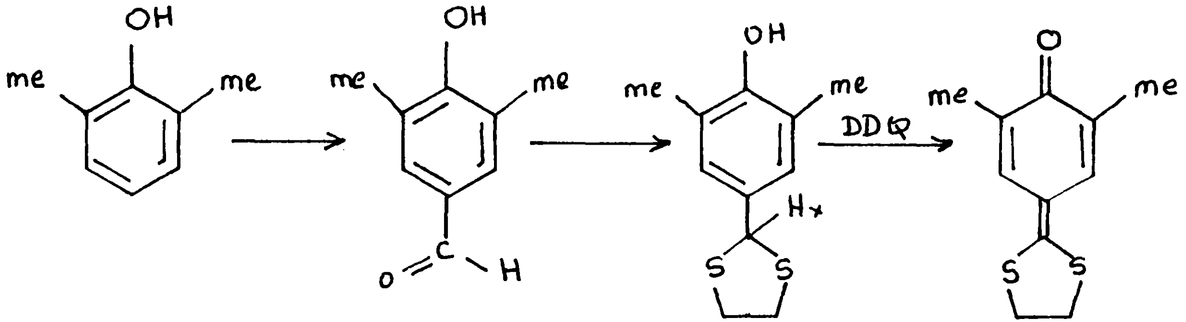
Compounds (6) and (10) were shown to be different by discrepancies in colour, melting point and spectral data (see table). The presence of the hydrogen bonding in the compound (6) obtained by $LiAlH_4$ reduction of the quinone methide even in dilute solution (bands at 3400 and 3300 cm^{-1}) suggests that the substituent is at the ortho position whereas in compound (10) there was a hydrogen bonded OH at 3320 cm^{-1} and a non-hydrogen bonded OH at 3605 cm^{-1}. The former disappeared on dilution. That suggests that the substituent is at the para position. In addition both ^{1}Hnmr and ^{13}Cnmr are rather different showing that the two dithio acetals are not identical.

This gives rise to more evidence of the wrong assignment of the structure of the quinone methide obtained from the CS_2 reaction.

Preparation of 2,6-dimethyl-4-formylphenol (20) and its conversion into a quinone methide

Before attempting oxidation of the naphthol thioacetal, the xylenol analog was investigated since the quinone methide in this case was known, though not made by this way.

The title compound (20) was obtained in moderate yield as pale yellow crystals, mp 109-110°C from a mixture of chloroform and petroleum-ether, by treating xylenol (18) with hexamethylenetetramine in refluxing trifluoroacetic acid following the literature [39]. After 12 hours, tlc showed mainly one spot and no starting material remained. The reaction was then worked-up by distilling off the solvent followed by a water work-up. The structure was confirmed by the aid of ^{1}Hnmr in chloroform, in particular the appearance of the aldehyde proton at δ 9.75 as a singlet.



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It should be noted that in this case the Duff reaction works fairly well.

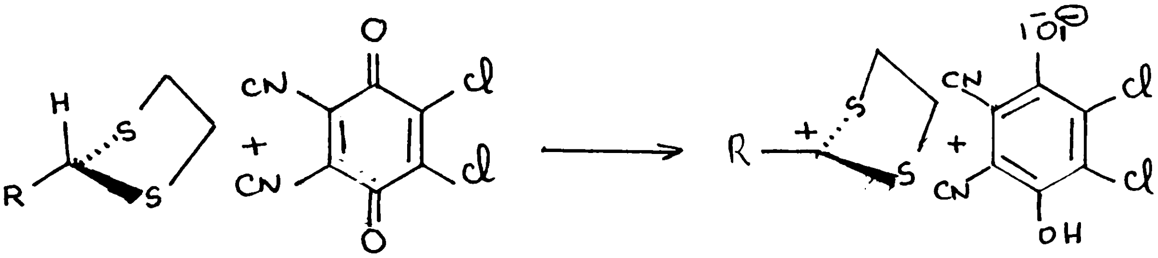
Treatment of the freshly prepared aldehyde with ethanedithiol in the presence of boron trifluoride etherate as Lewis acid catalyst in chloroform gave in a good yield the phenol (20). This compound crystallised out from petroleum ether as white plates melting at 68-69°C; its ^{1}Hnmr in chloroform showed δ 5.57, S, H_x, 3.50, bs, $-CH_2-CH_2-$. DDQ oxidation of the dithioacetal (20) in chloroform gave in a good yield the corresponding quinone methide (21) whose structure was confirmed by ^{1}Hnmr in chloroform which showed the total disappearance of the signals of H_x at 5.57 and OH at 4.75. This quinone methide crystallises nicely as orange crystals melting at 121.5-123°C from a mixture of ethyl acetate and petrol.

Attempted Oxidation of phenols (6) and (10)

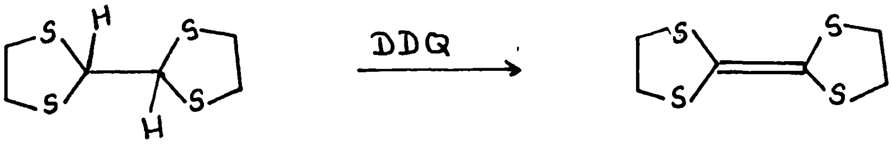
Having made these phenols, it was likely that it would be possible to obtain the corresponding quinonemethides through a hydride abstraction oxidation process.

For this reason, and due to their high reduction potential, quinones such as 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) seemed to be a likely oxidative agent to convert these phenols to their corresponding quinonemethides.

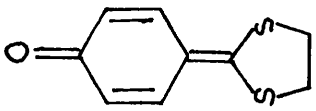
It has been reported[102] that an exposure to DDQ, certain thioacetals undergo oxidation according to the following reaction and the products derived from this reaction depend on the nature of the substituent (R).

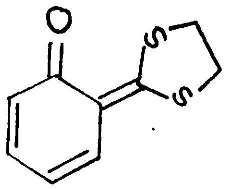


When possible, loss of a proton from the β-carbon atom occurs leading to ketene thioacetals in a yield of 50-70%.

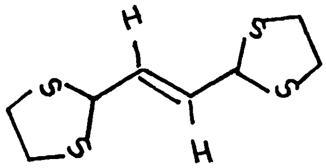
eg. 

Similarly, the thioacetals of ortho and para-hydroxybenzaldehydes afforded on exposure to DDQ the corresponding quinonemethides.

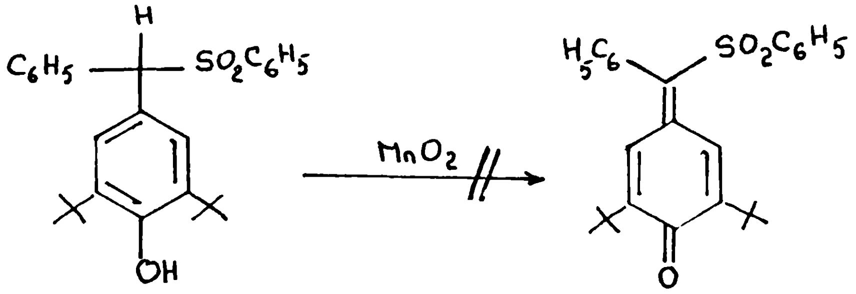




However, the DDQ oxidation of 2-ethyl-1,3-dithiolane, 2-benzyl-1,3-dithiolane and the bisthioacetal shown below were examined and found to fail.



Also, Koutek in 1976 failed to obtain the quinone methide derived from the sulfone via DDQ oxidation by manganese dioxide oxidation[103].



No one has established the mechanism, and the factors of success and failure of this reaction.

In the present work an attempt at oxidising the phenol (20) with DDQ in chloroform was achieved with success giving the corresponding quinone methide (21) which was previously prepared by Gompper via the CS_2 reaction.

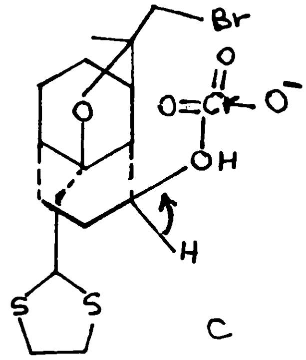
Several attempts at oxidising phenols (6) and (10) with freshly crystallised DDQ in different solvents such as chloroform, dimethyl sulfoxide, ether, acetone and dimethoxyethane failed to afford the corresponding quinone-methide. No trace of the desired yellow material was detected neither by tlc plate nor by ^{1}Hnmr.

Other attempted oxidations of phenols (6, 10)

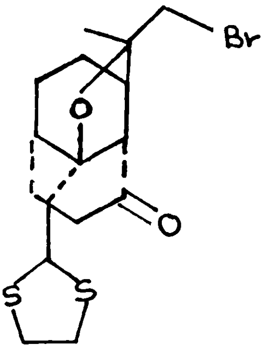
Despite the availability of many reagents for the oxidation of phenols to the corresponding quinone methide , such as, potassium hexacyanoferrate (III) $K_3Fe(CN)_6$, lead oxide, silver oxide, iodine, dimethylsulphoxide , pyridinium dichromate,..., etc, the choice of suitable oxidative agents for the phenols (6,10) was very limited because of the presence of the sulfur atoms which are readily accessible to be attacked by metal ions and other electrophiles. For instance, Cr^{VI}, Ag^+, I_2,..., etc, which are strong electrophilic reagents, might oxidise or co-ordinate to the sulfurs rather than the phenol. However, a selection of these reagents was made and tried on these phenols as follows.

i. Pyridinium dichromate (PDC).

Corey has reported that unlike PDC in dimethylformamide (DMF), the reagent PDC in methylene chloride oxidises primary alcohols to the corresponding aldehydes and no further <u>via</u> the formation of a chromate ester followed by a hydrogen abstraction as illustrated below, regardless of the nature of the substrate[104]. On the



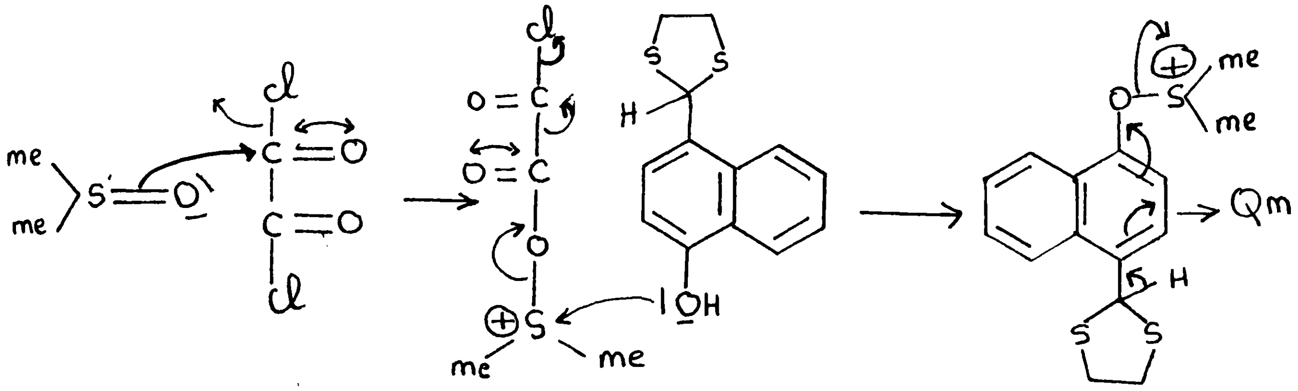
c



basis of his successful trial on the alcohol (c) without affecting the dithioacetal ring it was hoped that this reaction would work with phenols (6, 10). When these compounds were subjected to PDC-DMF and PDC-CH_2Cl_2 both reactions yielded a mess. ^{1}Hnmr was unable to detect what happened in this reaction and no starting material was recovered which means that some kind of reaction has happened but not in the right way. That might be due to the co-ordination of the Cr^{VI} to the sulfur atoms of the dithioacetal.

ii. Dimethylsulfoxide.

