STUDIES IN 2-NAPHTHOL DERIVATIVES

- presented by -

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I would like here to express my gratitude to

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for his invaluable guidance at all stages of this work, and for his patience and forbearance.

Also, to all those others who, in many and various ways, helped and supported me while I was engaged in this endeavour.

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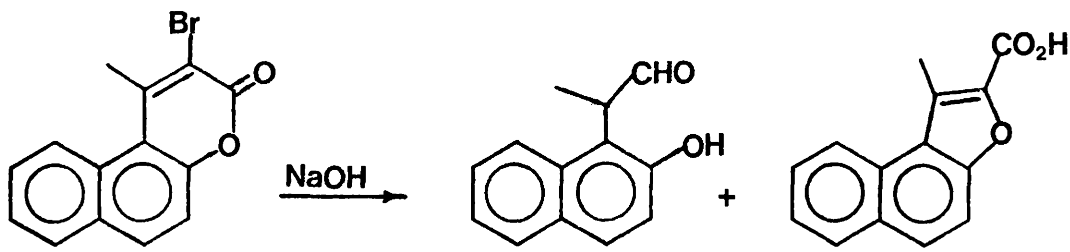
SUMMARY

This thesis consists of two sections.

The first section deals with the sodium hydroxide induced rearrangement of 1-methyl-2-bromo-3H-naphtho(2,1-b) pyran-3-one.

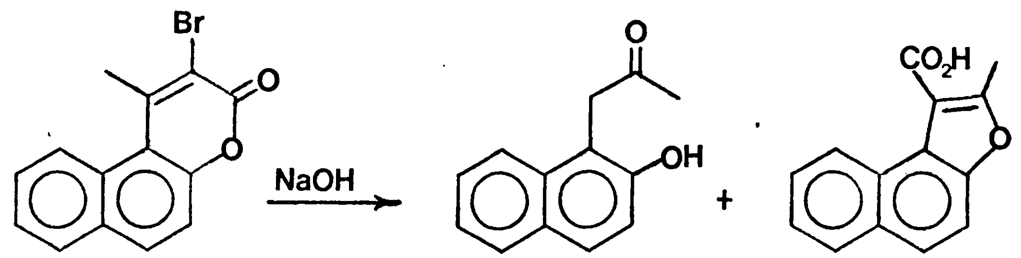
This reaction had already been studied by Dey and Lakshminarayanan (J. Ind. Chem. Soc. 1934, 11, 373), who identified the products as 2-(2-hydroxynaphth-1-yl) propanal and 1-methylnaphtho (2,1-b) furan-2-carboxylic acid:



The naphthylpropanal would be a useful starting material for the synthesis of 1-alkyl-2-naphthols, so we attempted to repeat this rearrangement.

When the Indians' conditions were followed, no clean and tractable products resulted. Air oxidation and dehydration of the initial products seemed to occur. The reaction and work-up were therefore performed under nitrogen and acidification of the reaction mixture was done with carbon dioxide.

Under these conditions, two products were isolated. The main product (78%) is 1-(2-hydroxynaphth-1-yl) propan-2-one. The minor product (7%) is 2-methylnaphtho (2,1-b) furan-1-carboxylic acid:



These structure assignments are supported by elemental analyses, full spectral data and chemical transformations on both products.

A critical review of Dey's published evidence suggests that he had isolated the same products as we did, but assigned an erroneous structure to each as a result of inadequate spectral evidence, uncritical interpretation of chemical evidence and over-reliance on analogies.

Mechanisms for the displacement of halides from sp^2 hybridised carbons, in α-halolactones and in related systems is reviewed in the Introduction. From this large group of reactions, only the formation of Feist's acid from 2-bromo-4,6-dimethyl-5-ethoxycarbonylpyrone seems to bear any similarity to the aryl shift we observe with the methylbromonaphthopyran. The unique occurrence of this rearrangement in this compound is rationalised in terms of the steric congestion due to the methyl group in this particular bromopyrone.

The second section deals with synthesis and epoxidation of various 2(1H) naphthalenones.

1-Hydroxy-1-isopropyl-2(1H) naphthalenone has been reported (D.G. Leppard, Ph.D. thesis, University of Glasgow, 1969) to give on treatment with Na_2CO_3/H_2O_2 in aqueous ethanol only one epoxide (90% yield) with the epoxide oxygen on the opposite face (trans) to the hydroxyl group. The same author also reported the 1-acetoxyl analogue to yield the trans epoxide exclusively. There are relatively few such cases of stereospecific epoxidation of dissymmetric enones in the literature and the factors controlling which face of the enone is epoxidised are not all understood.

Leppards epoxidations were repeated and the reported results confirmed, save that the 1-acetoxyl compound underwent substantial hydrolysis of the acetoxyl group (only 36% of a single acetoxy-epoxide was isolated).

In order to explore the structural requirements for this steric control a range of 2(1H) naphthalenones with different alkyl and oxygen-containing functions on C_1 was made. In addition to the two compounds already mentioned, 2 (1H) naphthalenones bearing the following pairs of substituents on C_1 were successfully synthesised: methyl and hydroxyl; methyl and acetoxyl; methyl and methoxyl; ethyl and acetoxyl; isopropyl and trimethylsilyloxyl. Attempts to synthesise and isolate the compound bearing isopropyl and methoxyl on C_1 by alkylation of the 1-hydroxyl compound were unsuccessful.

Epoxidation with alkaline hydrogen peroxide of 1-acetoxy-1-methyl-2(1H) naphthalenone and 1-isopropyl-1-trimethylsilyloxy-2(1H) naphthalenone led to the complete hydrolysis of the acetoxyl and trimethylsilyloxyl groups respectively. The epoxide isolated in both cases was the same as that from 1-hydroxy-1- alkyl -2(1H) naphthalenone.

Epoxidation of 1-hydroxy-1-methyl-2(1H) naphthalenone and of 1-methoxy-1-methyl-2(1H) naphthalenone gave one simple epoxide in each case (assumed trans). The 1-hydroxy-1-methyl compound also gave a material which seemed to be a dimer of the simple epoxide.

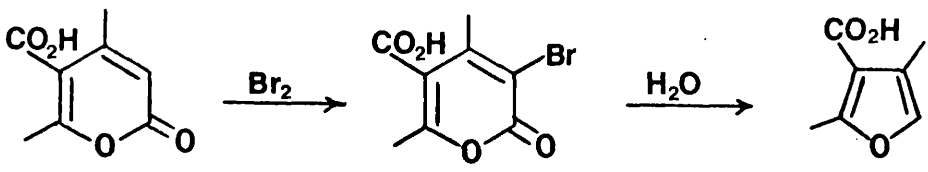
Although in all cases studied only one stereoisomer was formed in the epoxidations it was difficult to prove its stereochemistry. ^{13}C and lanthanide shifts of ^{1}H NMR spectra were studied but no conclusions could be drawn from them about the stereochemistry of the epoxides.

The Introduction consists of a selected survey of published examples of epoxidations and related processes in which stereoselective product formation took place. In some cases this outcome might have been anticipated, and in others not. A critical examination of the explanations given does not appear to reveal any underlying unity of cause.

INTRODUCTION.

The reaction of α -bromopyrones with hydroxide ion is a standard synthetic route to furans[1a,b], and has been deemed sufficiently general and well-established to be employed as a diagnostic test for the position of bromination on pyrone[1] and coumarin[2,3] nucleii.

Feist[4] brominated 4,6-dimethylpyrone-5-carboxylic acid (1), then hydrolysed the 3-bromopyrone so obtained with water to yield 2,4-dimethylfuran-3-carboxylic acid:



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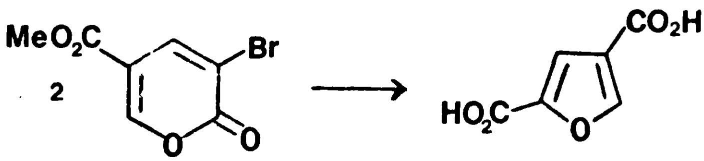
Similarly[5], 3-bromo-5-methoxycarbonyl-pyrone (2) gave furan-2,4-dicarboxylic acid:



The mode of bromide displacement is clearly a critical factor in any consideration of the mechanism of the foregoing reactions. Simple vinyl halides are known to be inert to nucleophiles, but when activated by suitable functionality react readily. This subject has been reviewed[6], and a number of mechanisms have been identified. Of these, only mechanisms in which the bromide is displaced from an sp^3 hybridised carbon will be considered here, since other routes do not appear to explain the reaction products of the α-halo-α,β - unsaturated lactones and related systems under investigation.

One way in which the foregoing results can be rationalised

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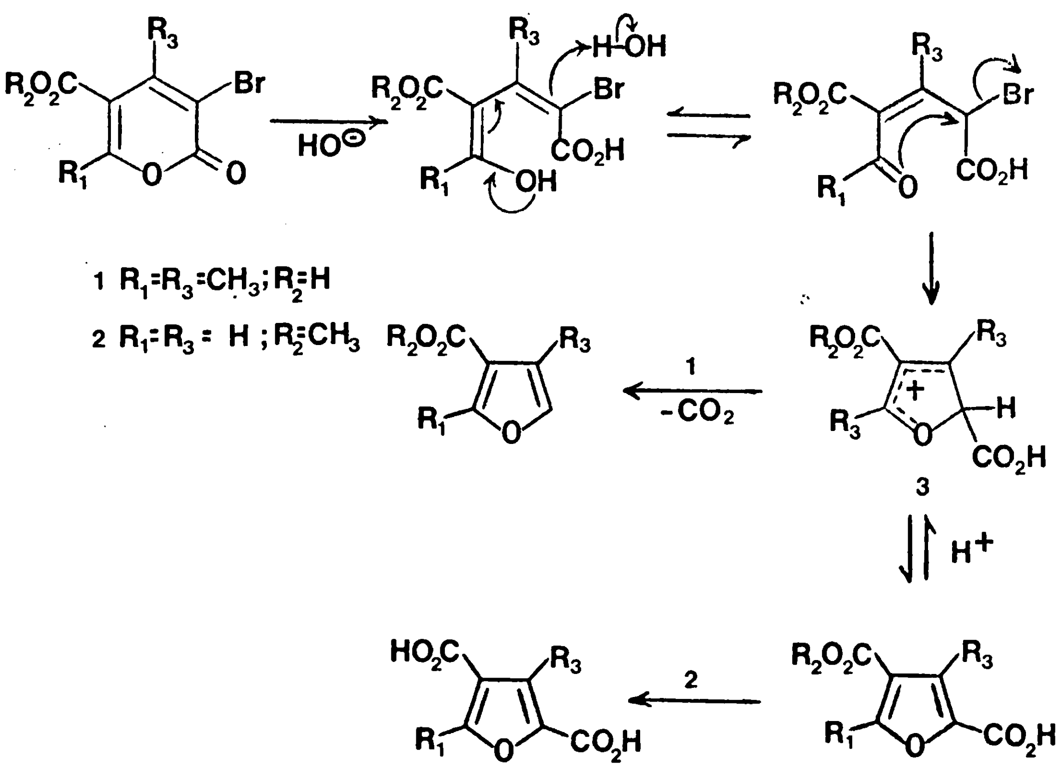
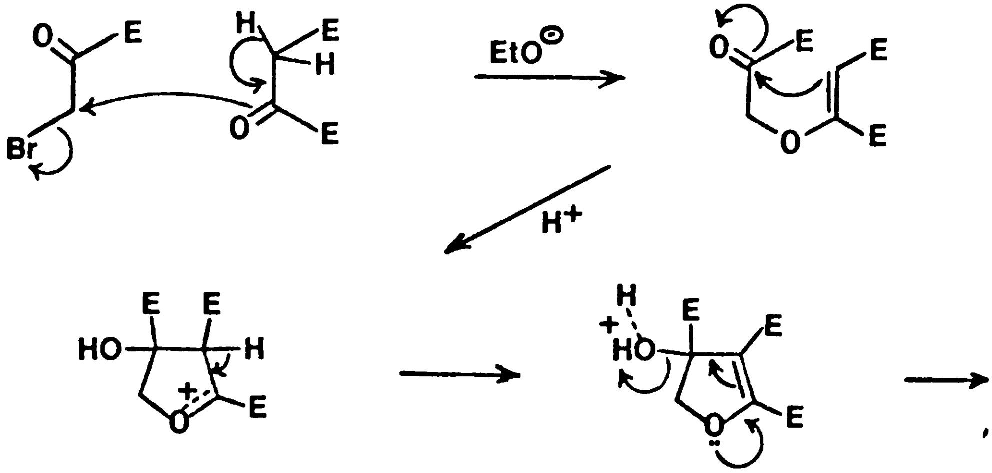
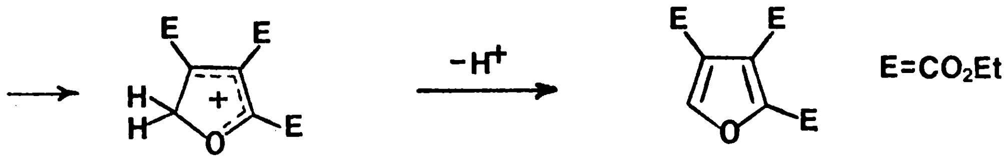
is shown in Scheme 1.



Other synthetic approaches to furans can be rationalised in terms of the intermediacy of a highly stablised carbonium ion similar to 3 above. Reichstein et al.[7] condensed ethyl bromo-pyruvate with diethyl oxalate yielding the furan derivative (4):





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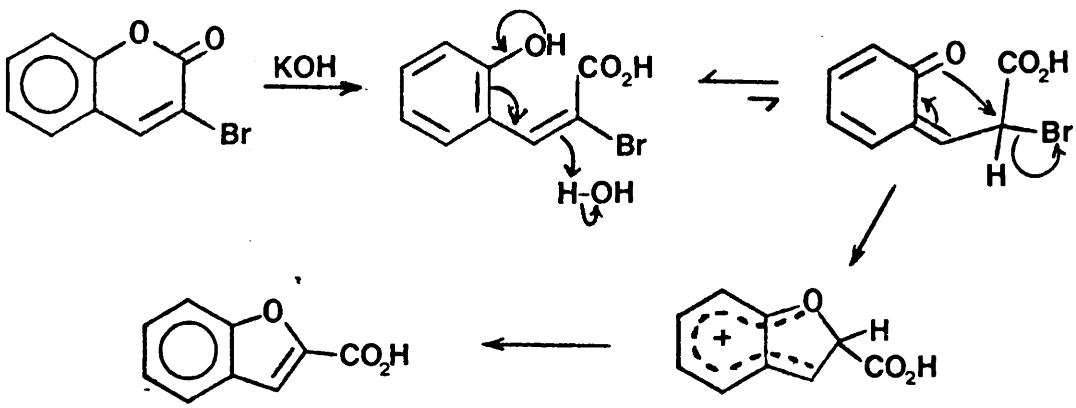
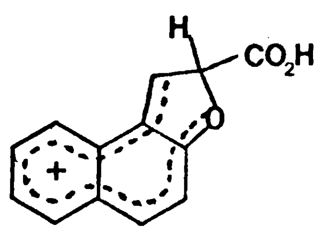
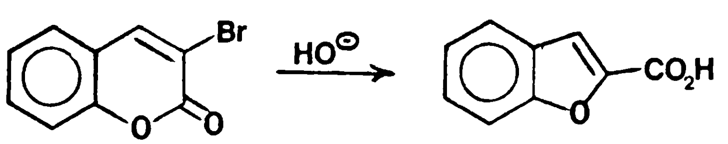
When 3-bromo-coumarins and higher systems such as benzo-coumarins are considered, it is apparent that a carbonium-ion intermediate of type 3 can achieve even greater stabilisation:

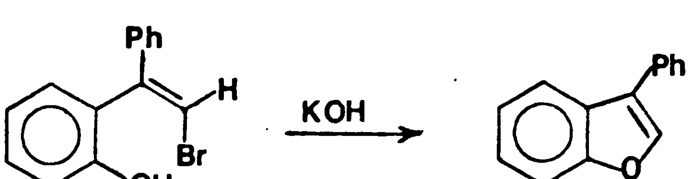




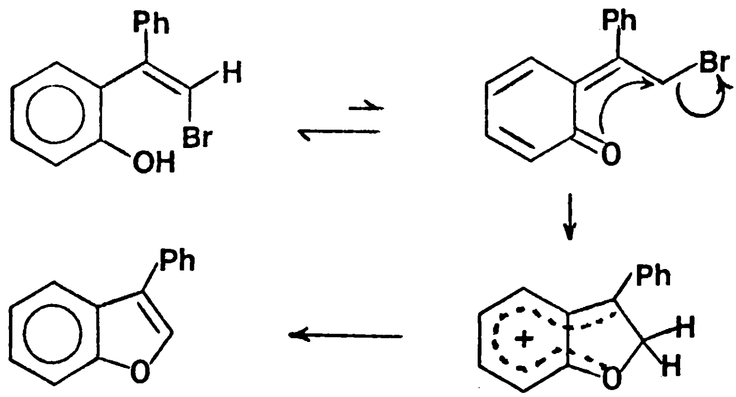
The first reported example of this reaction type was that of Perkin[8]



A closely related reaction, first studied by Komppa[9], is the alkaline hydrolysis of o-hydroxy-β-halostyrenes:

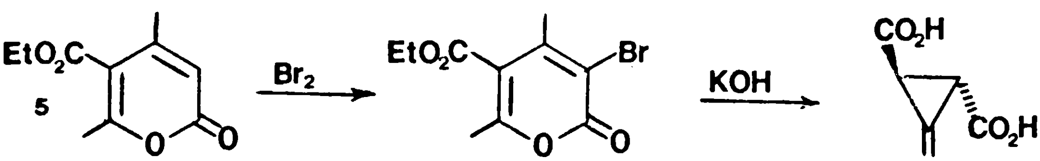


This reaction might conceivably also proceed via a γ -bromoenone and a delocalised oxonium ion:

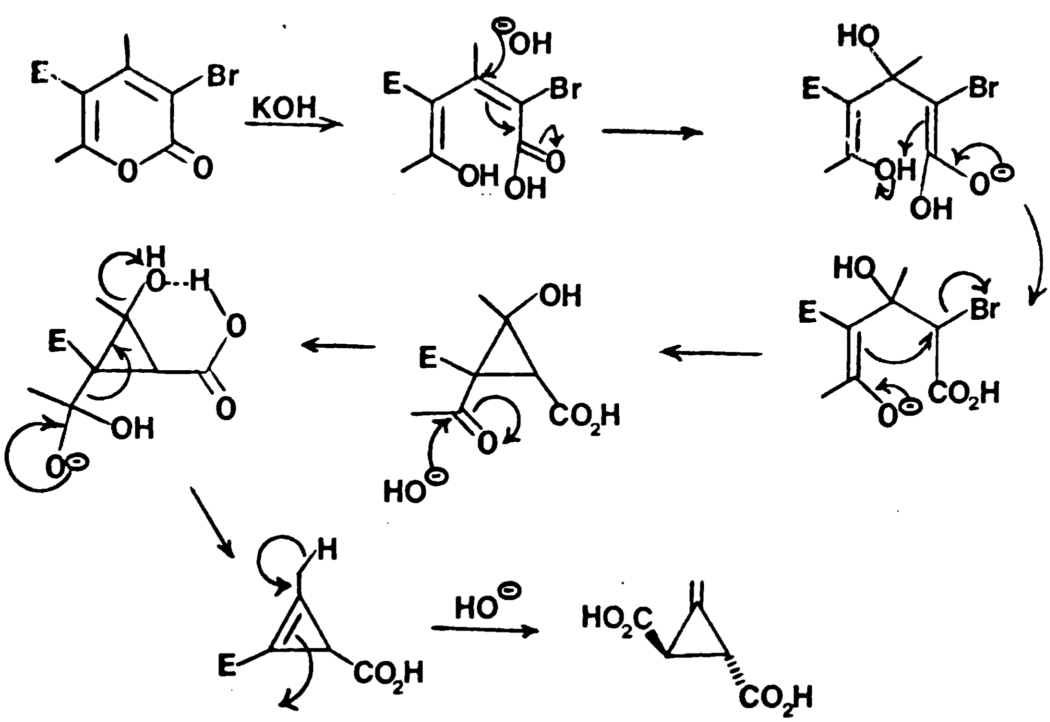


There are some cases however where the mechanistic path discussed above is clearly not followed.