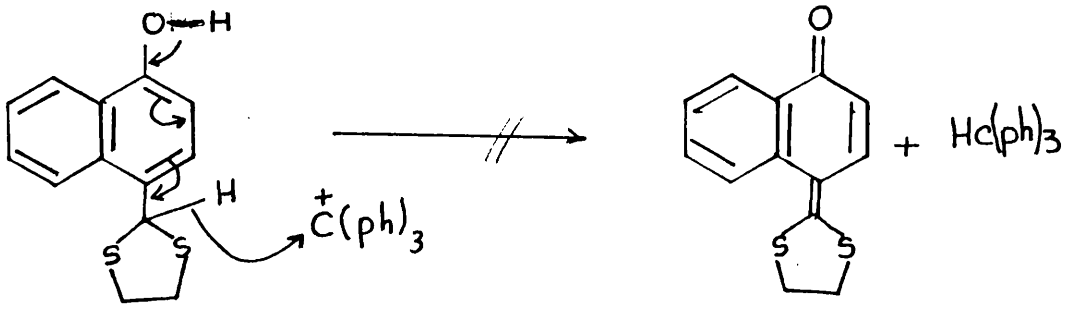
Swern has reported a mild yield oxidation of long-chain, saturated, unsaturated, acetylenic and steroidal alcohols to carbonyl compounds[105]. This method involves dimethylsulfoxide "activated" by oxalyl chloride at -60°C (because the oxalyl chloride reacts violently and exothermically above this temperature) to give the alkoxysulfonium salts convertible to carbonyl compounds in high yield. As the proposed mechanism below shows oxidation of phenol (10) might proceed similarly.



When compounds (6, 10) were treated under the same conditions none of the desired compound was observed.

iii. Triphenylmethyl tetrafluorobrate.

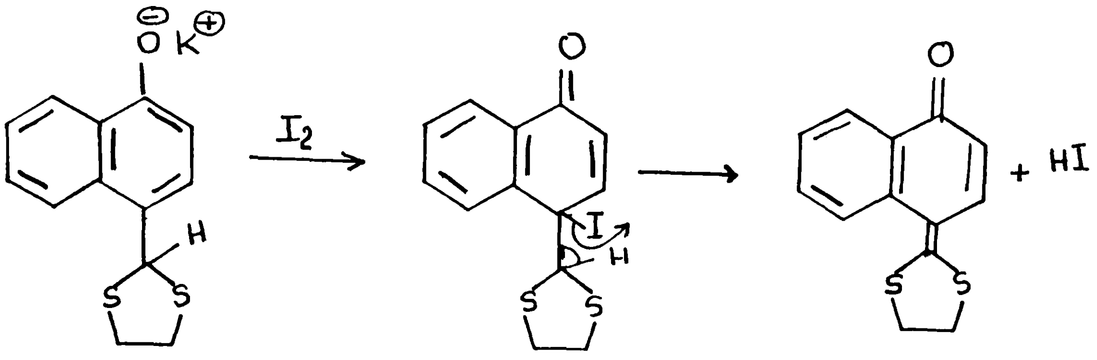
An attempt to oxidise the phenols (6, 10) with triphenylmethyl tetrafluoroborate via the following mechanism was met with failure and a total mess resulted from this reaction.



No sign of the desired compound was detected neither by tlc nor by ^{1}Hnmr.

iv. Iodine in the presence of potassium t-butoxide.

An attempted oxidation of the phenols (6, 10) with iodine and base in acetonitrile was made, where it was hoped that the iodine might iodinate the ring and then a subsequent elimination of hydrogen iodide might give the quinone methide. A possible mechanism is proposed. However, it met with failure as well.



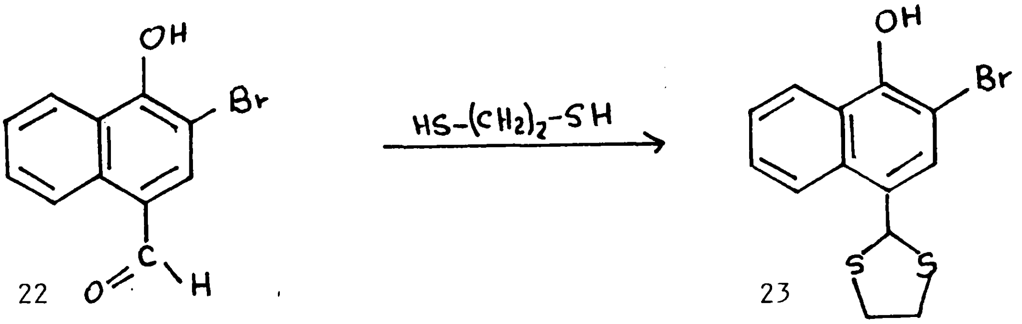
v. Oxygen in the presence of potassium t-butoxide.

An attempt of oxidation of phenol (6,10) by bubbling oxygen into a solution of the phenol (6,10) and t-BuOK in benzene with stirring at room temperature for 1 week failed and starting material was recovered.

Preparation of the dithioacetal (23) and its DDQ oxidation

Since at this stage it appeared to be difficult to obtain the parent para quinone methide(2), it was decided to try to make derivatives of it in which the 2-position was blocked by CH_3, Br or Cl and whose synthesis would not offer a choice of site of attack.

Treatment of 4-formyl-1-naphthol with a solution of bromine in glacial acetic acid at room temperature for ½ hour yielded the previously known bromoaldehyde (22) as a green solid mp 53-56°C whose ^{1}Hnmr in chloroform showed the disappearance of H2 (up-field proton) at δ 6.70 and the appearance of H3 as a sharp singlet at δ 8.04.



22 23

The TLC plate of the reaction mixture showed an extra spot less polar than 2-bromo-4-naphthaldehyde, it was believed on the basis of the ^{1}Hnmr of the mixture by comparing the integrals to be the 2,4-dibromonaphthol , which was thought to be formed in this reaction, as a result of the excess of bromine, which might substitute the aldehyde group. Therefore, it is concluded that this reaction requires high accuracy on the use of the reagent quantities.

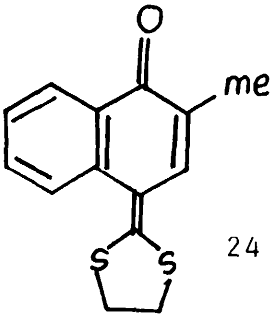
The substance (22) was converted almost quantitatively into its dithio acetal (a new compound), by treatment of compound (22) with ethane dithiol in chloroform in the presence of boron trifluoride for 12 hours at room temperature followed by a 2M sodium carbonate washing.

The dithioacetal (23) crystalised as greenish yellow plates from ethyl acetate/light petroleum, melting at 121.5-123°C. ^{1}Hnmr in chloroform indicated the presence of H_x as a sharp singlet at δ 6.30.

Attempted oxidation of the acetal (23) with DDQ in chloroform failed to give the corresponding quinone methide.

Synthesis of the 2-methyl-p-quinone methide (24)

Treatment of freshly prepared 2-methyl-1-naphthol with carbon disulphide and dibromo ethane in alkaline solution in DMSO yielded the title compound (24), a new quinone methide, as yellow crystals melting at 139-140°C from ethyl acetate/petrol. Elemental analysis results suggest the structure $C_{13}H_{12}OS_2$. Its ^{1}Hnmr in chloroform showed a singlet at δ 7.7 which refers to H3 and a multiplet at δ 6.4 which refers to the $-CH_2-CH_2-$ group. Uv and ^{13}Cnmr data have been discussed (see Table, Section 2).



24

In the hope to altering the yield of this reaction it was repeated in acetonitrile as solvent. However, the same results were obtained as above.

Improved yield of the para quinone methide from the CS_2 Reaction

Owing to the disappointing results of the attempted oxidation of the dithioacetals with DDQ, PDC, I_2, O_2, DMSO, it was decided to further investigate the original procedure with a view to altering the ortho/para ratio of the two isomers resulting from this reaction. As stated above changes in temperature and addition procedure had no effect but it was found that by the use of a less polar solvent than DMSO, namely acetonitrile, the two isomers were obtained in a combined yield of 25%

in a ratio of 50% of each isomer.

Therefore, it was concluded that this reaction is solvent-dependent; the para isomer was favoured by the less polar solvent whereas the ortho isomer was favoured by the more polar solvent.

Separation

The separation of the three components was achieved by preparative column chromatography on silica gel with gradually increasing proportions of ethyl acetate/petrol. 1-Naphthol was eluted first followed by the orange quinone methide and then the yellow one which was slightly contaminated with the orange quinone methide. The yellow one was purified by the use of t.l.c. plates (commercial preparative glass plates). In this manner both isomers were cleanly obtained in a yield of 12% para and 13% ortho. Therefore the overall yield was about 25%.

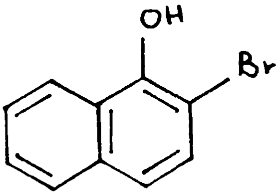
Having obtained a reasonable amount of the two isomers in a clean state a direct comparison of their ^{1}Hnmr, ^{13}Cnmr, ms, mp and uv was possible.

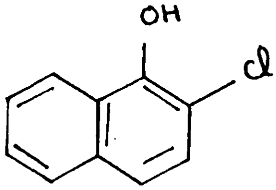
After I had resolved the problem of the isomeric quinonemethides and I came to the writing-up of this thesis a recent literature report[107] of Koutek was discovered, in which he tackled the same problem I was working on. He isolated the two isomers from the carbon disulphide reaction and reported their spectra and correctly assigned their structures.

His ^{1}Hnmr, ^{13}Cnmr data and mass spectra were very similar to the results reported in this thesis.

Treatment of 2-chloro- and 2-bromo-1-naphthol with carbon disulphide in alkaline solution

When each of the two title compounds were treated with carbon disulphide in alkaline solution in DMSO and then dibromoethane no sign of the corresponding quinone methides were observed. The electronic affect of the halogen atom on the ring may cause some stability and the attack may be difficult under these conditions.





Investigation of the spectral properties of the quinone methides (2,3,24,21)

These quinone methides exist in crystalline form, at room temperature and, are stable enough to be analysed. This great stability is probably a consequence of the presence of the push-pull effect (delocalisation) which is caused by the electron-withdrawing group (C=O) and the electron-releasing group (S).

In their ^{1}H nmr spectra in chloroform as solvent a peri proton in the para naphthoquinone methides was clearly seen at 8.41 ppm and is considerably deshielded compared to the other aromatic protons as a result of the anisotropic effect of the carbonyl group. Similarly, the 1,3-dithiolane group affects H5 and shifts it downfield to δ 8.34 ppm.