Feist[4] brominated the pyrone 5 , and hydrolysed the resulting bromo-compound. The product isolated was Feist's acid:

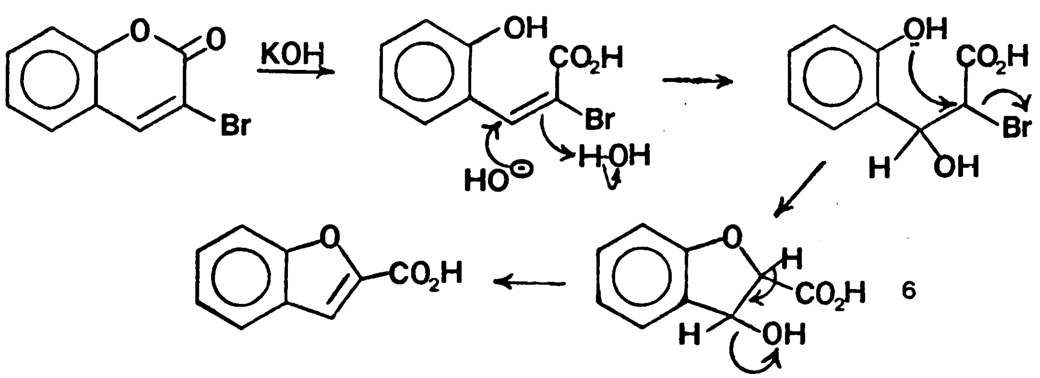


A possible route is as follows:



There are two crucial steps in this mechanistic scheme: the addition of water across the double bond bearing the bromine atom to produce an sp^3 carbon, and secondly, the displacement of bromide by the carbon of the enolate to form a cyclopropane ring.

It is also apparent that the formation of furan-2-carboxylic acids from α -bromo-pyrones and 3-halo-coumarins can equally well be explained by postulating addition of water across the bromine-bearing double bond:



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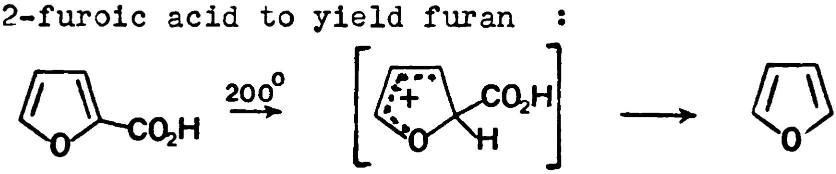
It must be said that the mechanisms proposed in this thesis for the formation of furan-2-carboxylic acids from α -bromo-pyrones and related systems, as well as the formation of Feists acid from an α -bromo-pyrone still leave some questions unanswered. The carbonium ion 3 would be expected to undergo facile loss of carbon dioxide to yield a simple furan, a reaction well established, for example in the thermal decarboxylation of 2-furoic acid to yield furan[10]:



The mechanistic hypothesis which involved the addition of water across the double bond (scheme 2) leading to an intermediate such as 6 would be subject to the same criticism as scheme 1 if loss of the hydroxide group in 6 involved the creation of a carbonium ion similar

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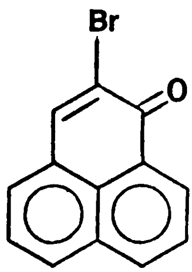
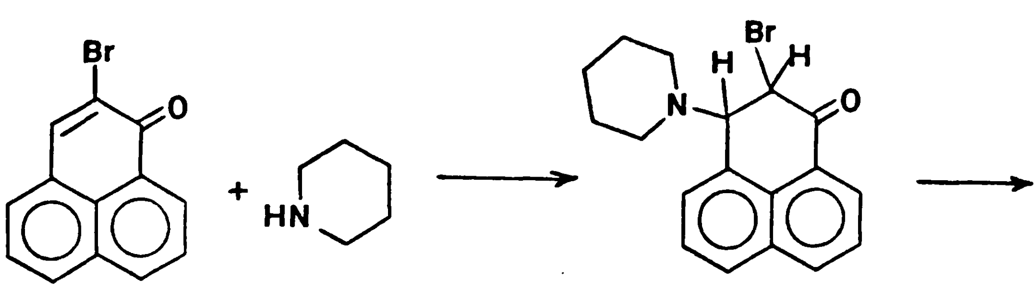
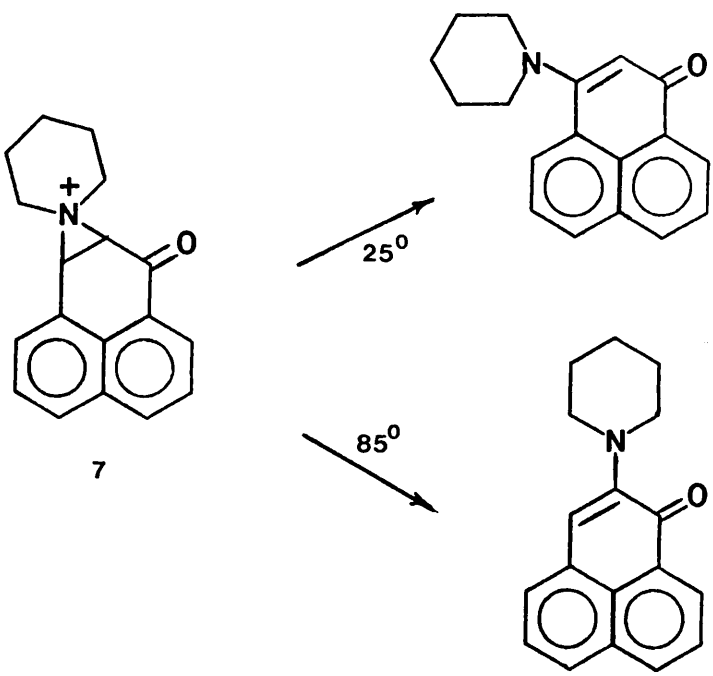
in type to 3 . On the other hand if elimination of hydroxide was synchronous with proton loss, as might well be the case under basic conditions, scheme 2 would emerge as the more convincing. β - Hydroxy acids (of which 6 is an example) normally undergo elimination of water to yield cinnamic acids,[11] and not of CO_2 and H_2O.

A measure of support for the hydroxide addition step of scheme 2 comes from the reaction of the ketone α -bromo-phenalenone with amine nucleophiles:



This compound was shown to be inert to silver acetate in acetic acid[12], but reacts with primary and secondary amimes[13]. The products depend on conditions. Thus with piperidine at 25°, the main product is the β -piperidino compound, while at 85° α -piperidino phenalenone results:





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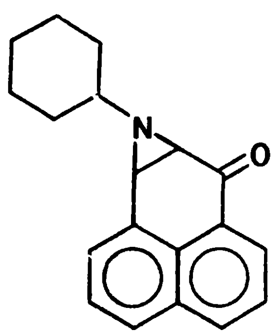

Intermediacy of the aziridinium ion (7) was supported by the isolation of an aziridine when cyclohexylamine was used.

Very little thought has been given to the mechanism of bromide displacement in the hydrolysis of α-bromo pyrones and related systems. For example, Dean[14] mentions this reaction as a route to benzo(b)furan-2-carboxylic acids, drawing an intermediate of this type:

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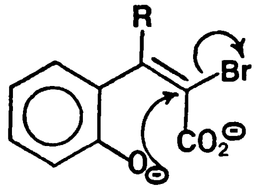
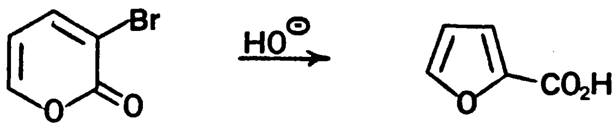


This suggests displacement of halogen from an sp^2 hybridised carbon, a comparatively rare occurrence[6,15].

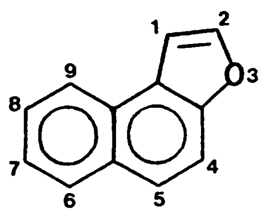
In summary then, the conversion



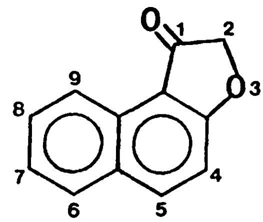
is a standard reaction, though the mechanism is not known. There are very few cases where alternative types of product are formed.

NOMENCLATURE

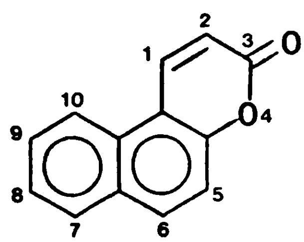
The tricyclic heterocycles discussed below belong to three types, The Chemical Abstracts nomenclature for these is used in this thesis. The Chemical Society recommended names are given here in cases where they are different.



Naphtho (2,1-b) furan



Naphtho (2,1-b) furan-1 (2H)-one

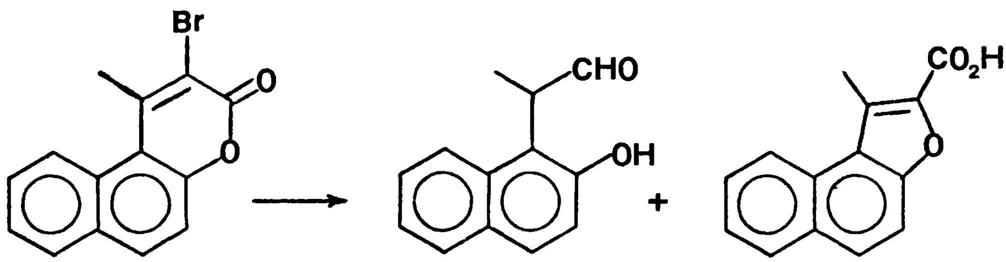


3H-naphtho (2,1-b) pyran-3-one

(Benzo (5,6) chromen-3-one)

RESULTS AND DISCUSSION.

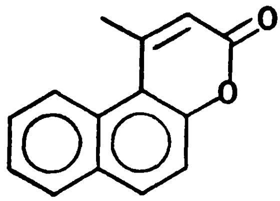
In 1934 Dey and Lakshminarayanan reported[16] the unusual observation that the bromo compound, 1-methyl-2-bromo-3H-naphtho (2,1-b) pyran-3-one (8), reacted with 2M NaOH at reflux to give two products. The major product, mp 136°, was assigned the structure 9 2-(2-hydroxynaphth-1-yl) propanal, while the minor product, mp 240°, was assigned structure 10, 1-methyl-naphtho (2,1-b) furan-2-carboxylic acid:



8 9 10

The following is a summary of the evidence on which these structures are based.

The bromo compound 8, was synthesised by the condensation in conc.H_2SO_4 of 2-naphthol and ethyl aceto-acetate to give 1-methyl-3H-naphtho (2,1-b) pyran-3-one (11),[17] along with some of the chroman-4-one isomer. Bromination with one mole of bromine in acetic acid gave 8.



11

The hydrolysis of 8 was conducted in 2M NaOH at reflux for 1h, the products being precipitated from the cooled reaction solution with mineral acid. The precipitate, was then allowed to stand in contact with aqueous bicarbonate, only a portion dissolving. Acidification

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of the filtrate precipitated a substance A, mp 240^{o} in about 25% yield. No direct evidence was cited for the assignment of structure for A, but it was stated to be the same as an acid, mp 240^{o}, isolated in unspecified yield from a vigorous base hydrolysis (20% KOH, 2h at reflux) of 1-methyl-2-chloro-3H-naphtho (2,1-b) pyran-3-one[16]. An acid of structure 10 would be the product expected from both these reactions (see introduction).

The bicarbonate-insoluble residue B was crystallised from hot water to give glistening rectangular plates mp 136^{o} (about 48% yield). This compound reportedly analysed for $C_{13}H_{12}O_2$. It gave an acetyl derivative with acetic anhydride/pyridine. The presence of a carbonyl group was demonstrated by the formation of phenyl-hydrazone, oxime and semicarbazone derivatives. B was soluble in cold aq. sodium hydroxide, decolourised cold acid permanganate and reduced both Fehling's solution and ammonical silver oxide. These positive oxidative tests were taken in conjunction with the formation of carbonyl derivatives as proof of presence of an aldehyde. Aldehydes ought to give carboxylic acids with (net) insertion of one oxygen atom. Oxidation of B with aq. ammoniacal silver oxide on a preparative scale gave a compound mp 156^{o}. This species was titratable, and gave an equivalent of 220. $C_{13}H_{12}O_3$ (B + 10) would require 216. The introduction of one additional oxygen atom to give an apparently acidic product was again consistent with an aldehyde. The foregoing evidence suggested the structure 9 for B. This structure should also exist as a hemi-acetal 12 :

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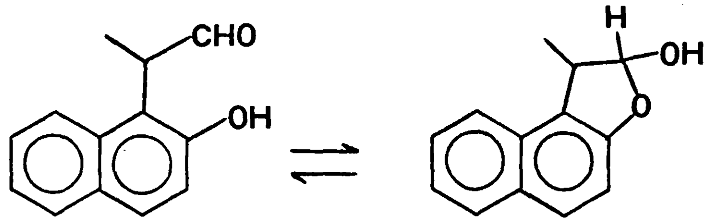
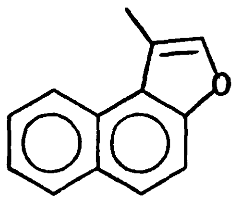


12

Dehydration of B with HCl gas in absolute alcohol gave colourless needles, mp 57°, which analysed for $C_{13}H_{10}O$ (B - H_2O). No evidence for the structure of the furan was given. It was assumed to be 13 , 1-methylnaphtho (2,1-b) furan:



13

The structure 9 was of interest to us mainly as a potential precursor for 1-t-butyl-2-naphthol, a compound which was the focus of synthetic endeavours in this laboratory[18]. Consequently it was decided to re-examine this sequence of reactions.

Following the procedures employed by Dey and Lakshminarayanan and outlined earlier, the bromo compound 8 , mp 145-6° was prepared. When the reaction of 8 with base was attempted under the conditions described originally[16], the only product which could be isolated (apart from intractable tar) was a small quantity of a white solid mp 55-6° obtained from an ether extract of the cooled, acidified reaction mixture. The PMR and mass spectra of this compound (m/e = 182; δ 2.51, doublet, J small, 3H; 6.81, broad singlet, 1H; 7.2 - 8.2, multiplet, 6H, aromatic) suggested that it was a methyl-naphthofuran, the type of product which would have been expected to result from the acid-catalysed

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dehydration of a compound such as 9 (see below).

This initial failure made us aware of the system's sensitivity to oxygen (hence the tarring) and to acid-catalysed dehydration of at least one of the products (yielding the furan). As a consequence, reaction conditions were modified to allow the isolation of pure primary products. Oxygen was excluded by purging the sodium hydroxide solution with nitrogen for about 1h prior to the introduction of the bromo compound 8, and by conducting the reaction, and as far as possible the workup, under a nitrogen flow. These precautions effectively prevented tarring. Acidification of the cooled reaction mixture was avoided, carbon dioxide gas instead being bubbled through until the pH dropped to about 9 and (in principle) the solution had become one of sodium carbonate and no longer sodium hydroxide. The suspected phenolic portion of the product was removed by extraction into ethyl acetate before acidification of the carbonate solution was undertaken to precipitate the acidic fraction of the product. The reflux period of the reaction was approximately 2h.

Under these conditions, the bromo compound 8 reacted to give two products. The main product C was obtained from the ethyl acetate extract of the cooled carbonated reaction mixture as a pale yellow solid which was repeatedly crystallised under nitrogen to give glistening white platelets mp 151-2^{o} from aq. ethanol. C was soluble in cold sodium hydroxide, decolourised permanganate instantly and gave a silver mirror with Tollens' reagent. It formed an acetyl derivative when refluxed in acetic anhydride with a drop of pyridine under a nitrogen stream, and gave an oxime and a semicarbazone. The melting points of the derivatives of Dey's material and ours are compared in Table 1:

	Dey's report	This work
phenol	136^{o} (B)	$151\text{-}2^{o}$ (C)
oxime	182^{o}	$181\text{-}3^{o}$
semicarbazone	186^{o}	$184\text{-}6^{o}$
phenylhydrazone	144^{o}	-
acetate	117^{o}	$116\text{-}7^{o}$

The close agreement in the melting points of derivatives of B and C as well as their identical behaviour with oxidising tests and sodium hydroxide strongly suggests that these two compounds are the same, despite the substantial disparity in their melting points.

The material which we isolated C, gives a positive iodoform test, instantly precipitating yellow iodoform from a basic solution of iodine in potassium iodide. This test is generally characteristic of a methyl ketone. The fact that C can be extracted from a carbonate solution with ethyl acetate (reaction workup) but will dissolve in sodium hydroxide suggests phenolic character, a conclusion substantiated by the formation of an acetyl derivative. The I.R spectrum showed a broad, strong band at 3220 cm^{-1} and a strong band at 1695 cm^{-1}. These bands are typical of phenolic OH and a saturated ketone respectively. The presence of a naphthalene ring system was suggested by strong, sharp bands at 815 cm^{-1} and 757 cm^{-1}, which are characteristic of two adjacent and four adjacent aromatic hydrogens respectively. These latter bands also infer a 1,2 substitution. The PMR spectrum shows two sets of

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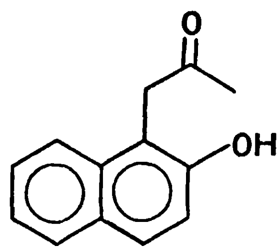
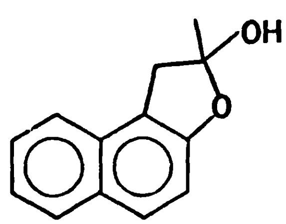
peaks. One set consists of a singlet at 1.58, intensity 1H which vanishes on D_2O shake, a singlet at 2.27, 3H and another singlet at 4.14, 2H. The other set comprises a singlet at 1.83, 3H, a broad peak at 3.17, 1H which vanishes on shaking with D_2O and yet another singlet at 3.5 of intensity 2H. In addition, aromatic protons are evident as a multiplet between 6.67-8.16. The mass spectrum of C shows a parent ion at m/e 200.

These facts are interpreted as proof for the structure of C as 14:



14

The PMR spectrum is explicable in terms of tautomeric equilibrium of 14 with the hemi-ketal form 15:



15

Dey and Lakshminarayanan cited the dehydration of their phenol B to give a furan as evidence of structure. But it is obvious that 15 (which is isomeric with B) should yield 2-methylnaphtho (2,1-b) furan (16) on dehydration, and that 16 will have the same molecular formula as the furan of Dey and Lakshminarayanan.

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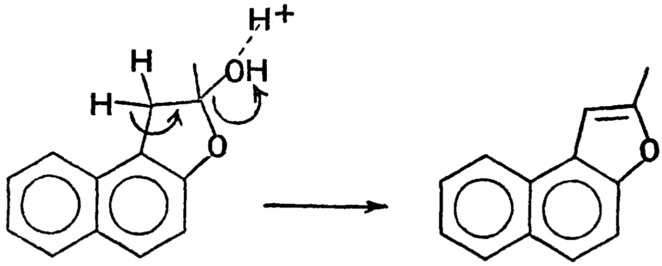
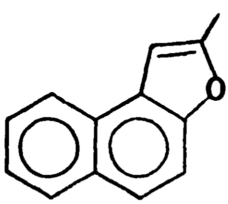
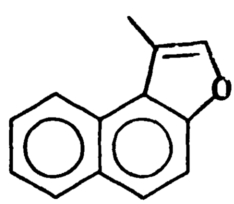


15 16

Our phenol C was stirred with a few drops of HCl in methanol for two hours at room temperature. On adding water and cooling, white crystals mp 55-6° formed. Recrystallisation from aq. methanol gave mp 56.5-7°, which analysed for $C_{13}H_{10}O$. The yield of this reaction was almost quantitative. Dey and Lakshminarayanan's furan had mp 57°, and was assigned structure 13. In order to establish the structure of our furan, a literature survey of the physical properties of both possible isomers viz. structures 13 and 16 was undertaken. The results are summarised in Table 2:



16



13

ref.	H_1	CH_3	mp.	ref.	H_1	CH_3	H_9	mp.
19	6.55	2.4	liq.	21	7.3	2.55	-	
20	6.72	2.49	55°	26	7.9-7.25*	2.49	8.26(dxd)	59.3-59.5°
	6.68	2.50						
				28	-	-	-	60°
21	6.86	2.52	-	29	-	-	-	59°
22	-	-	52°	30	-	-	-	59°

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Data on 16 contd.

ref.	H_1	CH_3	mp
23	-	-	56-7°
24	-	-	51-2°
25	-	-	54°
26	6.76	2.54	55.8-56.6°
27	-	-	54°

*with other aromatic H.