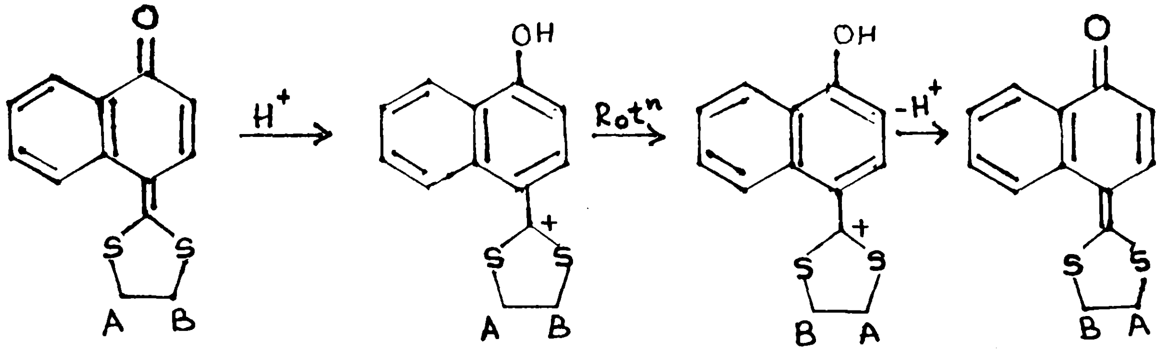
Thus both of H8 and H5 appear superposed as a complex multiplet. By the use of deuterated acetone as solvent this multiplet splits out into two doublets; a double irradiation experiment indicated which was which; and it was found that H5 is at slightly higher field than H8 in this solvent.

The ^{1}Hnmr of the para quinonemethide (3) as originally recorded shows the $-CH_2CH_2-$ as a broad singlet at δ 3.45.

Warming the sample to 60°C sharpens the singlet. Adding two drops of pyridine changes the appearance of the $-CH_2CH_2-$ signal to a complex symmetrical $AA'BB'$ pattern of 8 lines centred at δ 3.4. Apparently when there is no acid present rotation does not happen and the two CH_2

groups are well distinct. Traces of acid allow rotation to occur and heating accelerates this giving a sharp line.

The rotation is probably caused by the easy protonation of the carbonyl group giving a cation with a much lower barrier to rotation (lower double bond character in the exocyclic C=C bond). Rotation and loss of the proton gives back the original quinonemethide, but with the CH_2 groups inter changed.



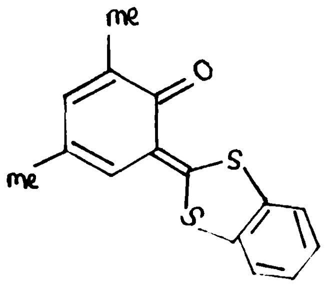
Only traces of the cation would need to be present to allow this to happen. The methylnaphthoquinonemethide behaved in exactly the same way when pyridine was added, but pyridine had no effect on the orthoquinone methide, presumably because the two CH_2 groups have the same chemical shift by accident, and pyridine had no effect on the xylene derivative as well since it is symmetrical.

It was then decided to add acid to the para isomer. When a few drops of trifluoroacetic acid were added to the chloroform solution of the quinonemethide a completely new spectrum was observed and the solution became red rather than yellow. This was believed to be the spectrum of the cation. Therefore, a few drops of acid are sufficient to convert all the quinone methide to the cation. No further changes were found even when trifluoroacetic acid was used as solvent.

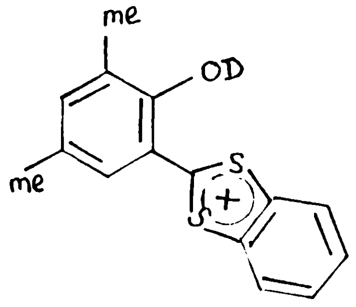
The other quinonemethides were studied. In acid there was in each case a downfield shift of the whole spectrum by about 0.6ppm (see table). It is noteworthy that in the case of (2) and (24) H8 was shifted downfield by a smaller amount than were the other aromatic protons or the dithiolan. This might be because the downfield shift produced on protonation is cancelled out by the removal of the downfield shift observed in chloroform and which is caused by the anisotropy of the carbonyl group.

Therefore, the protonation alters the π system and may reduce the anisotropy effect of these groups. In the spectra of the cations the $-CH_2-CH_2-$ was always a fairly sharp singlet indicating that rotation of the dithiolan was easy.

I later found that a similar observation had already been made.[106] Quinonemethide (A) behaves similarly as above. It was found on changing the solvent from deuterochloroform to deuterotrifluoracetic acid a completely different spectrum was observed.



A



B

This spectrum was shifted downfield by 0.6ppm and contains an AA' BB' pattern for the protons of the benzodithiole ring which in deuterochloroform solution, ie. in A, had been a complex multiplet since all four protons are different. This new spectrum is that of the positively changed 1,3-dithiolylium ion (B) in this solvent, and indicates that free rotation about Ar-C^{+} can take place. These authors did not, however, observe the effect of traces of acid which allows rotation without shifting the whole spectrum.

A similar effect was observed in the ^{13}C nmr spectrum of the para quinone methide. The sample as first isolated showed a very broad lump centred at 38 ppm and sharp lines for the aromatic carbons. When two drops of d5-pyridine were added the broad band was replaced by two singlets at 35.35 and 40.50 ppm. Traces of acid in the sample must have accelerated rotation causing the line broadening. The orange quinonemethide and the 2-methyl naphthoquinonemethide gave two sharp lines; ie. no acid was present in these two samples.

Fragmentation patterns of the P and O isomers

Fig.1

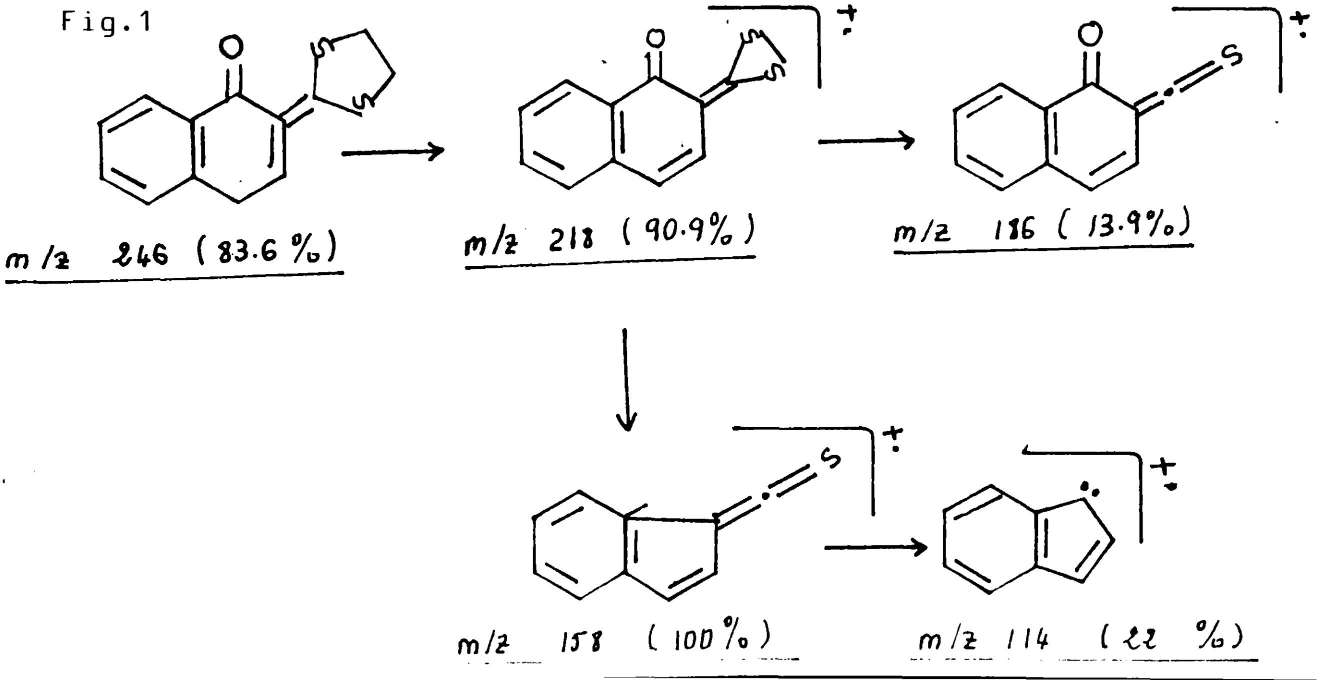
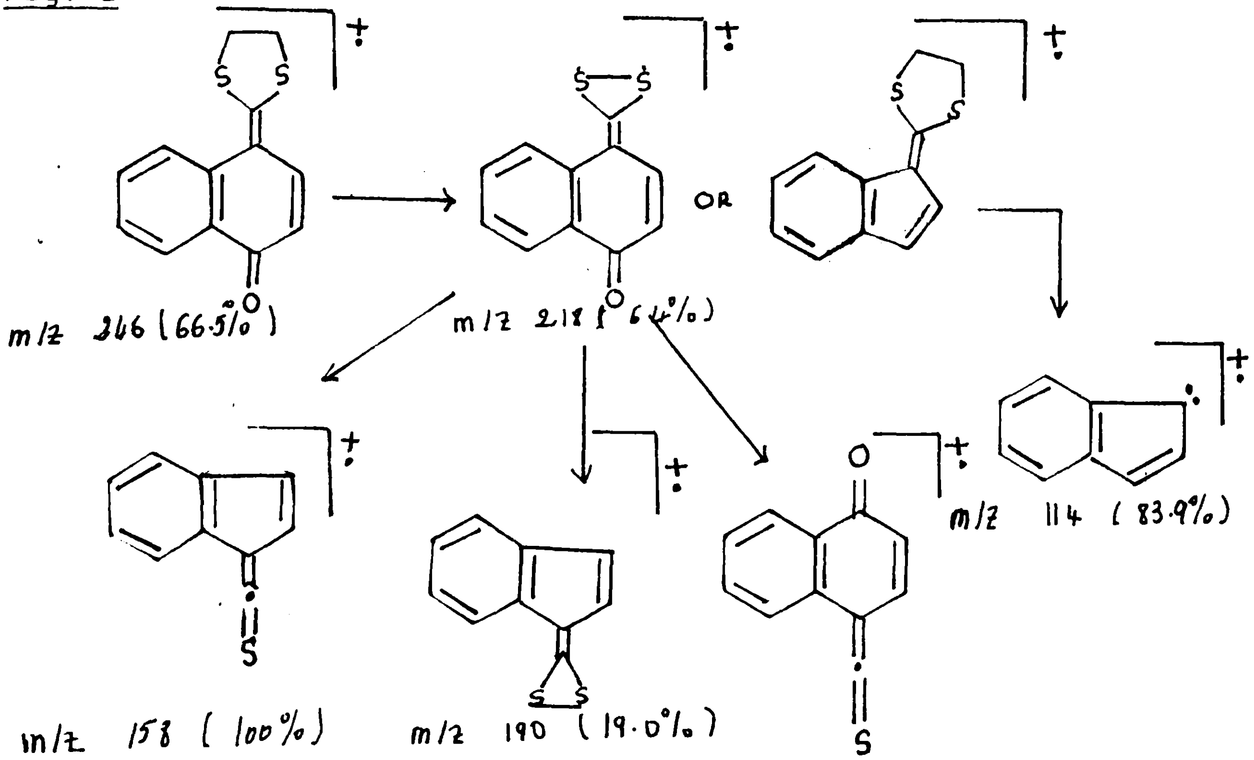
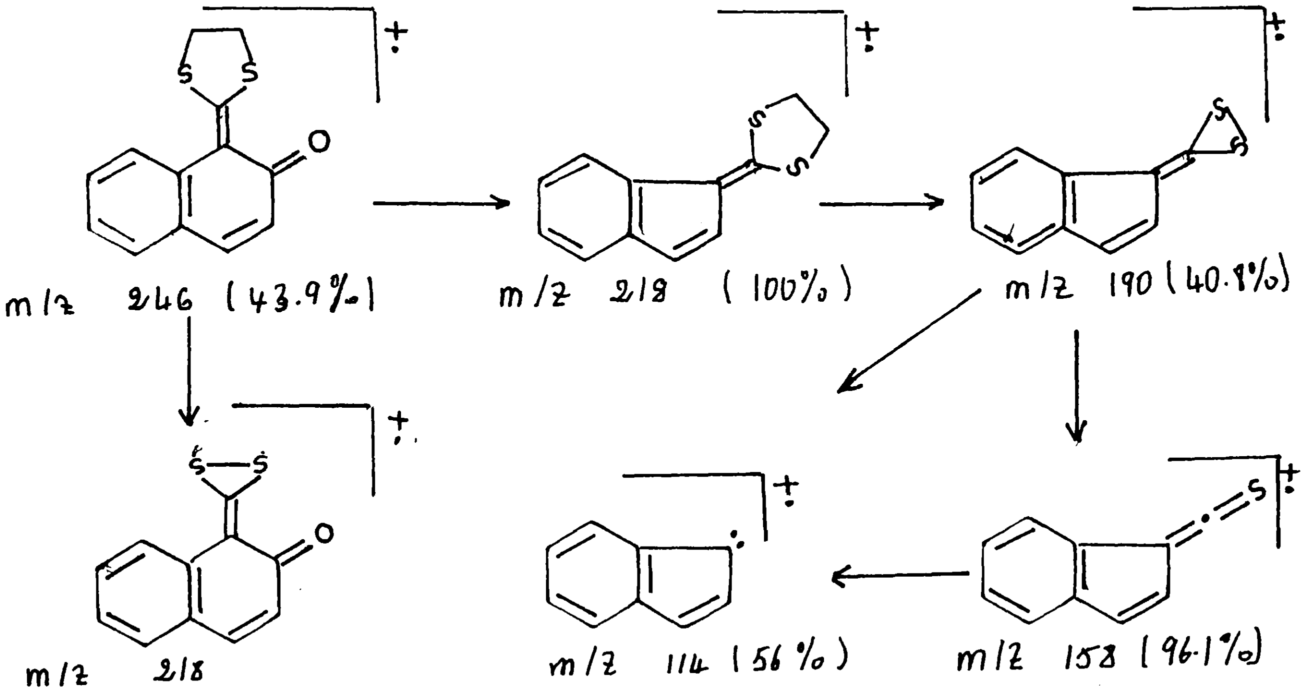