Our furan had mp 56.5-7° when purified by crystallisation, and further crystallisations did not raise this melting point. The PMR spectrum showed the aromatic region to consist of a four proton multiplet between 7.2 - 7.7, and a two proton multiplet between 7.8 - 8.2. A broad singlet of intensity 1H at 6.81 and a doublet with a very small coupling, intensity 3H at 2.51 accounted for the remainder of the protons. These facts seem to suggest that our furan is 2-methylnaphtho (2,1-b) furan. A further piece of evidence for this conclusion was obtained when a direct comparison of the PMR spectrum of our furan was made with the PMR (recorded in these laboratories) of an authentic specimen (mp 59.3 - 59.6°) of 1-methylnaphtho (2,1-b) furan (13) supplied by M. Mülly[31]. These spectra show obvious and gross differences, and demonstrate beyond question that our furan can not be 1-methylnaphtho (2,1-b) furan. In view of this fact and the close concurrence evident in the physical properties of our furan with those listed in Table 2 for 2-methylnaphtho (2,1-b) furan, it would seem justified to assign our furan as 2-methylnaphtho (2,1-b) furan. The other physical properties were in accord with this assignment (see experimental section), and the spectra were identical with those of the furan isolated from the cooled, acidified reaction mixture (see pp12-13)

The final piece of evidence which Dey and Lakshminarayanan

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presented was the oxidation of their phenol B to give an apparently acidic product.

C was oxidised with aq. ammoniacal silver oxide under reflux, the conditions which Dey and Lakshminarayanan had employed. A plethora of products and considerable tarring resulted. None of the products could be isolated in sufficient quantity for characterisation. The oxidation of C was therefore repeated, but the ammoniacal silver oxide solution was purged with nitrogen prior to introduction of C and a positive pressure was maintained over the reaction by means of a balloon. The reaction mixture was stirred at 0^{o} for 4h, then at room temperature for another 22h. A silver mirror formed on the walls of the flask during the course of the reaction. The reaction mixture was poured into 5M HCl and extracted with ether. Evaporation of the ether left a pale yellow solid mp $172-5^{o}$. Dey's acid melted at 156^{o}. This appeared to be the only product formed, and was insoluble in aq. sodium bicarbonate but soluble in cold dilute sodium hydroxide, and hence would be titratable. The IR spectrum showed a strong sharp OH band at 3290 cm^{-1} and a carbonyl absorbance at 1673 cm^{-1}. The presence of strong bands at 817 cm^{-1} and 758 cm^{-1} suggested that the oxidation product was a 1,2 substituted naphthalene. The PMR showed 5 aromatic protons as a multiplet between 6.8 - 8.0, and a 1H doublet centred on 8.3 (J = 8.5 Hz). A broad peak at 4.1, relative intensity 1H, vanished on shaking with D_2O. A 3H singlet at 1.68 completed the spectrum. A molecular ion appeared at m/e 214. The fact that this oxidation product was not soluble in bicarbonate tends to rule out the possibility that it is an acid, but a molecular weight of 214 is consistent with the gain of one oxygen atom and the loss of two hydrogens

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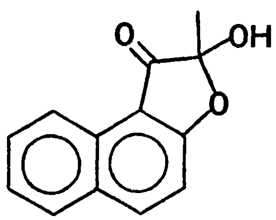
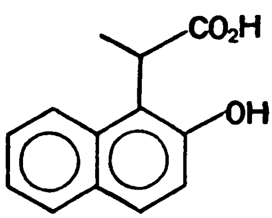
from C . The presence of a methyl group in both C and its oxidation product precluded the possibility that the loss of the two hydrogens could have come from the methyl, but the absence of any signal in the PMR which could be assigned to the methylene protons known to be present in C suggested that the structure of this oxidation product is:



17

The lowfield aromatic doublet centred on 8.3 would be consistent with H_9 of this structure being deshielded by the C_1 carbonyl. 17 is a cryptophenol and hence would be soluble in base as the open-chain diketone tautomer. The titration equivalent of Dey's oxidation product was reported to be 220, a figure which, given experimental error, could hardly distinguish between the molecular weight 214 of our oxidation product and 216 required for the carboxylic acid derived from 9 :



The minor product D of the reaction of bromo compound 8 with sodium hydroxide was precipitated as a yellow-white solid when the aqueous carbonate layer from which C had been extracted with ethyl acetate was acidified (5M HCl).

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D was readily soluble in bicarbonate, confirming the presence of a carboxyl group. Recrystallisation from methanol gave white needles, mp 220-40^{o} which showed a very broad band centred at about 2700 cm^{-1} in the IR, as well as a strong carbonyl at 1675 cm^{-1}. These bands confirmed that D was an acid, the frequency of the carbonyl suggesting α,β unsaturation. A 1,2 substituted naphthalene ring was evidenced by strong bands at 808 cm^{-1} and 754 cm^{-1}. The PMR spectrum (d_5 pyridine) was probably the most informative. A 3H singlet at 2.9, a multiplet between 7.27 - 8.34 integrating for 5 aromatic H, a 1H signal centred at 10.22, d x d, Jortho = 8Hz, Jmeta = 2Hz, and lastly a broad peak of relative intensity 1H at 13.92 which vanished on D_2O shake. The mass spectrum showed m/e 226, and D analysed for $C_{14}H_{10}O_3$. These facts were consistent with a methylnaphthofuran - carboxylic acid. Dey had assigned the structure 10 to the acidic product A mp 240^{o} which he had isolated. If D had the structure 10 , then decarboxylation ought to give furan 13 .

When D was decarboxylated in refluxing quinoline with copper-bronze catalyst, a brown oil was produced. Purified by thin layer chromatography, a white solid mp 55-6^{o} resulted in 77% yield. The spectral characteristics of this material were, however, identical to those of furan 16 which had been obtained from the acid-catalysed dehydration of C . A mixed melting point of the two specimens exhibited no depression. As noted previously, an authentic sample of furan 13 had been obtained[31], the PMR spectrum recorded and seen to be grossly different from that of our furan. The clear disparity between the PMR spectrum of our furan from the decarboxylation of D and that of 13 was

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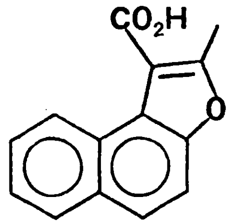
equally evident. The conclusion drawn from these findings was that D had structure 18 , 2-methylnaphtho (2,1-b) furan -1- carboxylic acid:



18

Furthermore, it is obvious that if our furan from the decarboxylation of D had structure 13 then decarboxylation should have had very little effect on the dxd at 10.22 in D , as this signal must correspond to H_9. The fact that no signal could be seen anywhere within 2 ppm of 10.22 in the decarboxylation product clearly indicates that the carboxyl group in D was directly responsible for the exceedingly lowfield shift of the proton at 10.22. The extremely lowfield shift of H_9 in D can hardly be due to steric (van der Waals) crowding of this proton by a methyl group on C_1, since[26] the furan 13 shows H_9 at 8.4 (M. Mülly reports H_9 in this furan at 8.26). In any event, steric crowding alone would not normally be expected to produce such a dramatic effect as a downfield shift of 2 ppm or thereabouts[32]. But the combined effect of steric crowding and the magnetic deshielding associated with carbonyl groups could explain such a low value for H_9. This situation would apply with structure 18 . H_9 would be required to be in (approximately) the same plane as the CO_2H group to experience magnetic deshielding. That the CO_2H group lies in the same plane as the naphthofuran nucleus (and hence H_9) is

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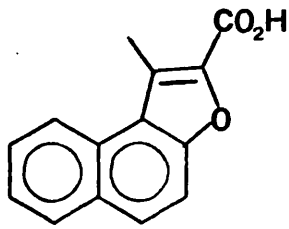
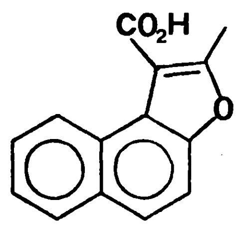
evidenced in the IR stretching frequency of the acid carbonyl at 1675 cm^{-1}. This value is typical of an α,β unsaturated acid, meaning that the p-orbitals in the carbonyl group are parallel to and overlapping with the p-orbitals in the 1,2 double bond, so the carboxylic acid group must lie in the same plane as H_9.

Literature searching revealed that both of the structures 10 and 18 had been reported. Some degree of disparity appears to exist in the physical data, as Table 3 shows:





	10	18
16*	240°	-
28a	253-4°	-
33	-	208-10°
This work	-	220-40°

* mp and structure of Dey and Lakshminarayanan .

Dey produced no evidence at all for his structure assignment. The acid isolated in this work may not be the same as that isolated by him. The routes used[28a, 33] to synthesise the two isomeric acids appear unambiguous. The disparity in mp remains unexplained. An attempt to repeat the preparation of the acid 18 by hydrolysis of

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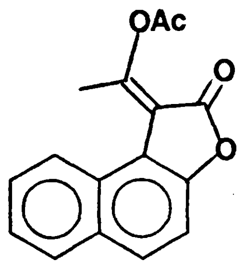
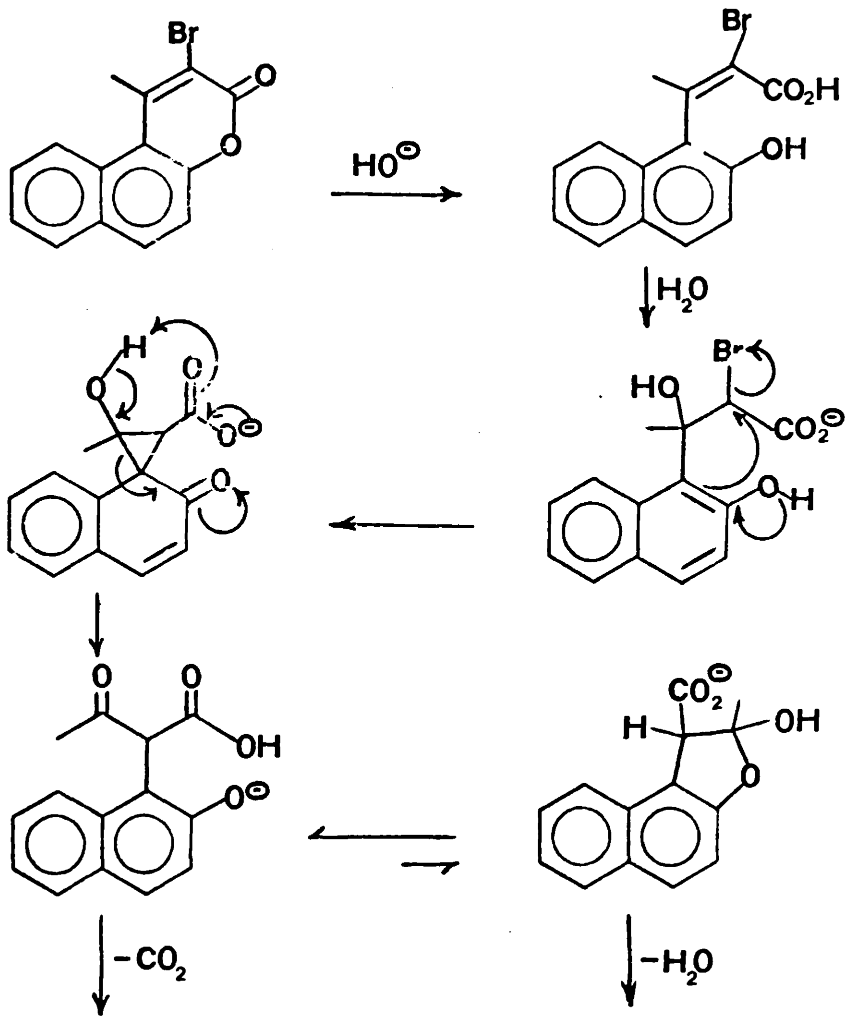


gave only traces of acidic material melting between 185-200°.

OVERALL SCHEME and MECHANISM: SCHEME 1.

The following offers mechanistic rationalisation for the products formed on reaction of 8 with sodium hydroxide and subsequent transformations.



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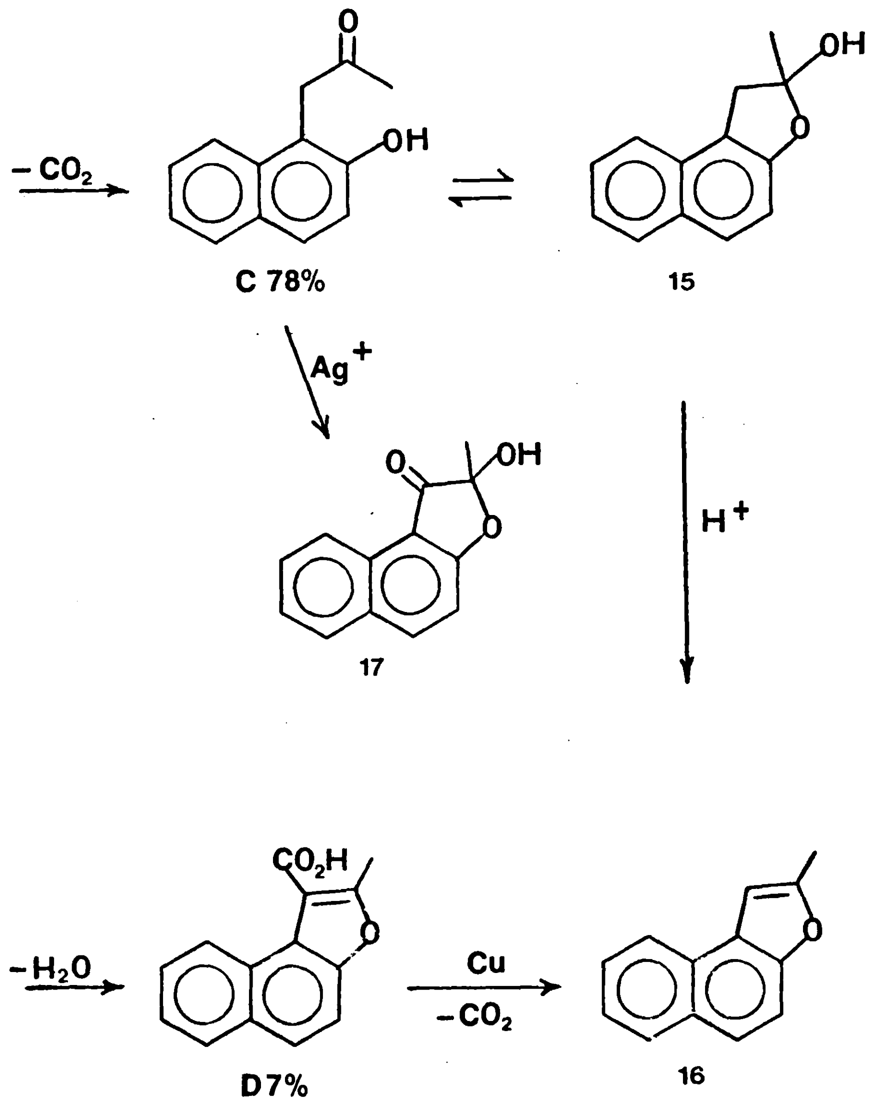
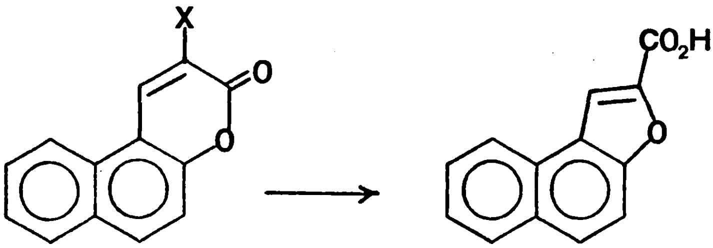


The transformation of bromo compound 8 into C and D i.e., 14 and 18 respectively, is an unusual rearrangement for a compound such as 8. The course which might have been anticipated (see introduction) would have been reaction to give 1-methylnaphtho (2,1-b) furan-2-carboxylic acid (10). The chloro analogue of 8, 1-methyl-2-chloro-3H-naphtho (2,1-b) pyran-3-one is reported[16] to react with 20% KOH at reflux to give an acid mp 240° reportedly identical to that isolated from the bromo compound 8. No physical evidence was produced to establish the structure of the acid isolated. The yield was not quoted.

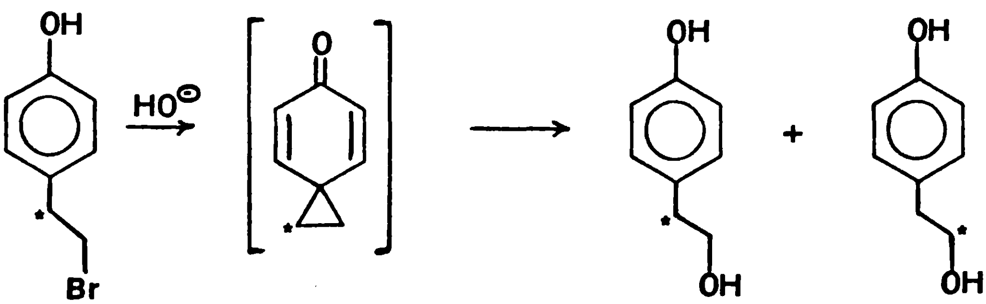
2-Bromo-3H-naphtho (2,1-b) pyran-3-one and the chloro analogue are reported[34] to undergo reaction with 2M KOH to give naphtho (2,1-b) furan-2-carboxylic acid:



X=Cl,Br

This transformation appears to be authentic, the product having the same melting point as the acid of this structure synthesised by other routes[28a,b]. It is not clear why the presence of the methyl group should so alter the course of the reaction.

The crucial step of the mechanism outlined in Scheme 1 is the formation of the intermediate cyclopropane. This type of intermediate is often encountered in the reactions of suitable phenols, and has been demonstrated by rate enhancement and label scattering experiments of this type[35]:



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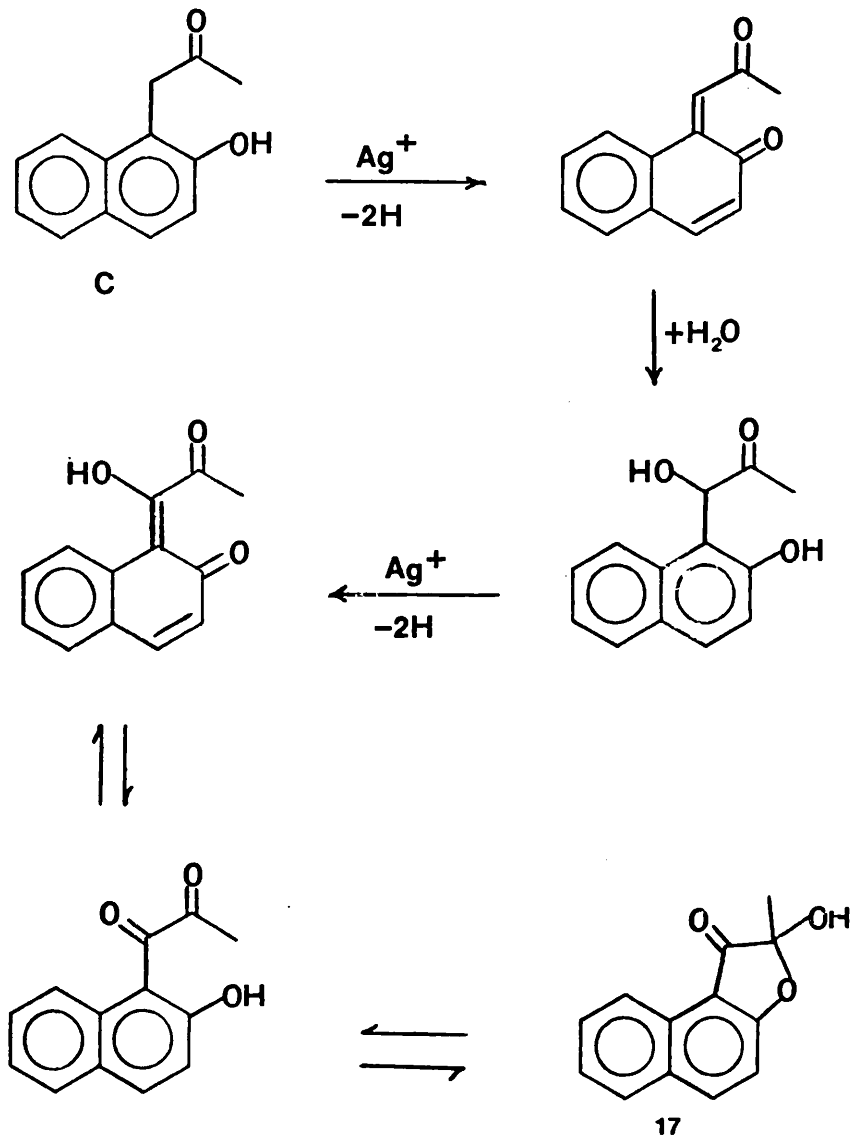
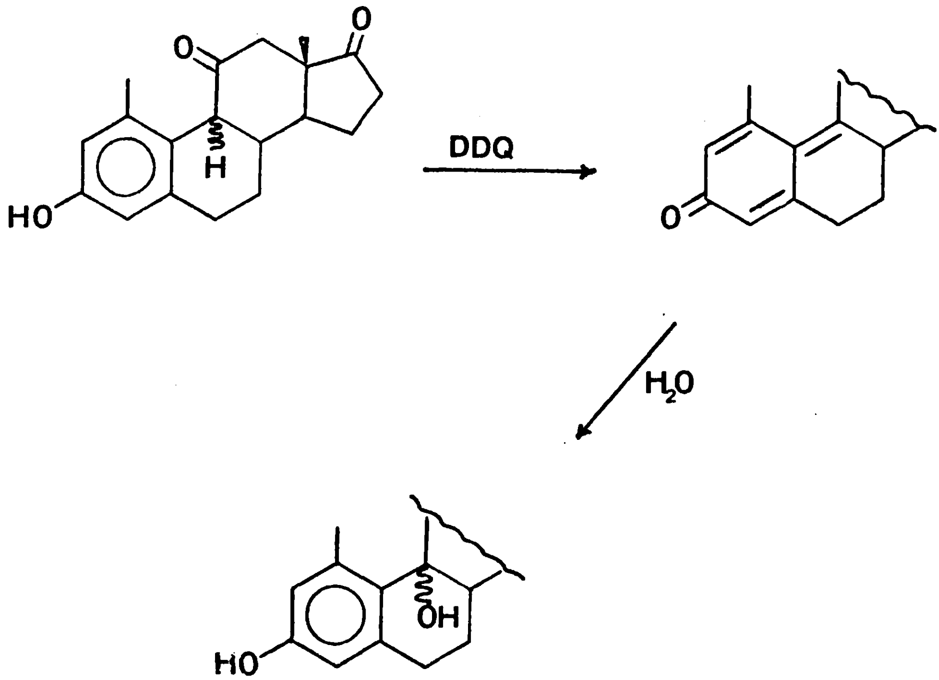
The formation of Feist's acid, discussed in the introduction, can also be rationalised by a cyclopropane intermediate, in that case formed from an enol.

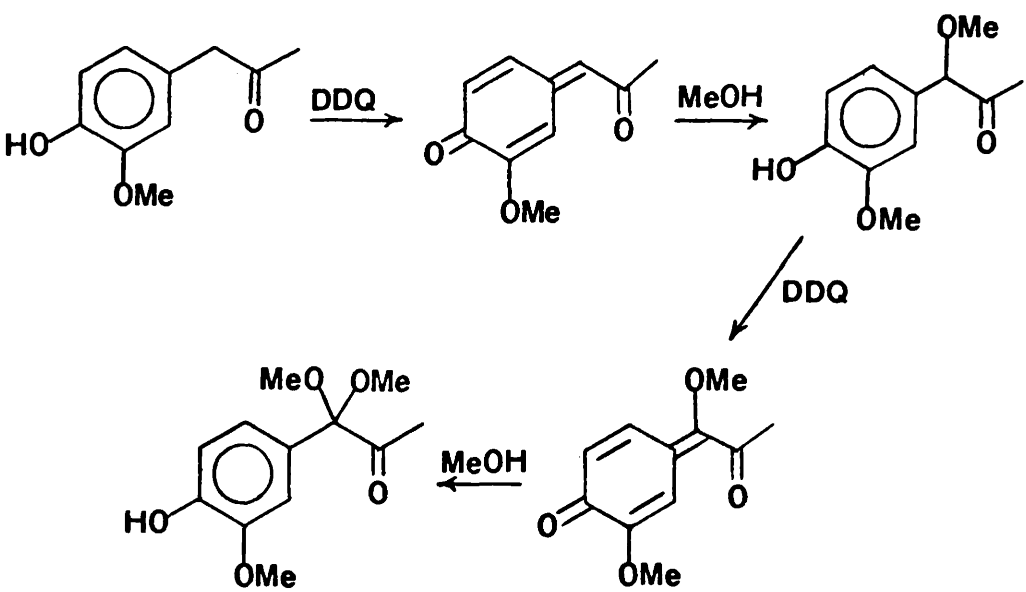
The oxidation of C with ammoniacal silver oxide merits further consideration. The following steps offer a mechanistic rationalisation:



Oxidation of α-ketols with silver ion is a facile and well-established process, and C may be regarded as a vinylogous α-ketol. An example of benzylic hydration directly analogous to the oxidation of C has been published[36], and suggested to involve a quinone-methide. Thus 3-hydroxy-1-methyloestra-1,3,5-(10)-triene-11,17-dione was oxidised by DDQ in aqueous dioxan to give the 9β-hydroxy derivative by addition of water to the intermediate quinone-methide:



That both hydrogens of a benzylic function can be removed was shown by a similar reaction with guaiacyl acetone in methanolic dioxan:



EXPERIMENTAL

Melting points (mp) were recorded on a Riechert microscope hot-stage, and are uncorrected.

Proton magnetic resonance (PMR) spectra were recorded on a Varian T-60 (60 MHz) spectrometer in deuterochloroform with tetramethyl silane (TMS) as internal standard at 0 ppm (δ).

Infra-red (I.R.) spectra were recorded on a Perkin-Elmer 257 spectrophotometer. Letters in parenthesis after a peak indicate its approximate appearance and relative intensity, (s) strong; (m) medium; (b) broad; (sp) sharp.

Mass spectra (MS) were recorded on a G.E.C.-A.E.I. M.S.12 spectrometer.

Ultraviolet (U.V.) spectra were recorded over the range 450-200 nm as solutions in methanol, and are quoted as λ MAX values in nanometers (nm) followed by log ϵ values in parenthesis. Only signals above 250 nm are quoted. A Pye-Unicam S.P.800 spectrometer was employed.

Analyses were carried out by Mrs. W. Harkness, and are given as percentages (%).

Preparative chromatography was conducted on plates coated with 1 mm of Merck Hf 254 fluorescent silica. Microslides were used for analytical tlc.

The organic phase of extractions was dried by shaking with saturated brine followed by anhydrous magnesium sulphate. Evaporation of solvents was conducted on a rotary evaporator (Büchi) under a water-pump vacuum over a

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hot-water bath.

Exceptions to any of these conditions are noted at the appropriate points.

1-Methyl-2-bromo-3H-naphtho (2,1-b) pyran-3-one (8).

Bromination[16] of 1-methyl-3H-naphtho (2,1-b) pyran-3-one (11) gave 1-methyl-2-bromo-3H-naphtho (2,1-b) pyran-3-one (8) as pale yellow needles from aq. ethanol or methanol mp 145 - 6^o (lit.[16] 145^o).

PMR: 2.95, singlet, 3H, CH_3; 7.6 (centred on), multiplet, 5H, H_5-H_9; 8.4 (centred on), doublet, signals broadened by finer coupling, J = 9Hz, 1H, H_{10}.

IR: 1730(s), C = O; 820 (s,sp), 2 adjacent H; 748 (m), 4 adjacent H.

MS: m/e 288, 290 (relative intensity 1:1). Typical of monobromo substitution.

UV: 353 (4.16), 323 (4.03), 257 (4.02).

$C_{14}H_9O_2Br$ requires:	C 58.16	H 3.14	Br 27.64
found:	C 58.03	H 3.22	Br 27.9

Base Catalysed Rearrangement of 1-methyl-2-bromo-3H-naphtho (2,1-b) pyran-3-one (8).

250 ml of 2M NaOH solution was placed in a three-necked RB flask equipped with a double-surface condenser and a nitrogen inlet. After vigorous flushing with nitrogen (about 1h), 17.1g (0.059 mole) of the bromo compound (8) was introduced. Maintaining the nitrogen flow, this solution was heated to reflux, the bromo compound slowly dissolving over a period of about 1h. Reflux was maintained for a further hour, and the reaction mixture allowed to cool. Carbon dioxide gas was bubbled through until universal indicator paper showed pH = 9, the solution was extracted

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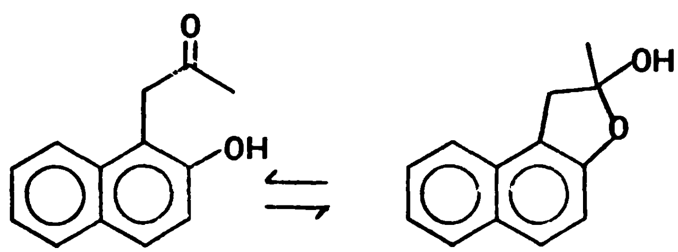
with ethyl acetate (2 x 50 ml) and the extract dried. Evaporation of solvent left a pale yellow solid (9.21g; 0.046 mole; 78%), which was crystallised from aq. ethanol under a nitrogen stream to give silvery-white plates mp 151-2^{o} (lit.[16] 136^{o}). This compound was shown to be 1-(2-hydroxynaphth-1-yl) propan-2-one (14).

PMR: 1.58, sharp singlet, vanishes on D_2O shake, 1H, phenolic OH; 2.27, singlet, $COCH_3$; 4.14, singlet, CH_2COCH_3; 1.83, singlet, hemi-ketal CH_3; 3.17, broad, vanishes on D_2O shake, hemi-ketal OH; 3.5 singlet, hemi-ketal CH_2; 6.67-8.16, multiplet, aromatic protons.

This spectrum clearly shows the presence of the tautomeric equilibrium:



The relative proportions of these two forms is about 2:1 in favour of the keto form, assessed on the integrals of comparable peaks.

IR: 3220 (s,b) OH; 1695 (s), C = O; 1632, 1583 (both m), C = C; 815 (s), 2 adjacent aromatic H; 757 (s), 4 adjacent aromatic H.

MS: m/e 200

UV: 335.5 (3.44), 327 (shoulder, 3.40), 290.5 (3.56), 279 (3.65), 269 (3.58), 260 (shoulder, 3.44).

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$C_{15}H_{14}O_3$ (acetate) requires: C 74.36 H 5.82

found: C 74.37 H 5.85

oxime[37] : formed instantly at room temperature in aq.KOH/$NH_2OH.HCl$. Recrystallised from aq. ethanol, mp 181-3^{o} (lit.[16] 182^{o}) as white needles.

semicarbazone[37] : grew slowly as white needles from aq. sodium acetate/$NH_2NHCONH_2.HCl$, mp 184-6^{o} (lit.[16] 186^{o}).

acetate[37] : prepared by refluxing (14) in acetic anhydride with a drop of dry pyridine under nitrogen. White needles, mp 116-7^{o} (lit.[16] 117^{o}).

iodoform[37] : immediate precipitation of yellow iodoform, recrystallised from aq. acetone, mp 119-20^{o} (lit.[37] 120^{o}).

The aqueous layer of the extract was acidified (5M HCl), the resultant precipitate extracted into ethyl acetate and dried. Evaporation of the solvent left a yellow-white solid (0.93g; 0.41×10^{-2} mole; 7%). This compound was purified by precipitation from bicarbonate followed by crystallisation from methanol as white needles, mp 220-4$0^{o}$ (for literature value, see Results and Discussion Section).

PMR: 2.9, singlet, 3H, CH_3; 7.27-8.34, multiplet, 5H, H_4-H_8; 10.22, doublet, peaks broadened by finer coupling, J = 8Hz, 1H, H_9; 13.92, broad, 1H, vanishes on D_2O shake, CO_2H. This spectrum was recorded in d_5 pyridine for solubility reasons.

IR: 2700 (b) OH; 1675 (s), C = 0; 808 (s), 2 adjacent aromatic H; 754 (s), 4 adjacent aromatic H.

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MS: m/e 226.

UV: 325.5 (3.47), 317 (shoulder, 3.67), 311 (3.77), 291 (3.92).

$C_{14}H_{10}O_3$ requires: C 74.33 H 4.46

found: C 74.36 H 4.46

Dehydration of 1-(2-hydroxynaphth-1-yl) propan-2-one (14)

0.268 g (1.34×10^{-3} mole) of (14) was dissolved in 10 ml of AR methanol and a few drops of 5M HCl added. The solution was stirred magnetically for 2h, when tlc (20% EtOAc in 60-80 petrol) showed the reaction to be complete.

2 ml of water was then added and the reaction cooled in an ice-salt bath. White crystals separated. These were filtered off and washed with distilled water (71 mg, mp 55-6^{o}). Recrystallised from aq. methanol, mp 56.5-7^{o} (for literature values, see table 1 in Results and Discussion Section).

A second crop of crystals was obtained when the mother liquors of the reaction were partitioned between water and ether, back extracted with ether and the combined ether extracts dried. Evaporation of solvent left a clear oil which solidified and was crystallised from aq. methanol, mp 55-6^{o} (146 mg; total yield 89%).

This compound was shown to be 2-methylnaphtho (2,1-b) furan (16) on the basis of the following data.

PMR: 2.51, doublet with very small coupling, 3H, CH_3; 6.81, broad singlet, 1H, H_1; 7.2-7.7, multiplet, 4H, aromatic; 7.8-8.2, multiplet, 2H, aromatic.

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IR: 1600, 1580 (both m), aromatic C = C; 800 (s), 2 adjacent aromatic H; 742 (s), 4 adjacent aromatic H.

MS: m/e 182.

UV: 326.4 (3.85), 318.5 (3.7), 312 (3.84), 295 (2.94).

$C_{13}H_{10}O$ requires: C 85.69 H 5.53

found: C 85.42 H 5.47

Oxidation of 1-(2-hydroxynaphth-1-yl) propan-2-one (14)[37]

A solution was prepared by mixing 10 ml of 10% aq. $AgNO_3$ and 10 ml of 10% aq. NaOH , dissolving the resultant precipitate of silver oxide in the minimum volume of ammonia and purging the solution with nitrogen prior to the introduction of (14) (198 mg; 0.99×10^{-3} mole).

The solution was stirred magnetically under a positive pressure of nitrogen on an ice-bath for 4h, then for a further 22h at room temperature. A silver mirror formed on the walls of the flask during the course of the reaction.

The solution was then poured in 5M HCl and extracted into ether (2 x 20 ml). The precipitate of silver chloride was filtered off and the ethereal layer shaken with bicarbonate, washed with water and dried. Evaporation of solvent left a yellow solid (0.25g; mp 172-5^{o}), identified from the following data as 2-hydroxy-2-methyl naphtho (2,1-b) furan-1-(2H) - one (17).

PMR: 1.68, singlet, 3H, CH_3; 4.1, broad, 1H, vanishes on D_2O shake, OH; 6.8 - 8.0, multiplet, 5H, aromatic H_4 - H_8; 8.3 (centred on), doublet, signals broadened by finer coupling, J = 8.5Hz, 1H, H_8.

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IR: 3290 (s), OH; 1673 (s), C = O; 1628, 1575 (both m), aromatic C = C; 817 (s, sp), 2 adjacent aromatic H; 758 (s), 4 adjacent aromatic H.

MS: m/e 214.

UV: 361 (3.16), 312 (3.39).

$C_{13}H_{10}O_3$ requires: C 72.89 H 4.71
found: C 72.82 H 4.79

<u>Decarboxylation of 2-methylnaphtho (2,1-b) furan-1-carboxylic acid (18).</u>[28a]

0.226g (10^{-3} mole) of the acid (18) was dissolved in 2 ml of redistilled quinoline (colourless). To this was added 0.015g of copper-bronze powder. The solution became black, and was refluxed for 0.5h, cooled and 10 ml of ether added. A black solid (copper) was removed by filtration, the residual ether concentrated and the resultant product (187 mg) purified by thin layer chromatography (two plates, mobile phase 60 - 80 petrol). This gave 140 mg (0.77×10^{-3} mole; 77%) of a white solid mp 55 - 6°, whose spectral characteristics were identical in all respects to 2-methylnaphtho (2,1-b) furan (16) obtained from dehydration of (14). Mixed melting point showed no depression.

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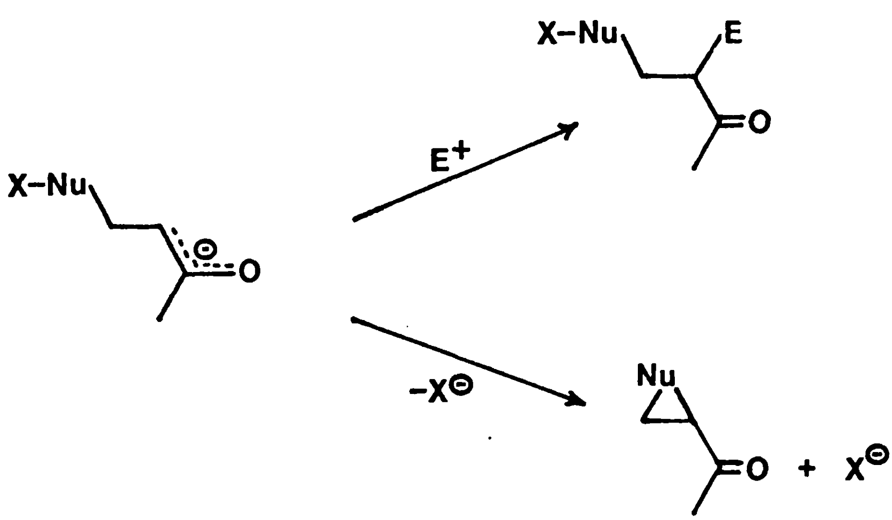
INTRODUCTION

The Michael reaction is one of the more widely used reactions in organic chemistry. First introduced in 1887 by Michael[1], it has, in the course of time, had its scope and synthetic utility broadened considerably and now includes a wide range of donor, substrate and catalyst combinations[2]. This diversity makes any general classification difficult, but in this thesis a Michael reaction will be considered as the formation of a bond between the nucleophilic atom of a donor molecule and a multiple bond in a substrate usually containing functionality which can stabilise the intermediate anion:

This anion can then suffer two fates. It can be captured by a suitable electrophile $\overset{+}{E}$ (usually a proton) or it can cyclise with expulsion of a group bound to the nucleophilic atom:

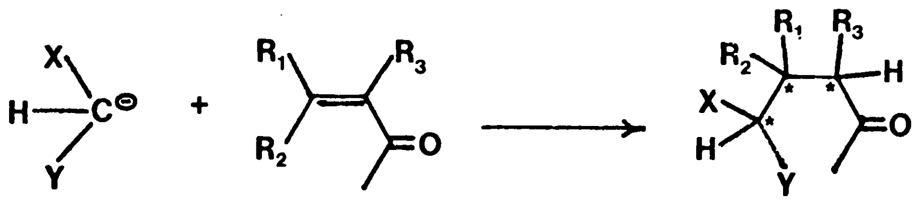


Epoxidation of α,β unsaturated ketones with alkaline hydrogen peroxide can be thought of as a Michael addition, and will be considered as such in this thesis. It is an example of the latter process.