Fig. 2



As it is shown in the diagram, almost all of the fragmentation patterns generated from both compounds (2) and (3) are identical and are dominated by ions of m/z 158 (100%) formed via ion m/z 218 by successive loss of ethylene and (CO + S). An ion of m/z 218 does exist in both spectra and is the source of further fragments. That of m/z 190 is due to a loss of CO from quinonoid ring, but in the spectrum of the ortho isomer this fragment is generated to the extent of 2.8% only of the 158 peak. Loss of sulfur from the dithiirane ring gives the ion of m/z 186. Further loss of sulfur and CO from the quinonoid system leads to the ion of m/z 158 as the major ion in both spectra. Almost all kinds of ions are produced in the same percentages from both isomers.

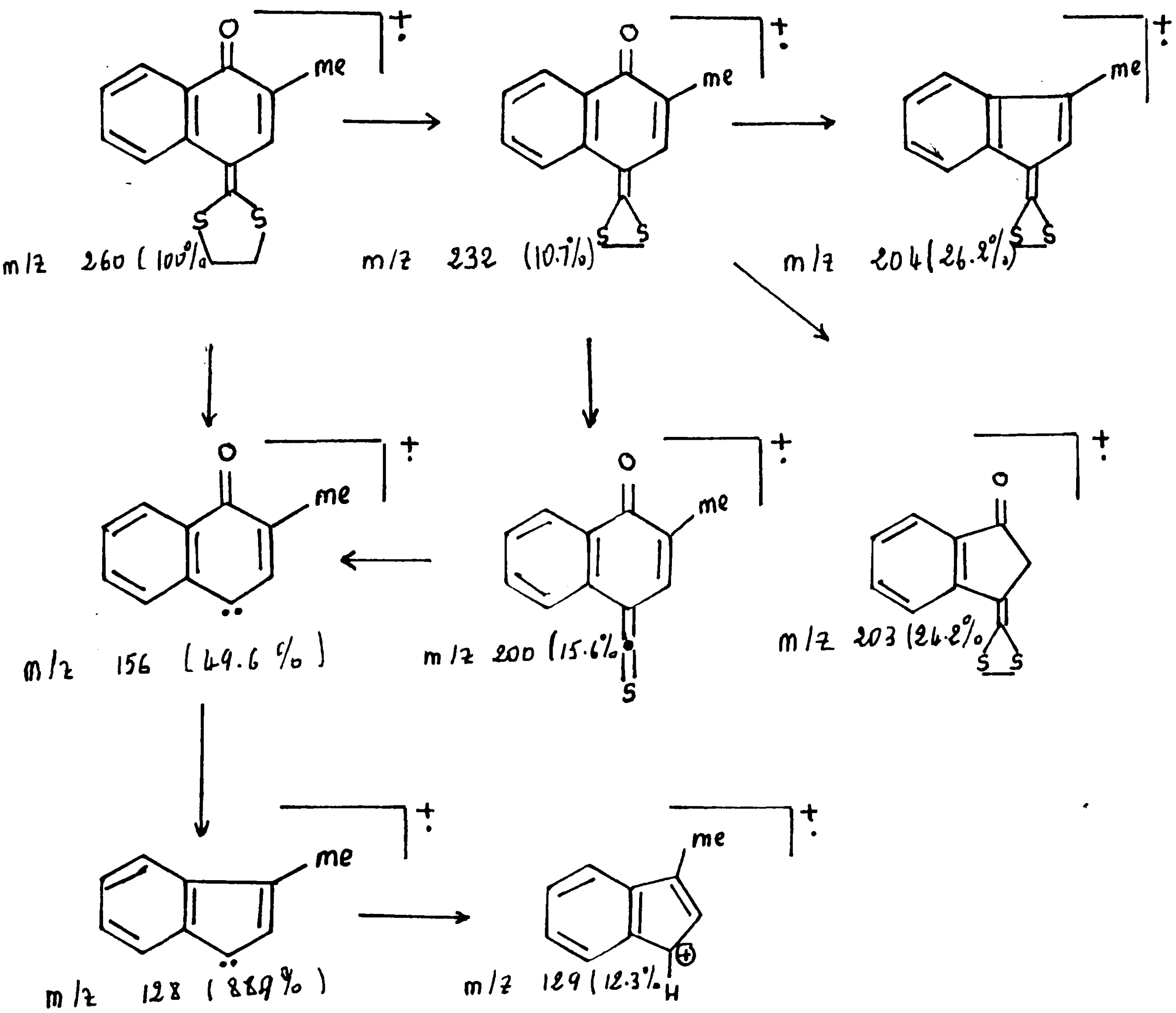
Fragementation pattern of the naphthoquinone methide from 2-naphthol (was prepared by Gompper's procedure).



The parent ion is a major ion. It loses either CO or CH_2-CH_2 giving the base peak at 218 and then the other fragment of mass 28 to give 190 then 158 and 114.

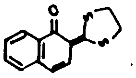
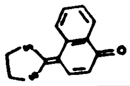
Fragmentation patterns of the 2-methyl-naphthoquinone methide

Fig 3

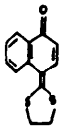
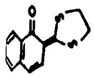
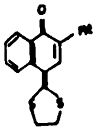
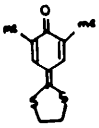


The spectrum shown above is dominated by the parent ion m/z 260, which by a loss of ethylene gives the ion of m/z 232. The latter loses a sulfur atom to give the ion of m/z 200. Loss of all the atoms of the dithiolan ring from the parent ion gives a major ion of m/z 156 and further loss of CO the major ion m/z 128.

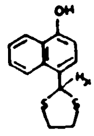
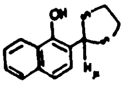
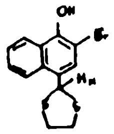
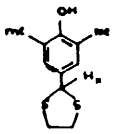
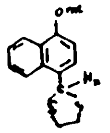
Comparison of ^{1}Hnmr chemical shifts and coupling constants of para - and ortho naphthoquinone methides.

		^{1}Hnmr	in $CHDCl_3$ as solvent	
	Chemical Shift	J.Hz.	Chemical Shift	J.Hz.
H2			6.44	$J_{e,3}$:10.1 J
H3	7.16	$J_{3,8}$.0.75 $J_{3,4}$ 9.50 $J_{3,7}$ 0.30 $J_{3,5}$ Tiny.	7.94	$J_{3,2}$ 10.1
H4	6.69	$J_{4,3}$ 9.50 $J_{4,8}$ 0.75 $J_{4,5}$ 0.35		
H5	7.45	$J_{5,4}$ 0.35 $J_{5,6}$ 8.10 $J_{5,7}$ 1.60 $J_{5,8}$ 1.00	8.34	$J_{5,6}$ 8.20 $J_{5,7}$ 1.10 $J_{5,8}$ 0.60
H6	7.56	$J_{6,5}$ 8.10 $J_{6,7}$ 6.60 $J_{6,8}$ 1.60	7.65	$J_{6,5}$ 8.20 $J_{6,7}$ 7.10 $J_{6,8}$ 1.60
H7	7.43	$J_{7,8}$ 7.50 $J_{7,6}$ 6.60 $J_{7,5}$ 1.60 $J_{7,3}$ 0.30	7.44	$J_{7,8}$ 7.60 $J_{7,6}$ 7.10 $J_{7,5}$ 1.10
H8	8.39	$J_{8,7}$ 7.50 $J_{8,6}$ 1.60 $J_{8,5}$ 1.00 $J_{8,3}$ 0.75	8.41	$J_{8,7}$ 7.60 $J_{8,6}$ 1.60 $J_{8,5}$ 0.60
CH_2CH_2	3.58		3.40	

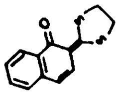
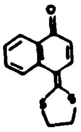
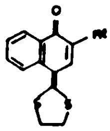
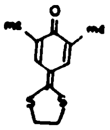
Solvent Effect on the ^{1}Hnmr of the quinone methides (90 MHz)