The stereochemical aspects of Michael additions have not been so exhaustively studied. For the purposes of this discussion, two main types of stereochemical situation may be distinguished, depending on whether or not the substrate contains an element of asymmetry.

Substrates lacking asymmetry.

There are at least three points at which asymmetry (i.e. d,l centres) can arise in the adduct in the course of a Michael addition between achiral reagents: the anionic atom of the donor and the α and β positions of the substrate:



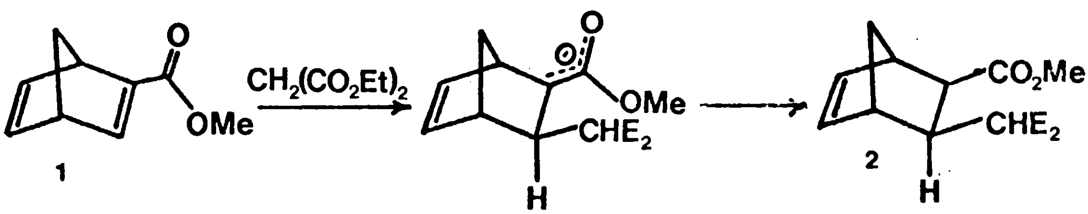
In the case of epoxidation, however, only the stereochemistry of the α and β positions of the substrate is problematical and in systems such as six membered rings where free rotation about the $\alpha - \beta$ bond is not possible, the stereochemistry at the β position will define the stereochemistry at the α position.

Substrates possessing asymmetry.

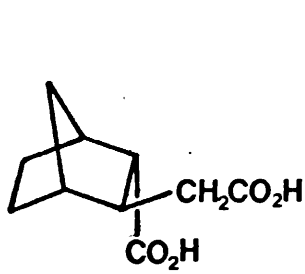
If the two faces of the alkene are distinct, addition may occur to either, and a new type of stereoselectivity is possible in Michael additions and their subclass, epoxidations.

There are relatively few cases where this problem has been studied, but of these, steric hindrance to approach is commonly offered as an explanation of face-selectivity. In others conformational factors seem to be at work, but in many cases no explanation is offered. Some explanations appear incapable of resolving all the experimental observations. Assignment of the stereochemistry of the product(s) of many reactions of this type frequently rests on little more than intelligent hypothesising, unsupported by direct evidence on the structure in question.

One of the simplest systems of this type was studied by Alder and Wirtz[3], the addition of diethyl malonate and two other donors to methyl bicyclo (2,2.1) hepta-2,5-diene-2-carboxylate (1):



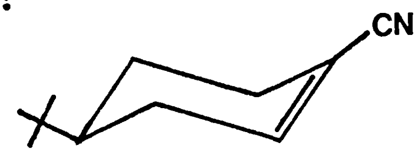
The adduct was reported (in all three cases) to have the exo-cis configuration shown, meaning that the nucleophile approached exclusively from the same face as the methano-bridge. The stereochemistry was established by hydrolysis, hydrogenation and selective decarboxylation of 2 to yield the diacid 3 :



3

A compound of gross structure 3 can exist in four stereo-isomeric forms. To establish which of these 3 was, all four were synthesised by the oxidative cleavage of exo and endo dicyclopentadiene. Although no explanation was offered, this result can probably be explained by steric hindrance to approach from the ethanato bridge.

A different system was studied by Abramovitch and Struble[4], the addition of diethyl malonate to 4-t-butyl-1-cyano-cyclohexene (4):



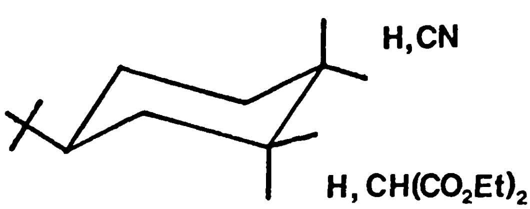
4

This compound has an asymmetric centre on C_4 and exists in the chair-like conformation shown, with the bulky t-butyl group Ψ- equatorial.

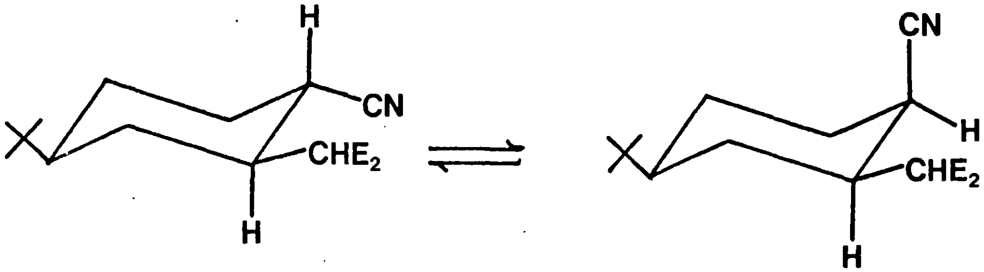
The results obtained for this system were shown to be heavily dependent on conditions, but the addition in refluxing ethanol with sodium ethoxide as catalyst allowed a mechanistic hypothesis to be discerned. The reaction went in 74% yield to give three products:

$$4 \longrightarrow A \;\; 8\% + B \;\; 11\% + C \;\; 81\%$$

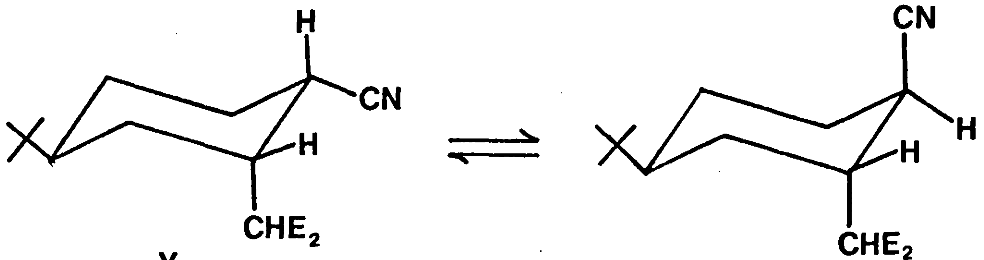
The relative amount of each was established by GLC. The gross structures of B and C were shown by spectral and chemical means to correspond to the expected Michael adducts of malonate on 4 :



B and C were shown to be interconvertible epimers, a process which can only involve C_1, bearing the cyano group. From this it was inferred that they must be one of the pairs:



W X



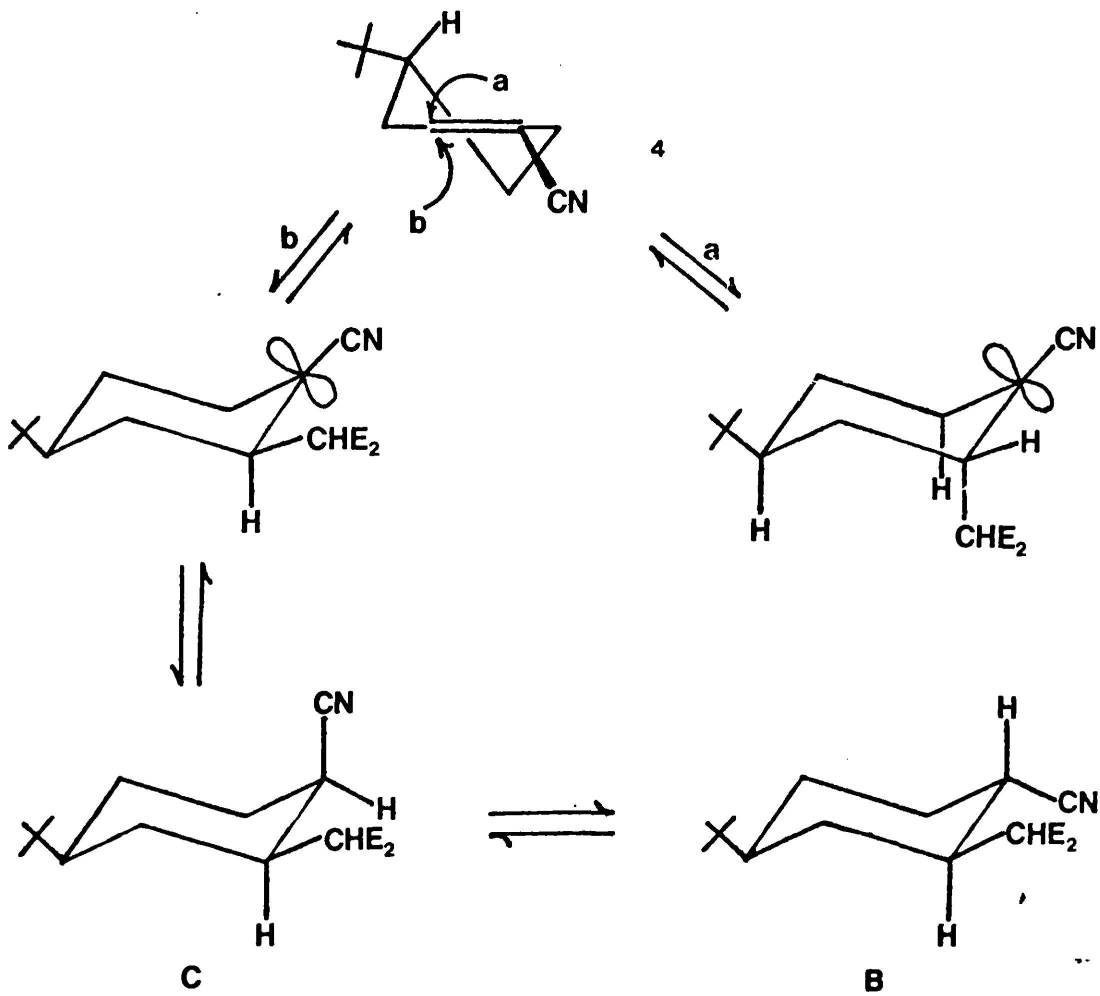
Y Z

The malonate residue was assigned the equatorial conformation from the calculated dipole moment of each of these isomers. The moment calculated for W , X and Y was 4.96D, while that of Z was 1.47D. The experimentally measured values for B and C were 4.95D and 4.17D respectively. Therefore B and C are W or X . Thus product formation arises almost solely from malonate attack on the same face as the t-butyl group.

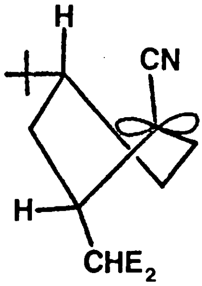
In this case, conformational factors governing the relative stability of the two possible transition states appear to offer an explanation.

Initial approach of the malonate must be perpendicular to the plane of the double bond. Models show little preference for attack on the same face as the t-butyl group. In this solvent (EtOH), malonate is thought to be strongly solvated and (hence) a relatively weak nucleophile. Thus the transition state should be product-like.

Attack from the same face as the t-butyl group leads to equatorial malonate, while attack from the opposite face gives rise to axial malonate. If the transition state is indeed product-like, then the 1,3 interaction of a bulky malonate residue present only in the transition state arising from axial attack, should raise its activation energy compared to the activation energy of the transition state arising from equatorial attack. The following scheme illustrates this line of reasoning:

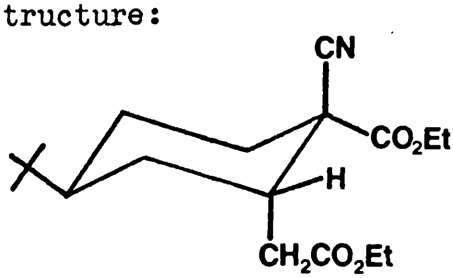


It might be objected that the product directly arising from equatorial attack would be in the twist-boat conformation

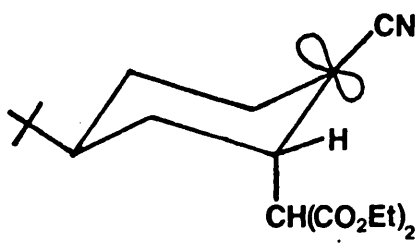


and as such of high energy. Whether it would be higher or lower than the chair conformation arising from axial attack by a bulky nucleophile and higher than the chair conformation arising from axial attack by a small nucleophile, seems problematical.

The minor product of the reaction A was shown by spectral methods and simple, unimpeachable chemical transformations to have the structure:

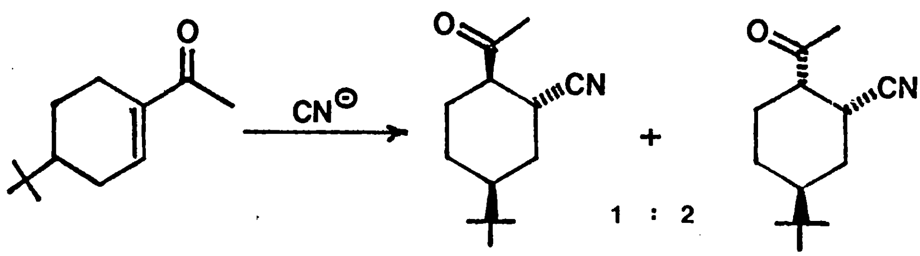


In other words A is formed via axial attack of the malonate on 4 . The intermediate arising from axial attack



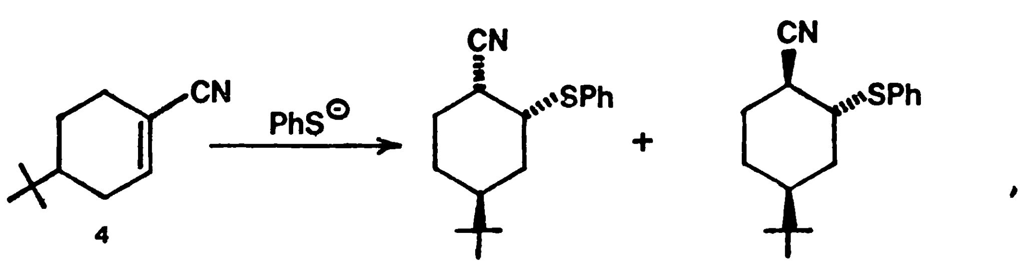
is thought to have the ester groups of the malonate residue oriented away from the cyclohexane ring, and in this position they are thought to be peculiarly well positioned for the development of the four-membered transition state required for migration of a carbethoxyl group from the malonate to C_1.

Preference for equatorial attack by malonate was confirmed in a subsequent paper[5] where the substrate was 1-acetyl-4-t-butyl-cyclohex-1-ene. This substrate has also been studied by Alexander and Jackson[6], who examined its reaction with calcium and potassium cyanides and found exclusive axial addition of cyanide:



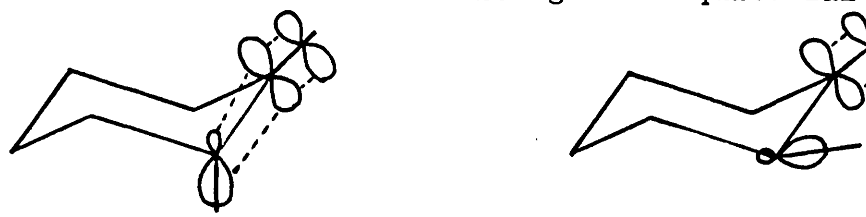
The two products were separated by GLC and the coupling constants $J_{1,2}$ found to be 1.5 Hz and 4 Hz for the major and minor components respectively. These values show that the protons can not be trans-diaxial, and hence cyanide must occupy an axial position.

These facts clearly show that the course of addition is dependent on the nucleophile as well as the substrate. Another paper, by Abramovitch et al[7] shows that addition of thiophenoxide to 4-t-butyl-1-cyano-cyclohex-1-ene (4) occurs to give two products, both with axial thiophenoxide:



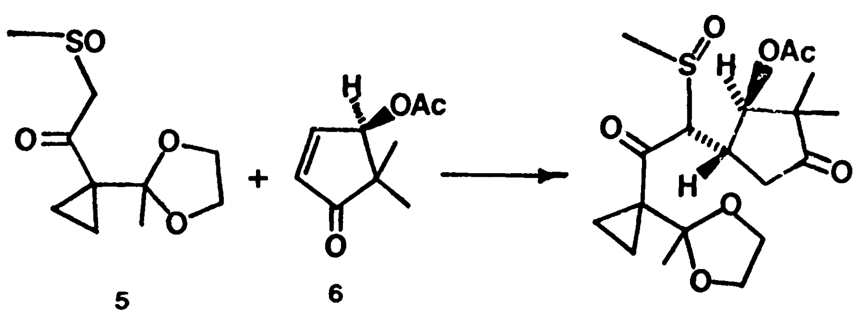
4

NMR couplings again were used to establish configuration. This latter paper suggests two reasons for these results. Firstly, nucleophiles such as cyanide and thiophenoxide are small compared to malonate, and so the 1,3 diaxial interation of a product-like transition state should be much less significant. Secondly, axial attack leads to a situation in the transition state in which the developing σ bond can overlap with the π system much more efficiently than in the transition state arising from equatorial attack:



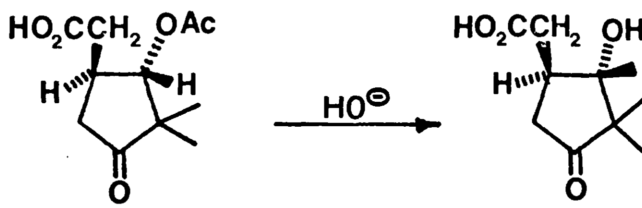
Other examples of axial preference by small nucleophiles are known[8,9].

Ichihara et al[10], in the course of their synthetic approach to illudin M noticed that the β keto sulphoxide 5 underwent Michael addition with 4-acetoxy-5,5-dimethyl-cyclopent-2-en-1-one (6) to yield only one adduct in 58% yield:



Trans stereochemistry was assigned tentatively from the coupling constant (J = 8Hz) of the proton α to the acetoxy group at 4.85 τ. This was taken to imply that the protons were both quasi-axial and trans as shown.

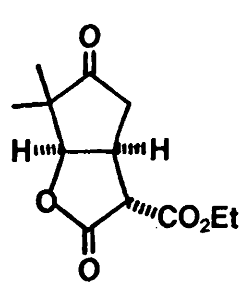
This finding stimulated these workers to investigate the stereochemical course of Michael additions to substituted cyclopentenones[11]. The addition of benzyl malonate to 6 in ethanol at room temperature (30 min.) gave only one adduct in 61% yield. The coupling constant (9Hz) of the proton α to the acetoxy group again suggested that the stereochemistry of approach was trans to the acetate group. Removal of the benzyl groups (Pd/C) followed by selective decarboxylation (160°) gave the acetoxy compound:



7

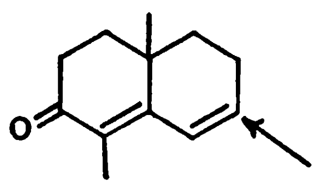
Hydrolysis of the acetate group to yield 7 should have involved spontaneous lactonisation under these conditions[12] if addition had been cis. No γ-lactone band was observed in the IR of the product, thus confirming a trans relationship. Similar findings were noted for 6 in benzene and ethanol with diethyl malonate, and the 4-hydroxy compound also gave a trans adduct under these conditions.

Reaction of 6 with 2.0 equivalents of DEM/NaOEt in ethanol at 60°, however, gave the cis lactone ester as the main product,



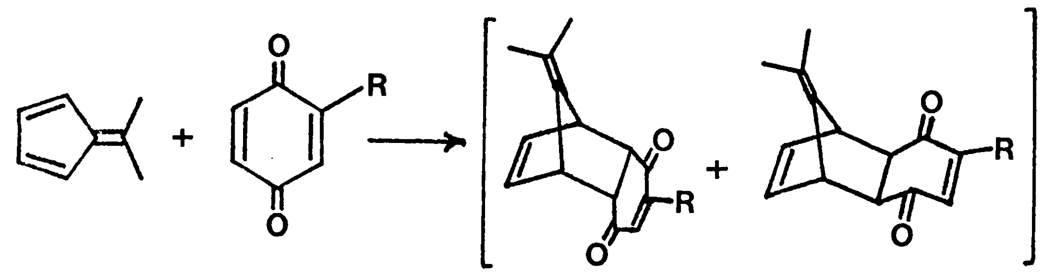
and under these more rigorous conditions the trans adducts of both 6 and its 4-hydroxy analogue underwent equilibration to the cis lactone ester. Since the Michael addition is reversible, the product is trapped as the thermodynamically more stable lactone under conditions which are sufficiently vigorous to allow the activation energy barrier leading to this product to be surmounted. The trans adducts are thus kinetic products, more easily formed (presumably) because of the steric interference that acetoxy or hydroxy groups offer to the nucleophile approaching from the same face.

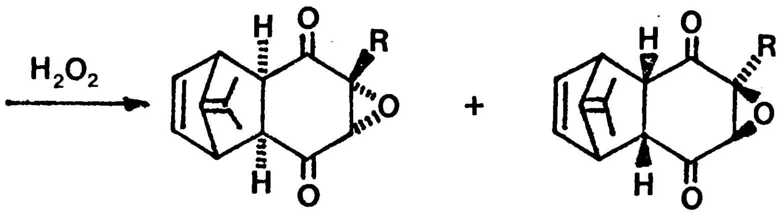
Another reaction which bears a superficial resemblance to the above is the report by Yanagita et al [13] that the addition of DEM to 3-keto-4,9-dimethyl-$\Delta^{4,5}$-hexahydronaphthalene at the position arrowed



gave as the predominant product an adduct with the malonate residue trans to the 10-methyl group under mild conditions, but a thermodynamically more stable cis adduct when the reaction mixture was refluxed. Equilibration of the trans adduct to the cis was also noted when the former was refluxed. The nature of the steric (or other) factors giving rise to trans adducts under mild conditions appear somewhat obscure for this system and the author did not offer any explanation.

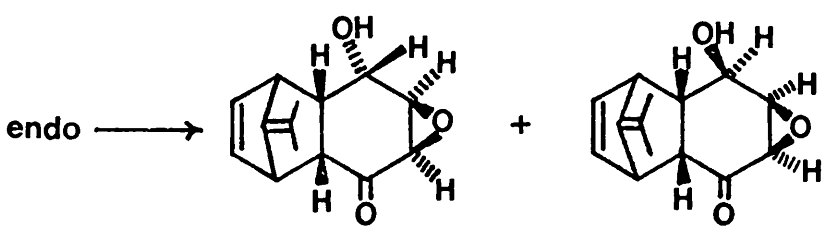
Ichihara et al [14], found (not unexpectedly) that the epoxidation of Diels-Alder products formed from the reaction of dimethyl-fulvene with quinones proceeded stereoselectively:





exo endo

The Diels-Alder adducts were not isolated, but epoxidised in situ, and only one epoxide was isolated for each. Consideration of their geometry shows one face to be highly favoured, while the other is sterically hindered. This conclusion was confirmed by the reduction of the epoxides to give ketols:



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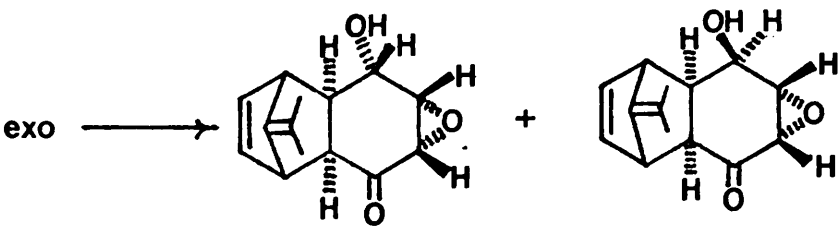
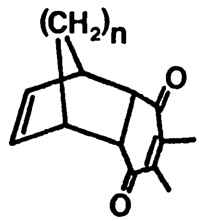


10 11

9 was assumed[15] to have the epoxy oxygen in an axial conformation. The coupling constant (9Hz) of H_{8a} was taken as proof of a trans diaxial relationship between H_{8a} and the C<u>H</u> of the secondary alcohol.

The same comments apply to 10 which also shows J=9Hz on H_{8a}. 11 but not 10 shows on high dilution a strong hydrogen bond (3550 cm^{-1}) between the hydroxyl group and the C_9 double bond. These observations substantiate what might have been guessed on a consideration of the geometry alone. Further confirmatory evidence was obtained on the retro Diels-Alder products of these ketols.

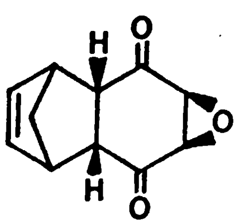
Similarly, O'Brien and Gates[16] epoxidised the Diels-Alder adducts obtained from cyclopenta and hexadienes with p-benzoquinones:



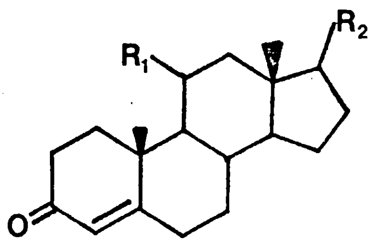
n=1,2

Only endo adducts were formed.

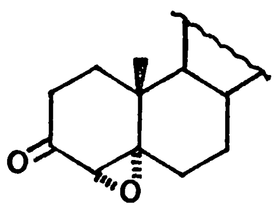
They found that only one epoxide resulted, both with alkaline hydrogen peroxide and t-butyl hydroperoxide. Little direct evidence was offered for the structure of the epoxide, but in view of the steric situation, it does not seem unreasonable to suppose that the hydroperoxy anion will approach from the least hindered face, giving:



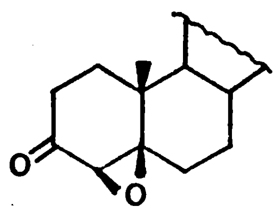
Henbest and Jackson[17] studied the effect of remote functionality on the epoxidation of 3-keto-Δ^4-steroids:



Epoxidation was conducted with hydrogen peroxide/sodium hydroxide in methanol at 0^{o}. Up to 30% of the α-epoxide was formed when the steroid contained a polar group at C_{17}



5α



5β

and beyond. Polar substituents at C_{11} had an even stronger directive effect on the steric course of epoxidation. In the absence of polar functionality β-epoxides are the sole product. The following table summarises these findings:

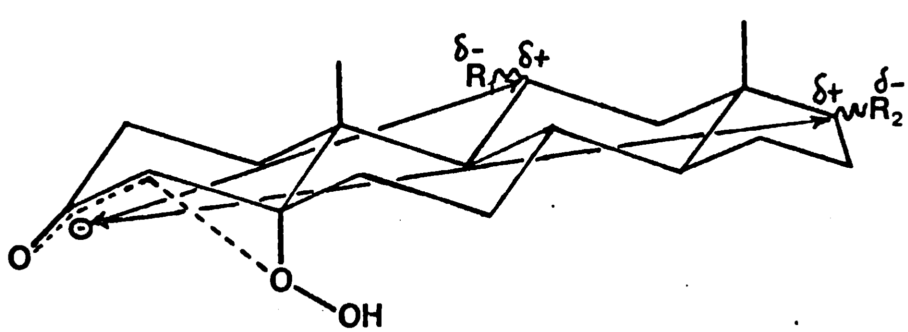
a) R_1 = H

R_2	% 5α	R_2	% 5α	R_2	% 5α
H	0	β-COMe	26	oxo	30
β-C_8H_{17}	0	α-OH	27	β-OH	31
β-CH(Me)$(CH_2)_3$OH	11	β-CN	28	β-$CO_2^{\ominus}$	60-65
α-Br	26	β-CO_2Me	30		

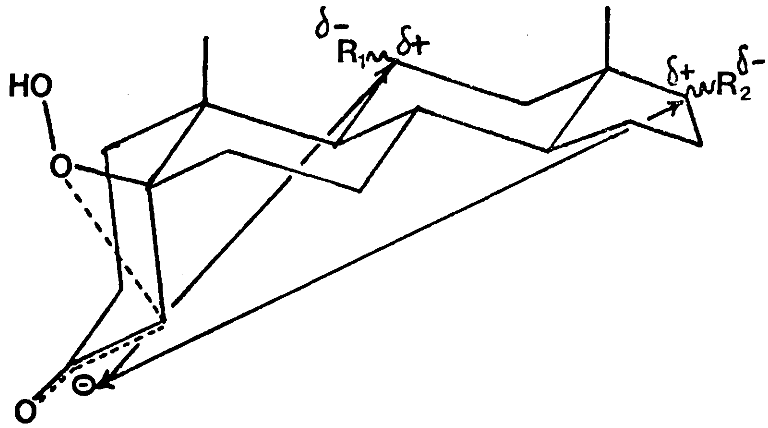
b) Variation in R_1 and R_2

R_1	R_2	% 5α
α-OH	β-OH	0
α-OH	α-Me	0
α-OH	COMe	25
β-OH	oxo	51
oxo	oxo	86

These results were rationalised as follows. Two possible enolate anions can be formed by addition of hydroperoxide anion to the enone system. The hydroperoxyenolate which leads to the α-epoxide can have a line drawn between the negative charge on the enolate and the positive end of the dipole on C_{11} or C_{17} which passes through the steroid skeleton, a region of low dielectric constant which allows efficient interaction between the charges and hence stabilises the transition state leading to α-epoxide. In the hydroperoxy enolate which leads to the β-epoxide, such a line would pass through a region of high dielectric strength occupied by solvent molecules, and hence any stabilisation of the transition state would be minimised or eliminated:



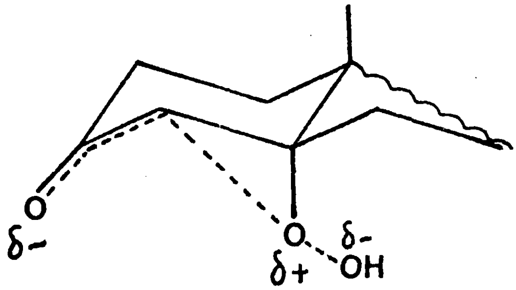
5α



5β

At first sight this theory may sound plausible, but a number of questions remain. Firstly, it assumes that the rate determining step in the epoxidation is closure of the epoxide ring, in other words that closure requires a higher activation barrier to be surmounted than has to be surmounted for addition of the hydroperoxy anion to the enone. Kinetic studies[18,19] of enone epoxidations (including steroids) have shown that addition, and not closure, is the slow step. Henbest's steroids may be exceptions to this rule, but he produces no evidence to show that they are and so this assumption remains unproven.

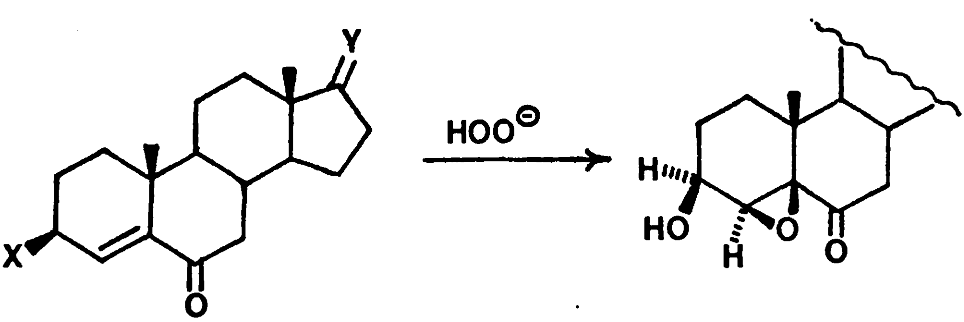
Second, this theory hardly seems self-consistent. The postulated charge-dipole interaction must stabilise the (ring closure) transition state between the α-hydroperoxy enolate and the α-epoxide if it is to explain the formation of α-epoxide. Yet this charge-dipole interaction is also present in the α-hydroperoxy enolate, and must be stabilising it, too, probably to an even greater extent than the transition state, since there the negative charge on the enolate must be diminished to some extent by the hydroxide ion leaving group:



Thus, a consideration of charge-dipole interactions could well infer that α-epoxide formation is less likely, by lowering the energy of the "ground state" hydroperoxy enolate even more than it lowers the energy of the transition state.

Henbest himself admits that the observation that 65% α-epoxide is formed when $R_2 = \beta\ CO_2^{\ominus}$ cannot be explained by his "charge-dipole" theory, and he fails even to offer an explanation for the formation only of β -epoxide in the absence of polar groups.

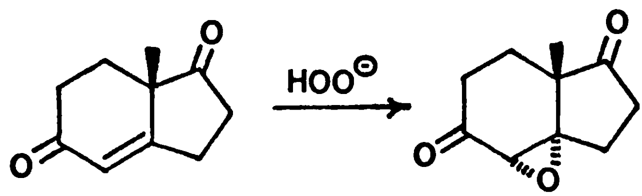
The exclusive formation of β -epoxide was noted also by Baldwin and Hanson[20] when they epoxidised 3β -acetoxy androst-4-ene-6,17-dione (12; X = OAc, Y = O):



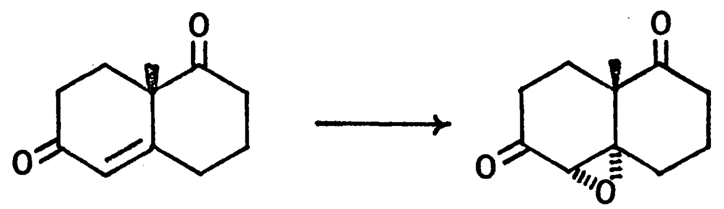
12

β -configuration in the epoxide was inferred from the coupling of H_4, $J_{3,4}$ = 2-3Hz. They suggest that the ring closure step is product determining, the enolate supposedly being capable of better π-overlap with the oxygen of a β -hydroperoxy group than with the α. Inspection of models seems to support this assertion. Models do not appear to suggest this explanation is valid in Henbest's examples. Baldwin did show that the presence of a (β) hydroxyl group on C_3 substantially enhances the rate of epoxidation compared with the rate in its absence, attributing this to hydrogen bonding with the hydroperoxy group. Since β -epoxide only is produced in the absence of the β hydroxyl group this group cannot be held responsible for the production of β -epoxide in these examples.

The diversity of possible mechanisms to explain stereospecific epoxidations is further illustrated in a communication by Trost and Salzmann[21] who showed that epoxidation of 7,7a-dihydro-7a-β -methyl-indane-1,5-(6H)-dione with 30% aq. hydrogen peroxide and 4N NaOH in methanol gave 94% yield of a single epoxy ketone, to which the trans stereochemistry was assigned:

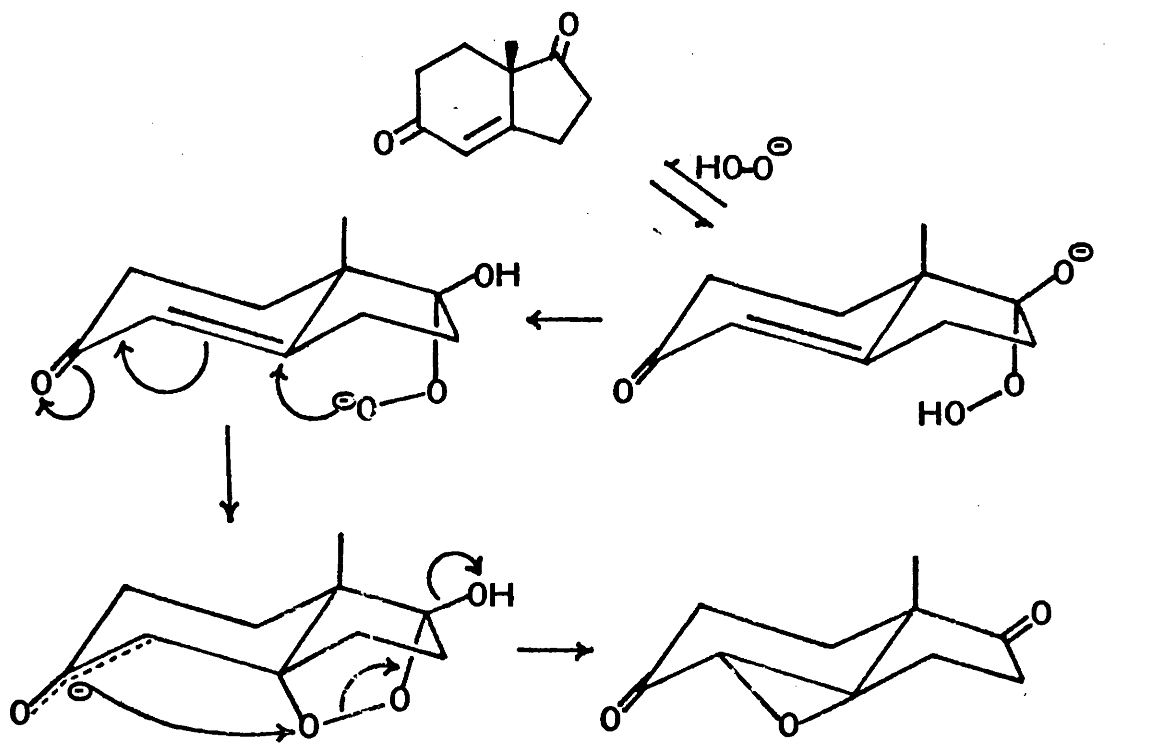


An analogous reaction with Wieland-Miescher ketone gave an 89% yield of trans epoxide:

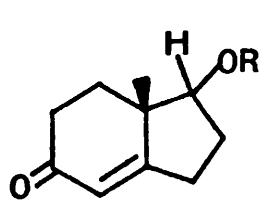


Steroid 4-en-3-ones give mainly the β -epoxide but an 11,17 diketo steroid 4-en-3-one gave 86% α -epoxide[17].

These results were rationalised by the following scheme:



An addition of hydroperoxide anion is postulated to take place on to the least hindered face of the unconjugated ketone, hence defining the stereochemistry of the epoxide. This explanation was supported by the observation that the systems

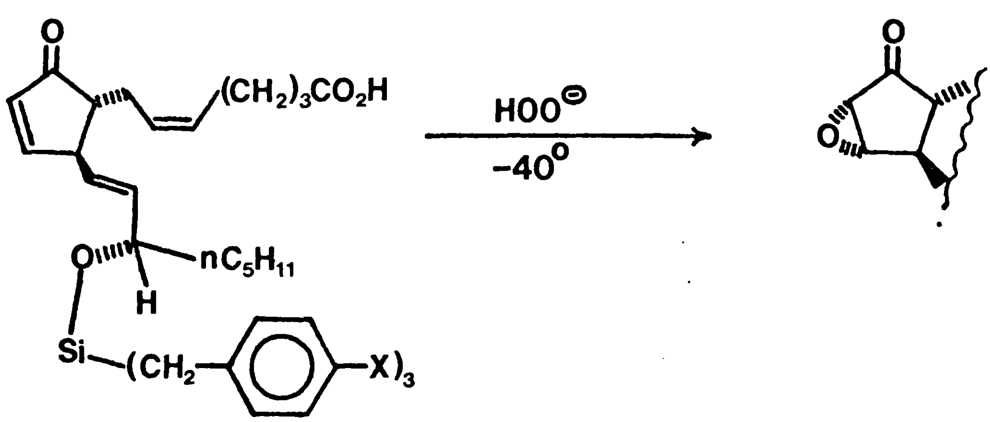


R=H,THP

failed to epoxidise under the same conditions, and gave only recovered starting material.

This paper casts serious doubt on the stereochemical assignments in earlier publications on analogous systems.[22a,b]

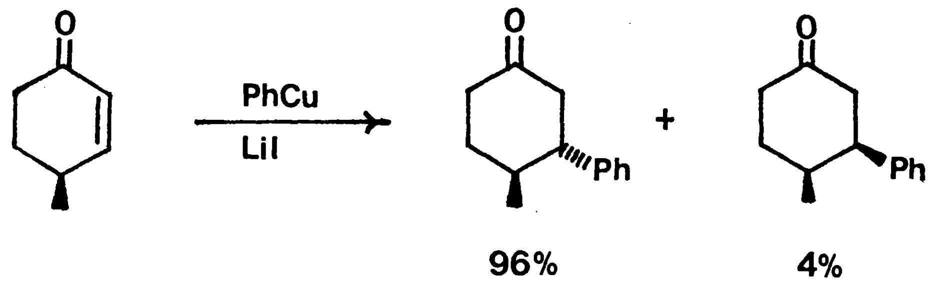
Stereospecific Michael additions have been achieved also as the result of deliberate stratagem. Thus Corey and Ensley[23] set out to achieve stereospecific α-epoxidation of the 10,11 double bond in Prostaglandin A_2. In so doing, they were extending earlier work which had produced a stereoselective route to A-type prostaglandins. Stereospecific α-epoxidation of the 10,11 double bond would transform these endeavours into a general synthesis of all primary prostaglandins. The approach which they adopted was very simply to shield the β face of the cyclopentenone ring by substituting the 15-hydroxyl group with a suitably bulky group, and the 15-tri-benzylsilyl ether and 15-tri-p-xylylsilyl ether of PGA_2 were prepared for this purpose.