Compound	^{1}Hnmr (δ)	
	$CDCl_3$ as solvent	CF_3CO_2H as solvent
	8.3-8.5 (2H, dd, H5 H8	8.3-8.35 (1H, bd, H5) 8.35-8.45 (1H, bd, H8)
	7.9 (1H, d, H3)	8.5 (1H, d, H3)
	7.35-7.6 (1Ar-H, 2H,H6H7)	7.4-7.65 (12H, m, H6,H7)
	6.45 (1H, d, H2)	7.0 (1H, d, H2)
	3.4 (4H, S, CH_2-CH_2)	4.1 (14H, S, CH_2-CH_2)
	8.40 (1H, bd, H8)	9.0 (1H, bd, H8)
	7.3-7.4 (3Ar-H,m,H5,H6,H7)	7.76-8.2 (3 ArH,m, H5,H6,H7)
	7.15 (1H, d, H3)	7.75 (1H, d, H_3)
	6.70 (1H, d, H4)	7.30 (1H, d, H_4)
	3.58 (4H, SS, CH_2CH_2)	4.18(4H, S, CH_2-CH_2)
	8.3-8.4 (2H, d, H8, H5)	8.8-9.0 (1H, bd, H8) 8.5-8.7 (1H, bd, H5)
	7.75 (1H, S, H3)	8.35 (1H, S, H3)
	7.35-7.55 (2Ar-H,m,H5,H4)	7.85-4.45 (2H, bm, H6, H7)
	3.55 (4H, S, CH_2CH_2)	4.25 (4H, S, CH_2-CH_2)
	2.12 (3H, S, CH_3)	2.55 (3H, bs, CH_3)
	7.25 (2H, S, H3, H5)	7.82 (2H, S, H3, H5)
	3.60 (4H, S, CH_2CH_2)	4.15 (4H, m, CH_2-CH_2)
	2.25 (6H, S, 2 Ma)	2.85 (6H, S, 2 Me)

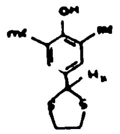
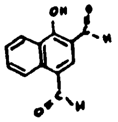
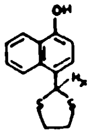
^{1}Hnmr chemical shifts of the phenols obtained in chloroform as solvent

Compound	Chemical Shift in $CDCl_3$
	8.2 (2H, m, H8, H5); 7.87 (1H, Sd, H3) 7.70 (1H,d,H2); 7.30 (2Ar-H, bm, H6, H7) 6.78 (1H, S, Hx); 6.40 (1H, lump, OH) 3.50 (4H, S,-CH_2-CH_2)
	8.3 (1H, m, H8); 7.75 (1H, m, H5); 7.4 (1H, d, H4); 7.35-7.45 (3H, m, 1.15, H6, H7), 3.35 (1H, d, Hz) 5.9 (1H, S, OH), 7.5 (4H, bm, (.CH_2-CH_2-)
	8.10-8.20 (2H, m, H5, H8); 8.00 (1H, S, H3), 7.40-7.60 (2H, m, H6, H7); 6.30 (1H, S, Hx) 6.00 (1H, lump, OH); 3.50 (4H, bs, CH_2CH_2)
	7.10 (2H, SS, H3, H5); 4.60-4.70 (H, lump, OH) 2.20 (6 H, S, 2CH_3); 3.15-3.65 (4H, dm, CH_2-CH_2); 5.55 (1H, S, Hx)
	8.2-8.25 (1H, m, H8); 8.0-8.15 (1H, m, H8); 7.90 (1H, d (J 10.Hz), H3); 7.40-7.60 (2H, m, H6, H7); 6.70 (1H, d (J 10Hz), H2) 3.50 (4H, bs, CH_2-CH_2); 5.57 (1H, S, Hx).

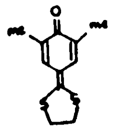
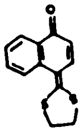
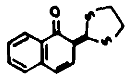
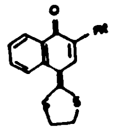
^{13}C nmr chemical shifts of the quinonemethides (2,3,21 and 24) in CDCl$_3$

Compound	C = O	$\underline{C} = C\langle^{S}_{S}$	$= \underline{C}\langle^{S}_{S}$	CH_2	$\dot{C}H$	$=\dot{C}-$	Me
	184.17	119.3	161.9	40.5 35.35	122.04 125.82 126.26 126.67 131.17 140.97	130.34 134.37	
	179.17	121.70	173.99	39.98 35.93	119.00 125.64 126.53 127.20 127.35 131.96	130.42 137.58	
	184.43	119.91	156.57	35.66 40.58	126.03 126.55 127.26 130.52 138.40	130.98 130.98 134.60	16.48
	186.80	121.4	121.4	38.61	$\ddot{C}$-H 164.44	$\underline{C}$-Me 131.91	16.53

^{13}C nmr data of other phenols

Compound	$\text{Ar-C}^{\text{S}}_{\text{S}}$	$\text{C}^{\text{O}}_{\text{H}}$	C-OH	C-R	C-H	C-Me	C=	Me	HS SH
	56.23		152	133.2	128.1	123.1		15.88	40.1
						C-CHO			
		195.57	166.38		139.65	113.13	134.24		
		191.00			133.40	124.48	124.48		
					127.34				
					125.16				
					124.62				
	52.96		151.46	132.16	107.92		124.62		39.56
					122.43		127.46		
					123.30				
					125.15				
					125.25				
					126.65				

UV data in methanol of the quinonemethides obtained compared with Gompper's data of the orange compound on the xylene analog

Compound	Gompper's Report		This work		Concentration
	λMax	log ε	λmax	log ε	
	258	3.56	258	3.600	
	302	3.60	302	3.720	
	420 sh	4.52	418	4.194	
	432	4.57	430	4.242	
	450	4.42	452	4.076	
			316	3.73	
			328	3.74	
			425	3.82	
			290	4.197	
	310	4.19	310	4.11	
	322	4.20	322	4.126	
	434	4.11	436	4.044	
	457	4.23	456	4.154	
	482	4.08	482	4.008	
			300	3.43	
			314 sh	3.30	
			330 sh	3.00	
			424	3.89	

EXPERIMENTAL SECTION

Treatment of 1-napthol with carbon disulphide in alkaline solution

A solution of 1-naphthol (14.4g, 0.1mol) in dimethylsulfoxide (60ml) was placed in three necked round bottomed flask equipped with a small separating funnel, a magnetic stirrer and a stopper.

The solution was treated with potassium hydroxide (11.2g, 0.2mol) as a saturated solution in water and carbon disulphide (6ml, 0.1mol) by the following procedure. Half the KoH solution was added, then, over 30 min, half of the carbon disulphide at 15°C, then half of the remaining potassium hydroxide solution followed over 30 min by half the remaining carbon disulphide, then the remaining potassium hydroxide and finally the remaining carbon disulphide.

After the addition was finished the mixture was allowed to stir at 10-15°C for a further 2.5h. The red solution was cooled down to 0°C, and treated dropwise with ethylene bromide (17.7g, 0.104 mol) and left to stir again at room temperature overnight. The resultant viscous red solution was diluted with water (250 ml) and extracted thoroughly with ether (3 x 100 ml). The combined ether layers were dried over magnesium sulfate over 30 min, filtered and evaporated to give a red gum. Tlc (25% ethyl acetate/pet. ether) showed two main spots showing in the daylight, Rf 0.20 orange, Rf 0.25 yellow along with the starting material. ^{1}Hnmr ($CDCl_3$) of the mixture showed mainly the orange quinone methide and very little of the yellow one.

Crystallisation from ethanol gave orange crystals melting at 127°C (lit. 177°); (found C, 63.28%, H, 4.09, S, 26.03% $C_{13}H_{11}OS_2$ requires C, 63.41%, H, 4.06%, S, 26.02. ^{1}Hnmr, ^{13}Cnmr, UV data are summarised in tables (section 2).

Separation of reaction mixture by chromatography

2g of the mixture obtained above were chromatographed on a preparative silica gel column with chloroform as the eluent. 1-Naphthol was eluted first (90 mg) followed by the orange compound (65 mg) and a new yellow compound (15 mg).

Raney nickel reduction of the orange quinone methide

i. Preparation of the catalyst

Nickel aluminium alloy (30 mg) was added slowly during 30 min to an aqueous solution of sodium hydroxide in water (4g in 15ml) at 78°C, then cooled down to room temperature, and washed thoroughly with water until pH7.

ii. Fairly pure orange quinone methide (100 mg) was dissolved in 5ml of ethanol and then was poured onto the catalyst and heated up to reflux for a further 15 min. The nickel was filtered off and rinsed with ethanol before disposal in the sink. The solvent was evaporated off to give 45mg of a dirty white solid. Tlc (30% EtOAc/Pet ether) showed mainly one spot Rf 0.7 and other components as a streak. ^{1}Hnmr ($CDCl_3$) was not very affirmative but suggested that the compound has been over reduced. The same reaction has been undertaken in THF as solvent and found to give the same compound.

Attempted reduction of the orange quinone methide with sodium borohydride

To a solution of orange quinone methide (100 mg) in dry tetrahydrofuran (5ml) placed in a test tube, sodium borohydride was added a little at a time. After 1 h time and even after 48h standing at room temperature no changes happened to the solution. Tlc (ethyl acetate/ pet. ether showed this to be only starting material which was recovered by evaporating the solvent off.

Reduction of the orange quinone methide with lithium aluminium hydride to phenol (6)

A solution of orange quinone methide (100mg) in dry tetrahydrofuran (5ml) placed in a test tube, was treated with lithium aluminium hydride until the orange colour of the solution became pale green. Tlc showed no starting material was left. Lithium aluminium hydride was then filtered off and treated with ethanol before disposal. The tetrahydrofuran solution was evaporated to give about 98mg of a new phenol (6) whose structure was identified by ^{1}Hnmr ($CDCl_3$)[a new singlet at δ 5.90 ppm (1H)] as white crystals from a mixture of ethyl acetate and petroleum ether, melting at (88-89°C) (Found C, 62.71%; H, 4.77%; S, 25.71% $C_{13}H_{12}S_2O$ requires C, 62.90%; H, 4.84%; S, 25.80%). ^{1}Hnmr, ^{13}Cnmr, IR data gave further evidence. They are summarised in Tables (section 2).

Treatment of the Phenol (6) with Raney nickel

Freshly prepared phenol (6) (98mg, 3.9×10^{-4} mol) was dissolved in ethanol (5ml) and pour onto a fresh batch of nickel (50 mg) prepared as above. The whole mixture was stirred to reflux at 80°C for a further 10 min. Tlc plate showed no starting material was left. The nickel was filtered off and washed with more ethanol before disposal in the sink. The ethanol was evaporated off to give about (60 mg, 3.8×10^{-4} mol) of 2-methyl-1-naphthol (5) which was proved by ^{1}Hnmr in chloroform (new singlet at δ 2.1, 3H, Me).

Preparation of 2-piperidinomethyl-1-naphthol

A solution of 1-naphthol (10g, 0.068 mol) in 75% ethanol (50 ml) was cooled to 0°C. This solution was slowly added to a stirred solution of piperidine (8ml) and 38% formaldehyde (5ml). The whole mixture was left to stir for 45 min at 0°C. The product precipitated out when water was added slowly to the stirred solution and was filtered off, washed with more water and recrystallised from acetone to give the amine 15g, 0.06 mol. mp. 137°C.