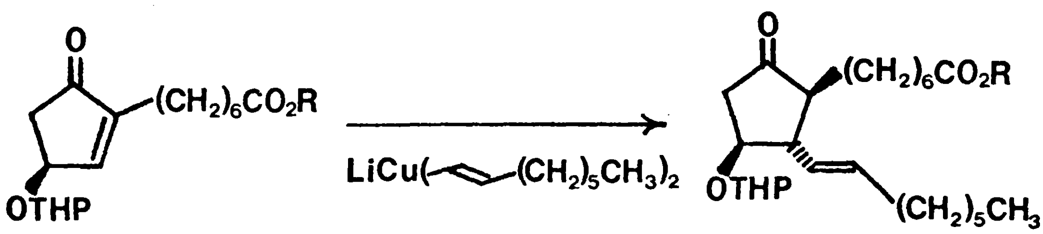
X=H,CH$_3$

The tribenzylsilyl ether gave 87.5% α-epoxide and 12.5% β, while the tri-p-xylyl ether gave 94% α and 6% β.

The addition of organocuprate complexes to enones is an example of a Michael-type process which can lead to high stereospecificity. Thus Luong-Thi and Riviere[24] showed that phenyl copper, generated by the addition of phenyl lithium to CuI (unspecified proportions), reacted with 4-methylcyclohexenone to give 100% 1,4 addition, with a trans/cis ratio of 24:



Mechanism was not investigated in detail, but in another paper, Sih etal[25] argue that the addition of the species produced from 2 equivalents of a vinyl lithium and 1 equivalent of a trialkyl phosphine copper (I) iodide complex, onto a cyclopentenone:



should go trans to the OTHP function on steric grounds alone. This prediction was confirmed by experiment. The species isolated after hydrolysis of the THP ether was 15 deoxy PGE_1 ethyl ester in 60% yield.

In considering the addition of these alkyl and aryl copper species to enones, it is well to remember that the mechanism may not correspond to the simple Michael model outlined previously. One electron transfers have been postulated[26] to be involved in these processes.

In conclusion, it is clear that selectivity between the two possible faces of an enone system is evidenced in many different Michael additions, but the reasons for this selectivity appear to depend on different factors in each case. No underlying unity is evident in the examples known.

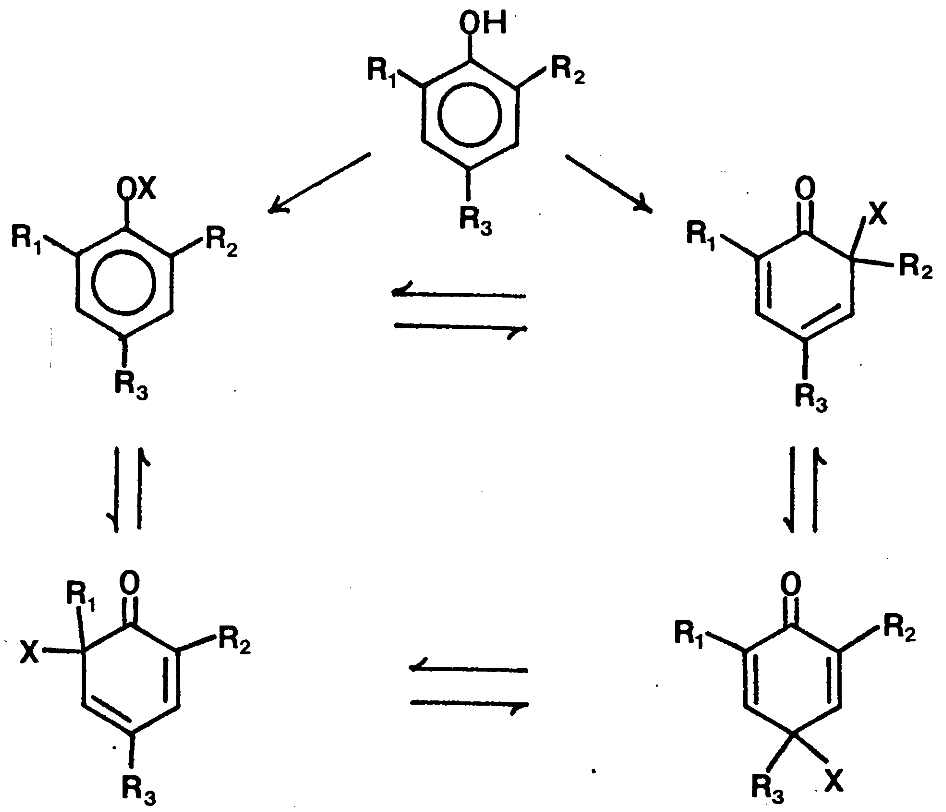
Cyclohexadienones from phenols.

The enones we have used are 6-alkyl-6-hydroxy-cyclohexadienones, and synthetic routes to these systems are discussed here.

Almost all syntheses of dienones of this type can be regarded as the interaction of the phenol with an electrophilic agent of the type:

$$\overset{\delta+}{X}-\overset{\delta-}{Y}$$

X becomes bonded to the phenol at either the ortho or para positions, or directly to the phenol oxygen, and YH is released:



The fate of these intermediates is laborious to describe but simple to comprehend. If X is a suitable group, then the cyclohexadienones may be isolable. More often X is displaced by attack of a solvent molecule, a process which could be effected at the 2, 4 or 6 positions in all three cyclohexadienones shown as well as from the O-X species. Hence three products are capable of formation. Should any of the R groups be H, then disubstitution is possible. Very often quinones are formed, and dimerisation reactions among the cyclohexadienones are common. In short, many products are liable to be formed unpredictably in reactions of this type, and hence their synthetic value is limited[27].

<u>1-substituted-2-naphthols as substrates.</u>

1-substituted-2-naphthols produce naphthalenones which are relatively stable and do not undergo dimerisation. The 1-position is far more reactive to electrophiles than position 3, and so only one of the two possible "ortho" sites is likely to be attacked. The "para" position

(10 in naphthalene numbering) is blocked, and hence 1-substituted-2-naphthols are good synthetic substrates for electrophilic reactions of this type.

Periodates have the serious drawback of cleaving α-ketols, so attack 6-hydroxy-cyclohexadienones.

Thallium trinitrate trihydrate (TTN, $Tl(NO_3)_3.3H_2O$) is a comparatively new oxidising agent in organic chemistry, with an impressive list of transformations to its credit, and has been employed successfully in these laboratories for the synthesis of naphthalenones.

Selective ortho hydroxylation of phenols to give cyclohexadienones can be achieved using diphenyl seleninic anhydride if the phenol is first converted into its phenoxide ion with sodium hydride in glyme.

Of the methods which I used, lead tetra-acetate was probably the most useful.

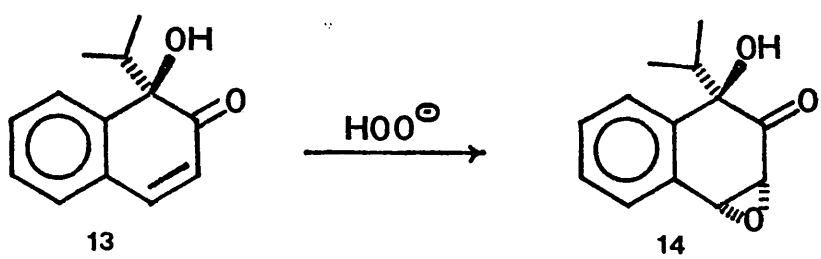
Conversion of one type of cyclohexadienone into another is also possible. Thus 1-methyl-1-nitro-2(1H) naphthalenone was converted into the 1-hydroxy compound by displacement of the nitro group by water. 1-Bromo naphthalenones are another system which can be formed by bromination of 1-substituted-2-naphthols. Interconversions tend not to be site specific, giving a lot of 6-substitution on the naphthalene nucleus as well as naphthalenone.

The following table gives a brief summary of the principal methods which have been employed to synthesise cyclohexadienones.

X-Y	Compound	Reference
IO_4^-	Periodates	28, 29
$Pb(OAc)_4$	Lead tetraacetate	29c
$Tl(NO_3)_3 \cdot 3H_2O$	Thallium trinitrate	30
$(PhCO)_2O_2$	Dibenzoyl peroxide	31
$(PhSeO)_2O$	Diphenylseleninic anhydride.	32
CrO_3	Chromium trioxide	33
Br_2	Bromine	34
NO_2^+	Nitronium ion	34

RESULTS AND DISCUSSION.

In 1968 the stereospecific formation of a single epoxide (90% yield) from the interaction of 1-hydroxy-1-isopropyl-2 (1H) naphthalenone (13) with aqueous ethanolic sodium carbonate and hydrogen peroxide was reported[35], the stereochemistry of this epoxide being assigned as trans 1-hydroxy-1-isopropyl -2(1H) naphthalenone-3,4-epoxide (14). For the purposes of this thesis, the term trans will denote the stereochemical relationship between the hydroxyl group and the epoxide oxygen, with respect to the (almost planar) bicyclic nucleus. Hence:



The epoxidation of 13 under the original conditions and with slight modifications (see experimental section) was undertaken. In both cases an almost quantitative yield of one epoxide was obtained, identical in all spectral characteristics to the previously obtained material. The modified technique gave, however, material of appreciably higher melting point, 72-3°, as compared to 62-3° originally reported[36].

Alkaline epoxidation (Na_2CO_3/H_2O_2) of 1-acetoxy-1-isopropyl-2 (1H) naphthalenone (15) has been reported[36] to proceed in aqueous ethanol to give trans 1-acetoxy-1-isopropyl-2(1H) naphthalenone -3,4-epoxide (16) in 89% yield. Hydrolysis of the acetate function of (16) gave an hydroxy-epoxide whose physical characteristics (mp, spectra) were identical to trans 1-hydroxy-1-isopropyl-2(1H) naphthalenone-3,4-epoxide(14). From this it was inferred that epoxidation of 15 must give the trans epoxide only.

In my hands, epoxidation of 15 at 60° for 6 hours (the original conditions) gave a 33% yield of trans-1-acetoxy-1-isopropyl-2 (1H) naphthalenone-3,4-epoxide (16) and 31% of trans 1-hydroxy-1-isopropyl-2 (1H) naphthalenone-3,4-epoxide (14).

Conducting the reaction at room temperature (with all other conditions identical) did not greatly increase the proportion of acetoxy epoxide formed. After 48h a 36% yield of the trans acetoxy epoxide 16 was obtained, along with 43% of trans hydroxy epoxide 14. These findings suggest that the relative rates of epoxidation and of acetate hydrolysis are comparable, and are not very sensitive to temperature. Whether the acetate function is lost before or after epoxidation remains unclear. Hydrolysis of the acetoxy epoxide formed in both these reactions did give material identical to trans hydroxy epoxide 14, confirming that epoxidation of 15 does occur in a trans manner.

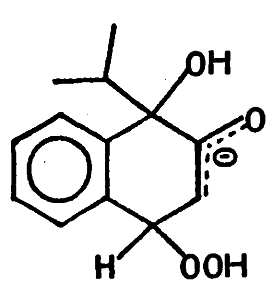
The significance of the original observations (and the need for confirmation) becomes evident when the mechanism of epoxidation is considered. Epoxidation of enone-like systems under alkaline conditions is generally held to proceed in two steps: initial (slow) addition of a hydroperoxy anion onto the β carbon followed by a (fast) ring-closure step, involving attack by the intermediate enolate on the oxygen atom bonded to the β-carbon[18,19]. Various stereochemical outcomes are possible in this process, and a number of the more common have been outlined in the Introduction. However, no case that I could find in the literature compares with the original observations of Carnduff and Leppard mentioned above and (substantially) confirmed.

It is clear from any consideration of the epoxidation of naphthalenones that the results in respect of 13 and 15 can only be explained in one of two ways.

a) approach of the hydroperoxy anion to the β carbon is very heavily favoured for the face of the naphthalenone on which the isopropyl group lies.

b) and/or ring closure is only possible when the hydroperoxy group is on the same face of the naphthalenone as the isopropyl group.

Neither of these possibilities seems to lend itself to a very persuasive explanation of the observations. The only asymmetric site in compounds 13 and 15 is C_1, and therefore this site must be responsible (at some level) for the observed preference for trans epoxide formation. Steric inhibition to approach cannot be an explanation, since the isopropyl group is considerably bulkier than hydroxyl. Moreover at such a distant site the difference between the bulk of an isopropyl group and the bulk of an hydroxyl group would hardly be expected to effect an outcome as dramatic as a 100% preference for one face over the other. Consideration (using models) of the limited conformational possibilities open to systems such as 13 and 15 only serves to confirm the latter assertion. Since approach of the hydroperoxy anion is trans to the hydroxyl group stabilisation by hydrogen bonding seems impossible. When models of the intermediate hydroperoxy enolate are considered,



the two possible isomers seem to be capable of adopting conformations of comparable stability (internal energy), and both would seem equally able to undergo ring closure.

The main body of work in this thesis is concerned with synthetic approaches to various 2 (1H) naphthalenones, with differing alkyl groups and differing oxygen containing groups at C_1. In synthesising and epoxidising such systems, we hoped to discover if the epoxidations of 13 and 15 were isolated occurrences or part of a wider class of stereospecific epoxidations. The standard literature methods of synthesising cyclohexadienone-type systems have been discussed in the Introduction.

Synthetic approaches to 2 (1H) naphthalenones.

1-Isopropyl-1-hydroxy-2 (1H) naphthalenone (13).

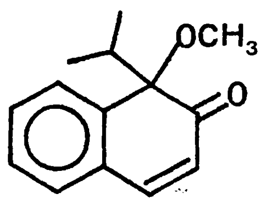
1-Isopropyl-1-hydroxy-2 (1H) naphthalenone had already been synthesised[36] from 1-isopropyl-1-hydroperoxy-2 (1H) naphthalenone (17) by reduction with iodide ion or with hydrogen over palladium/charcoal catalyst. Both of these methods were attempted, but in my hands were found to produce impurities whose removal proved difficult.

Reduction of 17 (which is readily obtained by aerial autoxidation of 1-isopropyl-2-naphthol) with dimethyl sulphide in alcohol proved entirely satisfactory, 13 emerging from the mother liquors of the reaction as white needles.

The unsuitability of acetates and TMS ethers for epoxidation studies became apparent when substantial or complete hydrolysis of these functions was observed (see later for details of TMS ether hydrolysis) during the course of epoxidations.

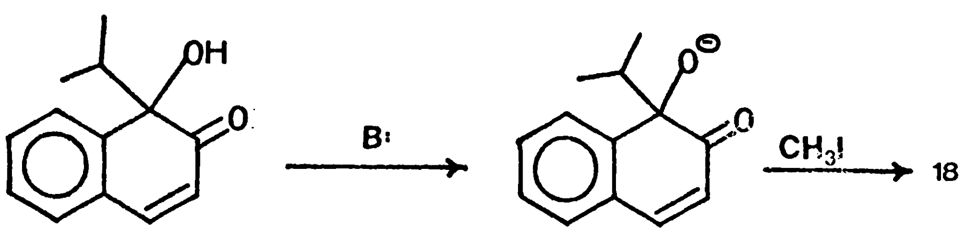
Clearly, a system stable to epoxidising conditions was required. 1-Alkoxy-1-alkyl-2 (1H) naphthalenones seemed obvious candidates. 1-Alkyl-1-hydroxy-2 (1H) naphthalenones also offered scope as they appeared stable to alkaline hydrogen peroxide, and a variety of alkyl (and aryl) groups could in principle be examined.

1-Isopropyl-1-methoxy-2 (1H) naphthalenone (18)



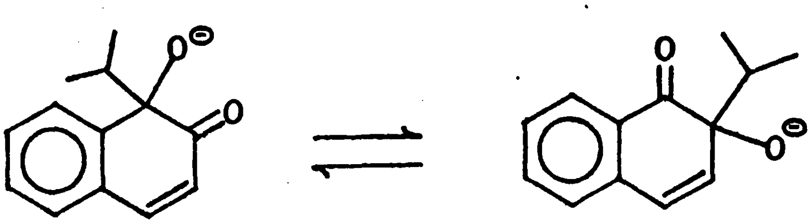
18

Synthetic efforts towards 18 centred on attempting to methylate the accessible structure 13. This approach involved the creation of the alkoxide ion 19 by the action of a strong base, followed by methylation:



13 19

A major complicating factor (both anticipated[36] and encountered) was α -ketol rearrangement of 19 . An equilibrium between 19 and 20 is established under strongly basic conditions:

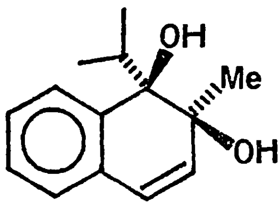


19 20

a) n-Butyl lithium/methyl iodide.

Attempts to generate anion 19 employing n-butyl lithium as base did not seem to be successful.

Reaction of 13 with n-butyl lithium in ether gave white crystals which resolved on chromatography into two bands. The 100 MHz spectrum of the main band seems to be consistent with a mixture of the diastereomeric diols:



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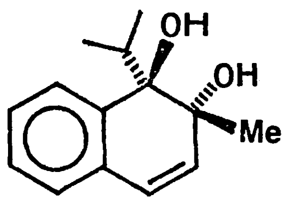

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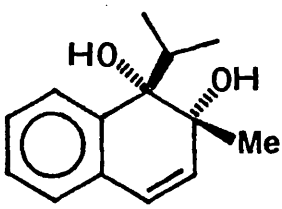
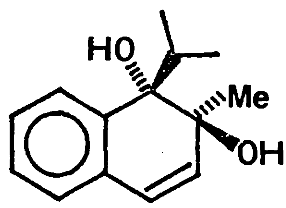




One diastereomer predominated by about 2:1.

The PMR spectrum ($CDCl_3$, 100 MHz) showed aromatic protons between 6.9 - 7.6. The major component of the mixture had an AM system, J = 10Hz at 6.42 and 5.58. Two isopropyl methine protons resonated at 2.5 and 2.25 as septets, J = 6.5 Hz. Integration proved difficult, but the signal at 2.25 seems to correspond to the major component. A singlet at 1.55 integrates well as 3 protons for the methyl group of the major component CH_3, and doublets, J = 6.5Hz, at 1.0 and 0.6 correspond to non-equivalent isopropyl methyl groups.

The minor component of this mixture exhibited an AB system at 6.15 and 5.9, J = 10Hz. The isopropyl methine proton is probably that resonating at 2.5. A singlet at 1.32 corresponds to a methyl group and non-equivalent isopropyl methyl groups appear as overlapping doublets, J = 6.5 Hz, at 0.9 and 0.85.

The presence of hydroxyl groups in the mixture was suggested by a broad peak overlying the methine septets. This peak vanished on D_2O shake, and a singlet corresponding to HOD appeared at 4.7.

The appearance of methyl groups in the product can only be explained by an exchange between n-butyl lithium and methyl iodide:

$$CH_3I + n\text{-}BuLi \rightleftharpoons CH_3Li + n\text{-}BuI$$

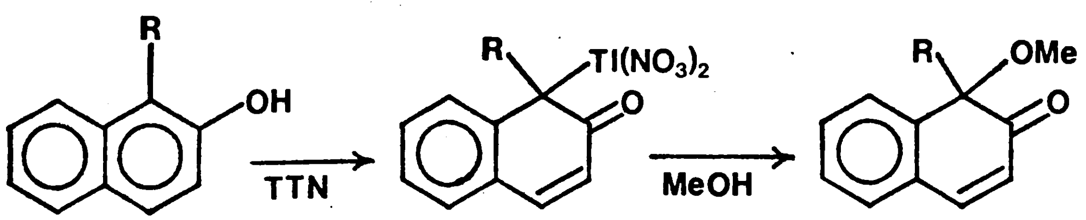
followed by reduction of the carbonyl group by methyl lithium. This type of exchange is well known[37]. The rate of methyl lithium attack on the carbonyl group is thus much greater than its rate of attack on the alcohol proton of 13 .