Attempted hydrogenolysis of 2-piperidine methyl-1-naphthol(7)

Freshly prepared piperidine methylnaphthol (7) (500mg, 2.2×10^{-3} mol) was dissolved in 75% ethanol (50ml), and 10% palladium charcoal (120mg) was added. After 24 hours no volume of hydrogen had been taken up. Glacial acetic acid (2 drops) was added to the solution; after a further 20h no volume of hydrogen had been taken up. The starting material was collected back by filtering the catalyst off and evaporating the solvent.

Reduction of 1-hydroxy-2-naphthoic acid[100]

Ethyl chloroformate (12g, 0.11 mol) was added at o-5°C over a period of 1h to a solution of 1-hydroxy-2-naphthoic acid (10.34g, 0.06 mol) and triethyl amine (11.1g, 0.11 mol) in tetrahydrofuran (75ml). And the whole stirred for a further 45 min at the same temperature, when a white solid had precipitated (triethylammonium chloride). This was filtered off and washed with 30ml of tetrahydrofuran.

The combined filtrate was added to a solution of sodium borohydride (9.0g, 0.2mol) with stirring at 10°C over a period of 1h. When the addition was finished, the reaction mixture was stirred at room temperature for a further 2h, then made acidic with dilute hydrochloric acid, diluted with water (200ml) and extracted with ether. The combined ether layer was extracted with 10% aqueous sodium hydroxide (50 ml) and the sodium hydroxide layer was neutralised with dilute hydrogen chloride and re-extracted with ether (3 x 5 ml). The combined ether layer was washed with water and 5% aqueous sodium bicarbonate to give about (6·5g., 55 %)of a brownish oil. Tlc indicated one spot. Crystallisation from ethyl acetate afforded white plates melting at (64.66°C) the structure was identified by ^{1}Hnmr in deuterated chloroform which showed the disappearance of the acidic proton at δ 11.65 and the appearance of a new singlet at δ 2.1 ppm.

1. Methoxynaphthalene (14)

In a 500 ml round bottomed flask equipped with a magnetic stirrer, were placed 1-naphthol (50g, 0.34 mol) dissolved in a freshly made solution of sodium hydroxide (11.5g, 0.41 mol) in water (200 ml) and cooled down to 0-5°C. Dimethyl sulfate (40 ml) was added dropwise over 1h with vigorous stirring. When the addition was finished the mixture was warmed up to 80°C over a further 1h, then cooled down again to room temperature and extracted thoroughly with ether. The combined ether layer was dried over magnesium sulfate over 45 min, filtered and concentrated to give a red oil. Tlc plate (10% ethyl acetate/pet. ether) showed mainly two spots due to 1-naphthol Rf 0.5 and methoxynaphthalene.

A portion of the previously obtained red oil was transferred into a 25 ml round bottomed flask and distilled in a Buchi GKR50 under reduced pressure to give very clean 1-methoxy naphthalene. Tlc (5% EtOAc/Pet. ether) indicated only one spot Rf 0.6 and the ^{1}Hnmr in $CDCl_3$ confirmed the structure to be 1-methoxynaphthalene (simglet, 3H, 4.1) and δ 10.1 (1H, S, CHO).

Preparation of N-methylformanilide(107)

A mixed solution of N-methylaniline (107g, 1mol), formic acid (100g, (90%), 2.2 mol) and 0.61 of toluene was placed in a 1l. round bottomed flask fitted with 3ft indented column to which a water condensor was attached. The solution was distilled slowly over 4h. Water came over first followed by toluene (about 0.45 l) at 108-110°C and the residue left behind was transferred into a suitable flask and distilled again under reduced pressure. The portions boiling at 113-121°C/8mm Hg were collected together by dissolving in ether and evaporated to give an oil freezing point 13.8 - 13.9°C(lit. 13.6 - 13.7)The structure has been confirmed by ^{1}Hnmr.

Formylation of 1-methoxynaphthalene by the use of N-methylfomanilide and phosphorus oxychloride(108)

In a round bottomed flask equipped with a stirring bar was placed a mixture of N-methylformanilide (4.3 g, 3.1 x10^{-2}mol). This was left to stir gently at room temperature for 30 min. 1-methoxynaphthalene (4.68g, 0.03 mol) was added dropwise then was allowed to warm up on a steam beath for a further 4h.

The mixture was poured onto ice and extracted with ether (3 x 100ml). The ether layer was washed with 2M sodium hydroxide solution, dried over magnesium sulfate, filtered and evaporated to give a dirty looking oil. Tlc (10% EtOAc /pet. etehr) showed a streak of spots. ^{1}Hnmr ($CDCl_3$) was complicated.

Distillation on the Kugelrhor under vacuum gave 1-methoxynaphthalene (14) followed by some reasonably pure 4-methoxy-1-naphthaldehyde (13) as an oil(lit mp 230°C) ^{1}Hnmr showed the presence of the aldehyde proton as singlet at δ 10.1.

Conversion of 4-methoxy-1-naphthaldehyde (13) to its dithioacetal (11)

4-methoxy-1-naphthaldehyde (13) was converted to its dithioacetal (11) in such a good yield following the same procedure used for 4-formyl-1-naphthol (see later on).

Formylation of 1-naphthol by the use of triethylorthoformate

To a vigorously stirred solution of 1-naphthol (1.44g, 0.01 mol) in 20 ml of dry benzene and 10ml of triethyl orthoformate, ground aluminium chloride ($AlCl_3$) (2g) was added. The temperature rose up to 40°C after 10 min. The mixture was cooled down to 10°C then 50% aqueous HCl was added dropwise. The reaction mixture was transferred after the addition of HCl was finished to a separating funnel and extracted thoroughly with ether, dried over magnesium sulfate over 30 min, and the solvent was evaporated off to give about (1.5g) of a mixture. Tlc plate and ^{1}Hnmr showed mainly starting material and very little of the desired compound was present.

Formylation of 1-naphthol with hexamethylenetetramine

A mixture of 1-naphthol (1.4g, 0.01 mol) and hexamethylenetetramine (1.4g, 0.01 mol) was dissolved in trifluoroacetic acid (5ml) and placed in a round bottomed flask equipped with a water condenser. The mixture was heated up at reflux (80-90°C) for a further 12h when a brownish solution resulted. The bulk of the trifluoroacetic acid was distilled off at 93°C and the brown gum left was mixed with 60g of iced water and the cooled mixture allowed to stir for a further 20 min and made basic to pH 10 with an aqueous solution of sodium hydroxide. It was then extracted thoroughly with ether (3 x 100 ml). The combined ether layer was dried over magnesium sulfate over 45 min and filtered. Tlc plate of the ether layer showed several spots Rf 0.25 Rf 0.35 Rf 0.6 along with starting material Rf 0.85. On standing at room temperature overnight an orange solid had precipitated out of solution it was filtered and recrystallisation from a mixture of ethyl acetate and petroleum ether to give about 0.85 g of orange crystals melting at 228-229°C (found C, 73.48%; H, 5.06%; N, 6.39%) $C_{13}H_{11}NO_2$ requires C, 73.24%; H, 5.16%; N, 6.37%. ^{1}Hnmr, ^{13}Cnmr data are summarised in tables (section 2).

The sodium carbonate layer was acidified with 5M hydrochloric acid and a dirty looking solid precipitated. It was extracted thoroughly with ethyl acetate, dried over magnesium sulfate over 30 min and then the solvent was filtered off to afford about 0.350g of a pale yellow solid. Tlc plate indicated two main spots; several recrystallisations from ethyl acetate/petroleum ether gave a new aldehyde as a pale yellow compound melting at 150-151°C (found C, 71.80%; H, 4.03%) $C_{12}H_8O_3$ requires C, 72.00%; H, 4.0%. ^{1}Hnmr, ^{13}Cnmr data are summarised in tables (section 2).

Formylation of 1-naphthol with zinc cyanide and dry HCl

A mixture of 1-naphthol (4g, 2.7×10^{-2} mol) and zinc cyanide (4.7g, 0.04 mol) was dissolved in dry ether (50ml) in a three necked round bottomed flask surmounted with a water condenser. A stream of hydrogen chloride (gas) was bubbled into the ether suspension with vigorous stirring. The mixture warmed up by itself to reflux. Zinc cyanide disappeared and a gummy solid gradually went yellow and crystalised over 1½h. Hydrogen chloride was stopped and the mixture was left stirring for a further 1½h. The ether was decanted and the yellow solid was dissolved in a mixture of (70% water and 30% ethanol (80 mls)) and left to stir overnight at room temperature to give pure 4-formyl-1-naphthol in a 60% yield (72% is reported). The structure was confirmed by ^{1}Hnmr (a new singlet at δ 10.0 and the AB system referring to H2, H3 at δ 7.00 and 7.90).

Conversion of 4-formyl-1-naphthol (12) into its dithioacetal(10)

A solution of ethane dithiol (1ml) in dry chloroform (10ml) and a solution of boron trifluoride etherate (1 ml) in dry chloroform (10ml) were prepared first.

Fairly pure 4-formyl-1-naphthol (12) (150mg) prepared above was suspended in a mixture of chloroform and (5ml) and methylene chloride (5ml) and placed in a 25ml round bottomed flask.

1.3ml of the thiol solution (contains 140mg of ethane dithiol) was added at once followed by the addition of boron trifluoride etherate solution (0.3ml) (contains about 0.03 ml of BF_3OEt_2). The whole mixture was swirled and left standing at room temperature for 14h. Tlc plate showed mainly one spot less polar than starting material which washed out with 5M sodium carbonate solution (5ml). The organic layer was separated, dried and evaporated to give about 180 mg (85%) of a new compound as pink crystals from light petroleum ether (60-80°C) mp 138-140°C. (Found 62.71%; H, 4.77% S, 25.71%) $C_{13}H_{12}S_2O$ requires C, 62.90%, H, 4.84%; S, 25.80%. ^{1}Hnmr in chloroform showed a new singlet at δ 6.78ppm. ^{1}Hnmr ^{13}Cnmr and it gave more evidence. See table (section 2).

Formylation of 2,6-dimethylphenol by the use of hexamine (HMT) in trifluoro acetic acid

2,6-Xylenol (7.0g, 50 mmol) was dissolved in trifluoroacetic acid (70ml). Hexamine (6.20g; 50.0 mmol) was added. The whole mixture was heated up to reflux at 80°C for 12h. The acid was distilled off and the remaining red dark viscous mixture was poured into iced water (500ml), then left to stir for 20 min. The pH of the mixture was brought up to 9.0 by adding a solution of sodium carbonate and extracted with diethyl ether three times, separated, dried over magnesium sulfate over 30 min, filtered to give the aldehyde (7.20g, 70.7%). Recrystallisation from chloroform/pet. ether gave material of mp 109-110°C. Its structure was confirmed by ^{1}Hnmr in chloroform (singlet at δ 10.70ppm, aldehyde protons).

Conversion of 4-formyl-2,6-dimethyl phenol into its dithioacetal (20)

Two solutions of ethane dithiol and boron trifluoride etherate were made as above.

Fairly pure 2,6-dimethyl-4-formylphenol (150mg, 0.001 mol) was suspended in a mixture of chloroform (5ml) and methylene chloride (5ml) and placed in 25ml round bottomed flask. 1.30 ml of the ethane dithiol solution in dry chloroform containing about (140mg) of $HS(CH_2)_2SH$ was added. Also about 0.30ml of the boron trifluoride etherate solution in dry chloroform containing about 0.03ml of BF_3OEt_2 was added as well.

The whole mixture was swirled around and left standing at room temperature for a further 12h. Tlc plate showed only one spot less polar than the starting material. The mixture was then washed with a 2M sodium carbonate solution (5ml). The chloroform layer was separated, dried and evaporated to give 160mg of a new phenol. Crystallisation from petroleum ether (60-80%) gave pale pink plates melting at 68-69°C.

Oxidation of the phenol (20) by DDQ

The dithiolanyl xylenol obtained above (0.035g 1.6×10^{-4} mol) was dissolved in chloroform (2ml) and mixed with a solution of 2,3-dichloro-5,6-dicyano benzoquinone (DDQ)(6.45 mg) in chloroform(2ml), when the colour became brown.

Tlc (50% EtOAc/Pet ether) showed one spot Rf 0.42 along with another spot which is due to the remaining starting material Rf 0.90. After 1h time tlc plate showed no starting material remained.

The mixture was then filtered off and then concentrated to give (0.30g, 84%) fairly pure quinone methide whose structure was completely identified by ^{1}Hnmr in chloroform, ^{13}Cnmr, mass spectra; uv.All of these data are summarised in tables (see section 2).

Attempted oxidation of the phenol (10) with DDQ

Fairly pure phenol (10) (0.25g, 0.001 mol) was dissolved in methylene chloride (2.5ml) and placed in a 25ml round bottomed flask.

Freshly crystallised 2,3-dicyano-5,6-dichloro benzoquinone (0.23g, 0.001mol) was dissolved in methylene chloride (2.0ml) and then added dropwise by the aid of a pasteur pipette to the previous solution at room temperature.

The colour changed by adding more and more of the DDQ solution until it became a dark red solution. The reaction was being monitored by tlc plates. At the beginning tlc showed two spots Rf 0.25, Rf 0.35, along with the starting material Rf 0.9. It was allowed to reflux at 50°C for a further 2h where the colour became more yellow; the tlc plate was still showing the same spots as before but no starting material was left. The solution was filtered and evaporated to give a red coloured solid. ^{1}Hnmr was very complex.

N.B. The above reaction was undertaken in chloroform and in deuterated acetone in an nmr tube and no quinone methide was observed.

Attempted oxidation of the phenol (10) with PDC CH_2-Cl_2

Phenol (10) (45mg) was dissolved in methylene chloride (1ml) and placed in 25ml round bottomed flask. A solution of pyridinium dichromate (PDC) (115mg) in dichloromethane was added slowly by the aid of a pasteur pipette, and then the mixture was allowed to stir vigorously at room temperature for 24h., Tlc (50% EtOAc/Pet. ether) against starting material showed two major spots Rf. 0.40 yellow, Rf 0.85, the same as starting material but it behaves differently from it when it is sprayed with Ce^{iv} spray.

The last traces of chrome were filtered off through a flash chromatography column. And then the solvent distilled off to give a red yellowish solid. ^{1}Hnmr ($CDCl_3$) was not affirmative.

N.B. The same observations were made when the above reaction was undertaken in dimethyl formamide (DMF) as solvent.

Attempted oxidation of phenols (6) and (10) by the use of DMSO "activated" by oxalyl chloride

i. A solution of oxalyl chloride (1ml) in methylene chloride (10ml) and a solution of dimethylsulfoxide (1.7mls) in methylene chloride (10ml), as well as, a solution of the phenol (90mg) in methylene chloride (3.0ml) was made first.

ii. 1.0ml of the oxalyl chloride solution was placed in a 50ml three necked round bottomed flask equipped with a thermometer, drying tube (silica gel) and serum cap through which the two other solutions were injected by the aid of syringes and needles. The solution was cooled down to -60°C.

Dimethylsulfoxide solution (1ml) was injected slowly into the stirred oxalyl chloride solution. The mixture was allowed to stir for a further 2 min at -50°C and then the phenol solution was added dropwise during 5 min with continuing stirring. When the addition was finished the mixture was allowed to warm up to room temperature.

Water about (50ml) was added and then layers were separated and the aqueous layer was re-extracted with more dichloromethane. The combined dichloromethane layer was dried over magnesium sulfate over 30 min and then filtered, concentrated to give a red oil. Tlc (20% EtOAc/Pet. ether) showed a streak containing two major spots Rf 0.25 and 0.40. No starting material was left. ^{1}Hnmr ($CDCl_3$) of the reaction mixture was not affirmative for presence of quinone methide.

Attempted oxidation of the phenols (6,10) with triphenylmethyl tetrafluoroborate

Phenol (10) (100g, 4×10^{-4} mol) in methylene chloride (7ml) was placed in 25ml round bottomed flask. Triphenylmethyl tetrafluoroborate (2ml) was added and the mixture was allowed to stir at room temperature, and the reaction was monitored by tlc plate. After 16h tlc against starting material and an authentic sample of the orange quinone methide showed no sign of the desired compound.

Attempted oxidation of the phenol (10) with oxygen and base

Phenol (10) (100mg, 4×10^{-4}) was dissolved in benzene (10ml) and placed in a 25ml round bottomed flask and oxygen was bubbled into it with continuing stirring. After 20h tlc plate showed only starting material.

Potassium tertiary butoxide (0.09g, 4×10^{-4} mol) was added and the oxygen was bubbled into solution again for a further 12h. Tlc still showing only starting material which was recovered almost without loss.

Bromination of 1-hydroxy-4-naphthaldehdye[109]

A solution of the pure aldehyde(1.5g, 0.009mol) prepared by Gattermann reaction in glacial acetic acid (60ml) placed in a three necked round bottomed flask surmounted with a separating funnel, drying tube and a stopper, was cooled in an ice bath. A solution of bromine (0.5ml, mol) in glacial acetic acid (20ml) was placed in the separating funnel and then allowed to drop slowly onto the stirred aldehyde solution over 40min. The brominated aldehyde (22) precipitated out of solution as colourless crystals and was left standing at room temperature overnight.

The acetic acid was filtered off and the solid was washed thoroughly with water and dried to give 2.0g 95% of fairly pure brominated aldehyde, mp 142-144°C (lit. 144-145°C). ^{1}Hnmr showed the disappearance of the doublet, of the up-field proton H2 at δ 6.70ppm and the changes of the doublet referring to H3 into a singlet at 6.30ppm.

Conversion of 1-hydroxy 2-bromo-4-naphthaldehyde into its dithioacetal (23)

Two solutions were prepared first.

a. ethane dithiol (1ml) in dichloromethane (10ml)

b. boron trifluoroetherate (1ml) in dichloromethane (10ml).

Bromoaldehyde (0.5g, 2.2 x 10^{-3} mol) was dissolved in chloroform (70ml) and then transferred into a round bottomed flask by the aid of pasteur pipette.

1.0ml of the ethane dithiol solution was added as well as 4ml of the boron trifluoride etherate and then the whole mixture was allowed to stir gently for 12h at room temperature.

Tlc showed no starting material remained and the reaction mixture was then extracted with a solution of 5M sodium carbonate. The organic layer was separated, dried over magnesium sulfate and evaporated to give the thioacetal (23) in about 90% yield. Crystallisation from petroleum ether (60-80°C) yielded orange crystals melting at 120-121.5°C. (Found C, 47.80%; H, 3.11%; S, 19.63%; Br, 24.85%) $C_{13}H_{10}S_2Br_1$ requires C, 47.85%; H, 3.07%; S, 19.63%) Br, 24.54%). ^{1}Hnmr, ^{13}Cnmr data are summarised in tables (see section 2).

Attempted oxidation of the dithioacetal (23) with DDQ

Oxidation of the dithioacetal (23) with 2,3-dichloro - 5,6-dicyano -benzoquinone typically as mentioned above was met with failure as well.

Synthesis of the 2-methyl-para naphthoquinonemethide (24)

Treatment of freshly prepared 2-methyl-1-naphthol with carbon disulphide and dibromo ethane in alkaline solution typically as reported by Gompper resulted in a red oil. Tlc (20% EtOAc/pet ether) showed Rf 0.25, yellow, and starting material. Crystallisation from ethyl acetate/pet. ether yielded yellow crystals of the quinone-methide melting pt. 139-140°C. (Found C, 63.32%, H, 4.41%; $C_{14}H_{2}OS_2$ requires (C, 64.6%; H, 4.61%; S, 24.62%). ^{1}Hnmr ^{13}Cnmr and uv data are summarised in tables. (see Section 2).

Preparation of 2-chloro-1-naphthol (25)[110]

In a 250ml three necked round bottomed flask equipped with a separating funnel, thermometer and a magnetic stirrer were placed 1 naphthol (20g, 0.139 mol) and an aqueous solution of sodium hydroxide (2N) (80ml). The mixture was cooled down to 0°C, vigorously stirred, and 5% aqueous sodium hypochlorite (200mls, 0.35ml) was dropped over 1.5h. The cooled solution was rapidly transferred into a 1 litre beaker and acidified with concentrated HCl to pH 1. The solid which precipitated was filtered and air dried overnight to give about 60% of crude product which was steam distilled to give white solid mp. 58-60°C in a yield of 50%. Tlc (10% EtOAc/pet ether) showed only one spot more polar (Rf 0.65) than 1-naphthol. ^{1}Hnmr ($CDCl_3$) δ 1.70-1.85, bd, H8; 2.20-2.40, bd, H5; 2.45-2.65, m, H3, H5, H6, H7; 4.0, SS, OH.

Preparation of 2-bromo-1-naphthol[5]

Bromine (7.2g, 0.1mol) was added dropwise at -25 to -35°C to a solution of t-buthylamine (31.8g, 0.2 mol) and dry toluene (500ml) placed in a 1 liter round bottomed flask equipped with a dropping funnel and a magnetic stirrer. At the same temperature a solution of 1-naphthol (7.2, 0.05 mol) in dichloromethane (3ml) was added over 5 min when the addition was finished the whole mixture was allowed to stir at room temperature for a further 4.5h. The mixture was washed with 500ml of water and separated. The organic layer was extracted with 10% sodium hydroxide and then acidified to give a yellow solid. It was re-extracted with dichloromethane, separated and dried over magnesium sulfate. The solvent was evaporated off and a dark red oil (7.5g) was obtained which became solid on standing at room temperature. Tlc (10% EtOAc/pet ether) against the starting material and an authentic sample of 2-chloro-1-naphthol showed only very little of the starting material and another tiny spot running behind the main spot referring to 2-bromo-1-naphthol Rf 0.5.

The mixture was steam distilled to give about (6.3g, 0.028 mol) in a yield of 56%. (lit 61%) of white crystals which was crystallised from ethyl acetate and petroleum ether. Structure was confirmed by ^{1}Hnmr ($CDCl_3$) showing disappearance of the up-field proton at δ 6.67ppm, and H3 as a singlet at 8.00ppm.

REFERENCES

1. (a) Kast, Ber, 1911, 44, 1337.
   (b) Lesser and Gad, Ber, 1923, 56, 963, 972.
2. Airan and Shah, J. Univ. Bombay., 1942, [2], 10, Part 5A, p. 128.
3. Franzen and Stauble, J. pr. Ch., 1921, 103, [2], 352-383.
4. Rosenmund, Kuhnhenn and Lesch, Ber., 1923, 56, 20, 42.
5. D.E. Pearson, R.D. Wysong and C.V. Breder, J. Org. Chem., 1967, 32, 2358.
6. Hodgson and Smith, J. Chem. Soc., 1935, 671.
7. Wieland, Ber., 1921, 54, 1776.
8. J.M. Tedder and G. Theaker, J. Chem. Soc., 1958, 2573.
9. P. Bevillard and J. Choucroun, Bull. Soc. Chim. France, 1957, 337.
10. (a) Freidlander and Taussig, Ber., 1897, 30, 1456.
    (b) Holdermann, Ber., 1906, 39, 1250.
11. Pollok, Gebauer, Fulnegg, Blumenstock-Halward, Monatsh., 1928, 49, 187.
12. Hardy, J. Chem. Soc., 1929, 1000.
13. Smith and Welch, J. Chem. Soc., 1934, 996.
14. Alberti, Ann., 1926, 450, 304.
15. Zamparo, Chem. Abs., 1925, 3447.
16. Castiglioni, Gazz., 1937, 67, 324.
17. Auwers and Dombrowski, Ann., 1905, 344, 289.
18. J.W. Cornforth, R.H. Cornforth and Sir Robert Robinson, J. Chem. Soc., 1943, 168.
19. Betti and Speroni, Gazz., 1901, 31, 11, 191.
20. Brode, Littman, J. Am. Chem. Soc., 1931, 53, 1531.
21. W. Nagata, K. Okada, T. Sutomu Akoki, Synthesis, 1979, 365.
22. M. Akram and R.D. Desai, Proc. Indian Acad. Sci., 1940, 11A, 149.
23. W.H. Hunter, R.M. Quinton, P.H. Sherman, C.R. Worthing and R.J. Boscott, J. Med. Chem., 1964, 7, 167.
24. Sudzuki, Science Reports Tohoku Imp. Univ., 1933; I22, 176.
25. Scholl and Seer, Ann., 1912, 394, 111, 151.

26. Eller, Ber., 1868, 1, 248.

27. Passerini and Grulis, Gazz., 1926, 56, 829.

28. Pribram and Glucksmann, Monatsh., 1894, 15, 605.

29. M. Komiyama and H. Hirai, J. Am. Chem. Soc., 1984, 106, 174.

30. Y. Sasson and M. Razintsky, J. Chem. Soc.Chem. Commun. 1985, 1134.

31. L. Gattermann and J.A. Koch, Ber., 1897, 30, 1962.
N.N. Crounse, Org. React., 957, 5, 290.

32. L. Gattermann, Ann. 1907, 357, 313; Moryan and Vining, J. Chem. Soc., 1921, 119, 117. W.E. Truce, Org. Reactions, 1957, 9, 37.

33. R. Adams and I. Levine, J. Am. Chem. Soc., 1923, 45, 2375.

34. J.B. Shoesmith and J. Haldane, J. Chem. Soc., 1924, 125, 2405.

35. K. Reimer and F. Tiemann, Ber., 1876, 9, 824; U.S. Patent 1928, 1, 807, 693., H. Wynberg, Chem. Rev., 1960, 60, 169.

36. M. Gomberg and H.R. Snow J. Am. Chem. Soc., 1925, 47, 198.

37. A. Vilsmeier and A. Haack, Chem. Ber., 1927, 60, 119.

38. L.N. Ferguson, Chem. Revs., 1946, 38, 227; N.S. Narasimhan and R.S. Mali, Tetrahedron, 1975, 31, 1005.

39. J.C. Duff and E.J. Bills, J. Chem. Soc., 1932, 1887, 3973; J.C. Duff, Ibid., 1941, 547. W.E. Smith, J. Org. Chem., 1972, 37.

40. H. Gross, A. Rieche and G. Matthey, Chem. Ber. 1960, 93, 88.

41. S. Jo, S. Tanimoto, T. Sugimoto and M. Okano, Bull. Chem. Soc. Japan, 1981, 54, 2120.

42. S. Tanimoto, T. Mikaye and M. Okano, Bull. Inst. Chem. Res., Kayoto Univ., 1977, 55, 276.

43. K. Hathnaka, S. Tanimoto, T. Sugimoto and M. Okano, Tetrahedron Lett., 1981, 22, 3243.

44. C. Westerlund, Tetrahedron Lett., 1982, 23, 4835.

45. T. Hirao, S. Kohno, Y. Ohshiro and T. Agawa, Bull Chem. Soc. Japan, 1983, 56, 1570.

46. R.A.J. Smith and A.R. Binmanas, Synthesis, 1984, 166.

47. P.G. Gassman and D.R. Amick, Tetrahedron Lett., 1974, 38, 3466.

48. P.G. Gassman and H.R. Drewes, J. Am. Chem. Soc., 1974, 96, 3002.

49. P. Grunager in Methoden der Organischen. Chemie (Houben-weyl) Vol. E/3, 1983, p. 350.

50. A. Bistrzycki and C. Herbst, Ber. Deut. Chem. Ges., 1903, 36, 2333.

51. H.U. Wagner and R. Gompper in The Chemistry of Quinonoid Compounds, Vol 2. S. Patai (ed) Wiley, 1974, p 1145.

52. P. Grunager in Methoden der Organischen Chemie (Houben-Weyl) Vol 7/3b 1979, p. 395.

53. K. Fukui, Topics Current Chem., 1970, 15, 1.

54. K. Freudenberg and H.K. Werner, Chem. Ber., 1964, 97, 579.

55. R. Gompper, E. Kutter and R.R. Schmidt, Chem. Ber., 1965, 98, 1374.

56. P.L. Julian and W.J. Gist, J. Amer. Chem. Soc., 1935, 57, 2030.

57. L.K. Dyall and S. Winstein, J. Amer. Chem. Soc., 1972, 94, 2196; L. Jurd, Tetrahedron, 1977, 33, 163.

58. W. H. Starnes and J.J. Lauff, J. Org. Chem., 1970, 35, 1978.

59. M. Wakschmann and M. Vilkas, Compt. Rend., 1964, 258, 1526.

60. D.A. Bolon, J. Org. Chem., 1970, 35, 715, 3666.

61. J. Brugidou and M. Christof, Bull Soc. chem. France., 1966, 2688.

62. T.R. Kastuvi and R. Sivaramakrishnan, Proc. Indian Acad. Sci., 1977, 86A, 399.

63. G.A. Nikiforov, B.D. Svividov, A.A. Volod'kin and V.V. Ershov, Izv. Akad. Nauk S.S.S.R., Ser Khim, 1971, 861.

64. G. Catterall, Chem. Commun., 1974, 41.

65. N.P. Newreiter, J. Org. Chem., 1963, 28, 3486.

66. K.H. Meyer, Annalen, 1920, 420, 135.

67. L.K. Dyall and S. Winstein, J. Amer. Chem. Soc., 1973, 94, 2196.

68. L.C. Anderson and M. Gomberg, J. Amer. Chem. Soc., 1928, 50, 2196.

69. C.D. Cook and Benorcross, J. Amer. Chem. Soc., 1959, 81, 1179.

70. N.P. Neureiter, J. Org. Chem., 1963, 28, 3486.

71. A. Bistrzycki and C. Herbst, Ber., 1903, 36, 2333.

72. M.G. Ettlinger, J. Amer. Chem. Soc., 1954, 76, 2769.

73. S. Hunig, H. Shweeberg and H. Schwartz, Annalen., 1954, 587, 132.

74. K. Hirai, Tetrahedron, 1971, 27, 4003.

75. R. Gompper and R.R. Schmidt, Ber., 1965, 98, 1385;
R. Gompper, R.R. Schmidt and E. Kutter, Annalen, 1965, 684, 37;
U. Berg and J. Sandstrom, Acta, Chem. Scand., 1927, 130, 534.

76. R. Gompper and E. Kutter, Angen. Chem., 1963, 75, 919; Chem. Ber., 1965, 98, 1365.

77. R. Gompper, R.R. Schmidt and E. Kutter, Annalen., 1965, 684, 37.

78. G.A. Reynolds, J. Org. Chem., 1968, 33, 3352.

79. N. Lozac'h and C.T. Pederson, Acta. Chem. Scand., 1970, 24, 3189.

80. P.L. Pausen, G.R. Proctor and R. Watson, J. Chem. Soc. (C), 1971, 2399.

81. J. J. Looker, J. Org. Chem., 1967, 32, 2941.

82. Fr. Pat. 1, 377, 346 (Nov.6, 1964); Chem. Abstr. 1965, 62, 11950.

83. W.R.H. Hurlley and S. Smiles, J. Chem. Soc., 1928, 534.

84. O. Fisher, Ber. Deut. chem. Ges., 1881, 14, 2523.

85. W.H. Starnes, J.A. Myers and J.J. Lauff, J. Org. Chem., 1969, 34, 3409.

86. L.J. Filar and S. Winstein, Tetrahedron Letters, 1960,25, 9.

87. S. Goldschmidt and H. Bernard, Ber. Deut. chem. Ges., 1923, 56, 1963.

88. C.M. Orlando, J. Org. Chem., 1970, 35, 3714.

89. Fr. Pat. 1, 395, 115 (1965); Chem. Abstr., 1965, 63, 1793 g.

90. H.D. Becker, J. Org. Chem., 1965, 30, 982.

91. H.D. Becker, J. Org. Chem., 1969, 34, 1203.

92. H.D. Becker, J. Org. Chem., 1967, 32, 2943.

93. D.L. Coffen and P.E. Garrett, Tetrahedron Letters, 1969, 2043.

94. H.D. Becker, J. Org. Chem., 1969, 34, 1211.

95. H. Junk, H. Hamboeck and B. Hornischer, Monatsh. Chem., 1967, 98, 315.

96. W.W. Sullivan, D. Ullmann and H. Schechter, Tetrahedron Letters, 1969, 457.

97. J. Ficini and A. Krief, Tetrahedron Letters, 1967, 2497.

98. J.L. Chitwood, P.G. Gott, J.J. Krutak, Sr., and J.C. Martin, J. Org. Chem., 1971, 36, 2216.

99. K. Auwers, N. O. Schroter, Ber., 1903, 36, 3236.

100. N. Ninami and S. Kijima, Chem. Pharm. Bull., 1979, 27, 816.

101. Vogel's Textbook of Practical Organic Chemistry, Longman, 1978, p 755.

102. D.L. Coffen and P.E. Garett, Tetrahedron Letters, 1969, 25, 2043.

103. B. Soucek, L. Pavlickova, J. Velek, V. Beranek and M. Soucek, Coll. Czech. Chem. Commun., 1975, 41, 2607.

104. E.J. Corey and G. Schmidt, Tetrahedron Letters, 1979, 5, 399.

105. A.J. Mancuso, S.L. Huning and D. Swern, J. Org. Chem., 1978, 12, 2481.

106. B. Koutek, L. Pavlickova, M. Budesinsky and M. Soucek, Coll. Czech. Chem. Commun., 1982, 47, 59.

107. L.F. Fieser and J.E. Jones, Organic Synthesis, Collective Volume II, p. 590.

108. N.S. Narasimhan and R. Mali, Tetrahedron, 1975, 31, 1005.

109. J.G. Kerkhof, Recueil des travaux chimiques des Pays Bas., 1932, 51, 739.

110. D. Ginsburg, J. Amer. Chem. Soc., 1951, 73, 2723.

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