When sodium hydride in THF was employed as a base, O-methylated material was formed. However α-ketol rearrangement took place, and 18 proved impossible to separate from the other products. Lithium di-isopropylamide in THF only effected ketol rearrangement, no methylated material being formed.

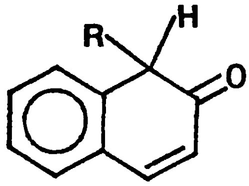
These failures led us to consider the possibility of blocking the carbonyl group, by converting it into a ketal, and hence prevent α-ketol rearrangement during the methylation step. Ketals are known to be stable to sodium hydride/methyl iodide alkylating conditions[38], and have been formed successfully with tertiary α-ketols[39].

The standard route to ketals, ethylene glycol in refluxing benzene with a trace of p-toluene-sulphonic acid, gave only a tar. The milder method of Anderson and Uh[40] employing ethylene glycol in acetonitrile with anhydrous oxalic acid at room temperature only succeeded in inducing α-ketol rearrangement, a 1:1 mixture of 13 and 2-hydroxy-2-isopropyl-1 (2H) naphthalenone (21) being formed.

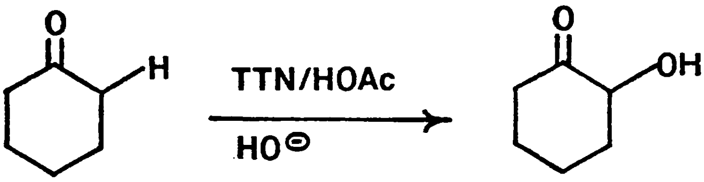
The possibility of synthesising a 1-alkyl-1-alkoxy 2 (1H) naphthalenone system directly from the 1-alkyl-2-naphthol was raised by the work of McKillop and Taylor[30] on Tl (III) oxidations. Among many other transformations, these workers have shown that thallium trinitrate trihydrate (TTN; $Tl(NO_3)_3 . 3H_2O$) can readily form a C-Tl bond with olefins. Electron rich olefins such as enols and enamines form such bonds especially easily. Subsequent cleavage of the C-Tl to form products is facile. TTN is used in a solvent containing sufficient trimethyl orthoformate to consume the three equivalents of water of crystallisation. This reaction produces methanol, and frequently more methanol is added. We hoped that reaction of TTN with 1-alkyl-2-naphthols would lead to 1-methoxy-1-alkyl-2 (1H) naphthalenones



by formation of a C-Tl bond at electron rich C_1, followed by displacement (which should be facile) of the thallium(I) by methanol. If a 1-alkyl-2-naphthol is considered in its keto form

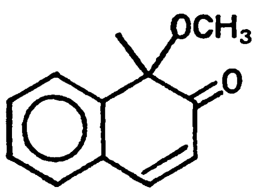


then this reaction becomes analogous (in overall terms only) to the formation of 2-hydroxy-cyclohexanone from cyclohexanone:



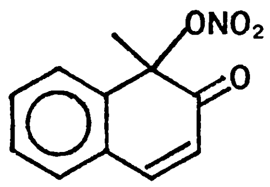
1-Methyl-2-naphthol was chosen as the most suitable 1-alkyl-2-naphthol for the proposed synthetic sequence, since it is stable to atmospheric oxygen (unlike 1-isopropyl-2-naphthol) and can be prepared in quantitative yield in one step from commercially available 1-formyl-2-naphthol[41].

Interaction of 1-methyl-2-naphthol with TTN gave 1-methoxy-1-methyl-2 (1H) naphthalenone (22) in 35% yield.



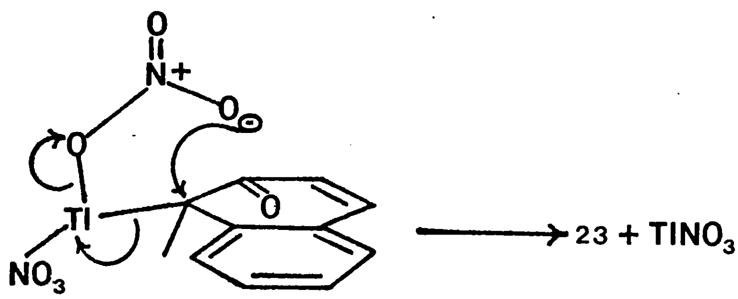
22

The product formed during the reaction had a PMR spectrum which seemed consistent with a mixture (1:1 when the reaction was performed at room temperature and about 2:1 at -40^{o}) of 22 and 1-methyl-1-nitrato-2 (1H) naphthalenone (23).



23

23 may be formed via a five-membered transition-state arising from the intermediate organothallium species:



The process is an intramolecular reaction and hence might be expected to compete effectively with intermolecular displacement of the thallium by methanol. Subsequent displacement of the nitrato group of 23 by methanol is still possible.

23 can be converted into 22 by treating the mixture with 5% sodium methoxide in methanol, a method suggested by Dr. A. McKillop[42]. However two species are present in the oil resulting from such treatment. In addition to 22, a white crystalline material of undetermined constitution, mp 165-7^{o} (24) was isolated. This compound was not in evidence in the mixture isolated from the reaction between TTN and 1-methyl-2-naphthol. Consequently, it must have arisen either by the

action of the methoxide ion on the mixture or by aerial oxidation, in which latter case some kind of dimeric structure seems probable. Repetition of both steps of the reaction sequence under an atmosphere of nitrogen should prove informative.

This reaction sequence is probably worthy of further study since it ought to be applicable to all 1-substituted-2-naphthols, and hence provide a relatively straightforward route into a variety of 1-alkyl and 1-aryl-1-methoxy-2 (1H) naphthalenones. The method does seem to be restricted to methyl ethers, however. Ethanol/triethyl orthoformate is not a suitable system for TTN[42], apparently as the ethanol is oxidised competitively. Presumably isopropanol would suffer the same drawback. t-Butanol should be inert to oxidation by Tl(III), but tri-t-butyl orthoformate has not been reported. Presumably steric crowding makes it unstable. Any attempt to synthesise aryl ethers would be fraught with possibilities of crossed products and coupling reactions.

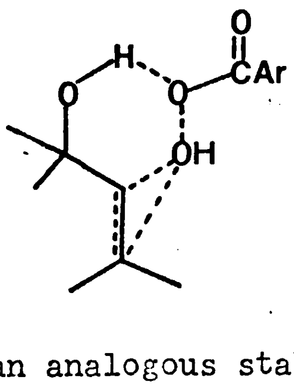
cis 1-Hydroxy-1-isopropyl-2 (1H) naphthalenone-3,4-epoxide (25)

The epoxidation of 13 under alkaline conditions gave only one epoxide, whose stereochemistry was assigned trans on the evidence of a base-catalysed rearrangement.[35]

However the determination of the stereochemistry of any epoxide isolated from 2 (1H) naphthalenones remained (and still remains) no easy matter. The cis 3,4-epoxide of 13 had not been reported, and we considered it worthwhile to attempt to synthesise this species in order to make a direct comparison with the trans epoxide 14.

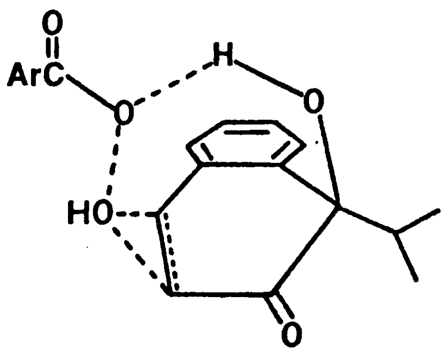
Peracids are standard reagents for epoxidising double bonds, but react only very slowly (if at all) with electron-poor olefins such as 13. If heat is employed to increase the reaction rate, then rapid O-O homolysis of the peracid leads to radical reactions. These have been shown to be slowed by the addition of small amounts of inhibitors which form stable radicals, and hence block the propagation step. Kishi[43] found that an unreactive olefin could successfully be epoxidised by m-chloroperbenzoic acid in dichloroethane at 90^{o} when small amounts (about 1% by weight of the peracid) of 2,2'-thiobis (4-methyl-6-t-butylphenol) were added. This inhibitor stopped all decomposition of the peracid for periods up to three hours.

Peracids were chosen as reagents since they give cis epoxides of allylic alcohols because of hydrogen bonding in the transition state[44]:



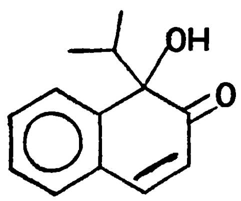
26

It was hoped that an analogous stabilisation would arise from the system present in 13 :

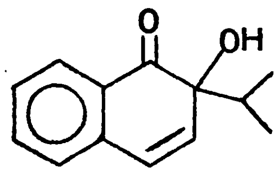


27

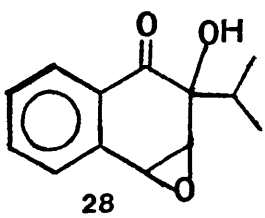
Reaction of 13 with m-chloroperbenzoic acid at room temperature was indeed slow. After 8 days only 6.5% conversion took place. When the reaction was performed at 90^{o} in the presence of the radical inhibitor, starch iodide papers showed that after 24h all the peracid had been consumed. Tlc assay of an aliquot showed a mixture comprising 30% of 13 and 21 (these compounds do not resolve chromatographically), 35% cis 2-hydroxy-2-isopropyl-1 (2H) naphthalenone-3,4-epoxide 28 and a compound of undetermined constitution, but which is not 25 and whose PMR spectrum is given on p.58.



13



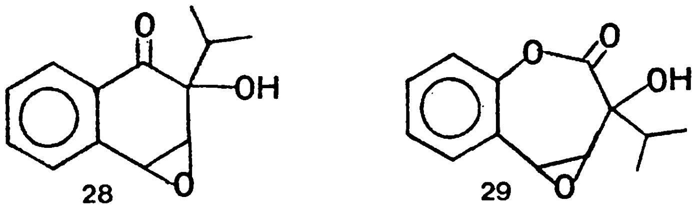
21



28

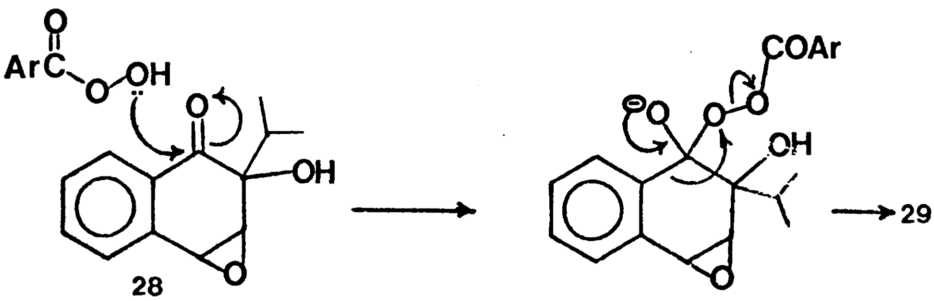
The structure of the major product (28) follows from its analysis and spectra. Its U.V. spectrum is typical of α tetralones. It was found to be identical to material made by Leppard by peracid epoxidation of isolated 21.

After another equivalent of peracid had been added and the residual mixture refluxed until tlc showed that 13 and 21 were consumed (24h), the mixture was then separated by column chromatography and found to comprise the compound mentioned above, 31% of 28 and 18% of a compound identified as 29:



28 31% 29 18%

The conclusion must be drawn that most of the mixture of 13 and 21 present before the addition of the second equivalent of peracid had been converted to 29, 2-keto-3-hydroxy-3-isopropyl-2,3-dihydro-benzo (f) oxepin-4, 5-epoxide. This species could be formed by a Baeyer-Villiger reaction on 28:



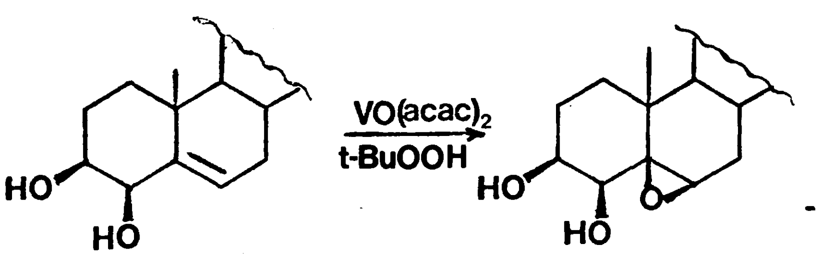
28

Alternatively, the Baeyer-Villiger could occur with 21, followed by epoxidation of the allylic bond. In any case, the bulk of the material isolated had undergone α-ketol rearrangement. The epoxide is cis to the hydroxyl group in 28 and probably also in 29, via transition state 26. The epoxidising reaction of peracids produces carboxylic acids which are better proton sources and this explains the α-ketol rearrangement which occurs, since 13 has already been noted to undergo such a rearrangement under acidic conditions (attempted ketal formation).

The long reflux period involved in this reaction led to considerable tarring.

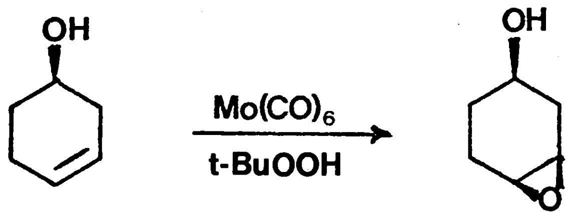
Attempts to inhibit α-ketol rearrangement by employing bases in the epoxidation in order to give the cis 3,4-epoxide of 13 a chance to form, were not successful. A blank run showed that under reaction conditions m-chloroperbenzoic acid is reduced to half its original concentration within 5 minutes in the presence of excess potassium carbonate.

Transition metal compounds and complexes such as vanadium acetylacetone are known to act as catalysts for epoxidation of olefins with a variety of peroxides and hydroperoxides[45]. These systems are often considered the analogues of peracids. Sharpless and Michaelson in their study of the epoxidation of a number of allylic and homoallylic systems[46] (employing VO $(acac)_2$ and $Mo(CO)_6$ with t-butyl hydroperoxide in refluxing benzene) found that allyl alcohols are stereospecifically epoxidised by these reagents:



and that stereoselectivity was greater than that found when peracids were employed.

Homoallylic systems were also epoxidised stereospecifically:

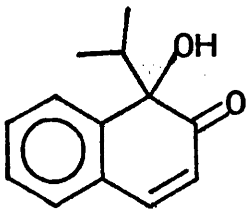
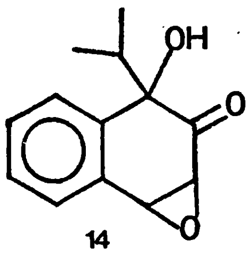
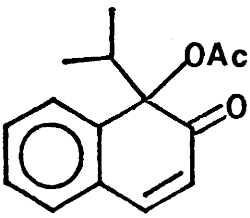
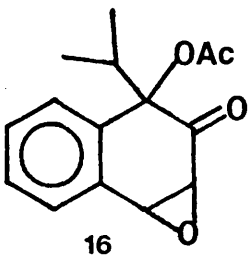
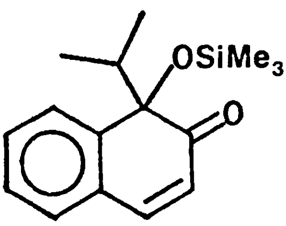
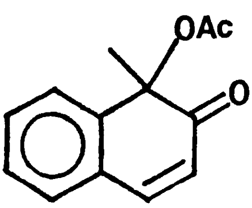


4-Hydroxy-cyclohexene is a system analogous to 13. These workers also noticed that molybdenum hexacarbonyl reacted more quickly with homoallylic systems than it did with allylic (unlike VO $(acac)_2$). No explanation of this interesting observation was offered.

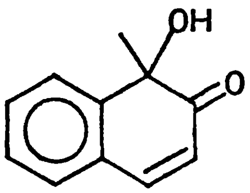
Despite the obscurity about the reason for stereospecificity in homoallylic systems, we considered the above $Mo(CO)_6$/t-butyl hydroperoxide system a reasonable synthetic proposition for the transformation 13 ⟶ 25. Unfortunately, however, after a 24h reflux (benzene), a 70% yield of 28 was obtained. Some tarring took place, but no other products were produced. 28 was isolated in a crystalline state from the mother liquors of the reaction.

Results of epoxidation of 2 (1H) naphthalenones with H_2O_2/base

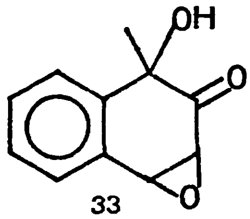
The following is a tabular survey of the results of epoxidising (alkaline hydrogen peroxide) the 2 (1H) naphthalenone systems synthesised in this work. In the absence of any better criterion (apart from 13 and 15) the stereochemistry of all the epoxides is assigned trans because the PMR signals of the epoxide protons closely resemble the AM system found in trans epoxide 14.

Substrate	Product(s)		
 13	 14	90%	Confirmed original work.
 15	 16	36% +14 43%	Ref.36 gives 16, 87%.
 30	14 55% +30 17%		
 31	33 70% + traces mp 120°		No acetoxy epoxide formed.

Substrate | Products

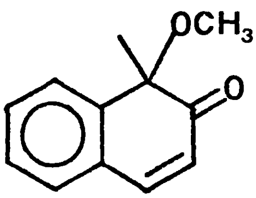


32

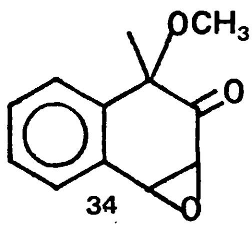


33

35% + unknown mp 115-8°



22



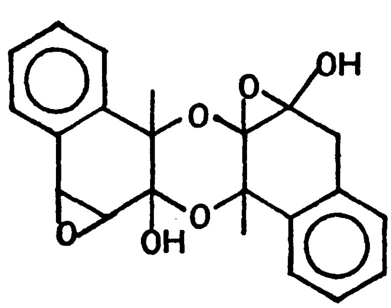
34

86%

In no case was any stereoisomeric cis epoxide detected.

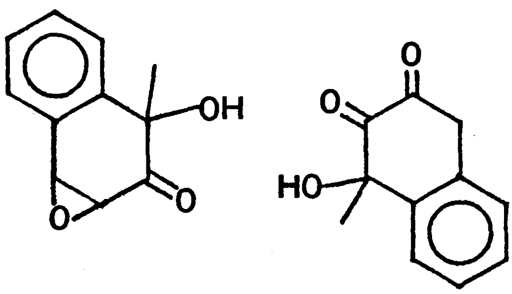
The failure of the silyl ether 30 to yield any silylated epoxide seems strange. This must imply that the hydroperoxide anion cannot approach either face of this enone and form a bond. It might be reasonable to say that the bulky silyl ether function blocks its face of the enone. But it cannot be said that the isopropyl group is capable of effecting such a blockage, since the only epoxide formed when 13 is epoxidised bears the epoxide oxygen on the same face as the isopropyl group. The only other way in which the absence of silylated epoxide might be explained is to assume that the rate of hydrolysis of the epoxy silyl ether is much greater than the rate of hydrolysis of 30 . There is no obvious reason why this should be so. Moreover, if this was the case, the rate of formation of the epoxy silyl ether might be expected to be comparable with the rate of epoxidation of 13 under similar conditions, since approach and bond formation by the hydroperoxy anion should not be very heavily dependent on the functionality on the opposite face of the molecule. The epoxidation of 13 was complete in less than 1h, while substantial amounts of starting material remained after 46h when 30 was epoxidised. The only viable explanation of the reaction seems to be that the silyl ether function of 30 is slowly hydrolysed by the hydroperoxy anion, and 13 so produced epoxidises relatively rapidly to give 14. Why no epoxy silyl ether is formed remains unclear.

Epoxidation of 1-hydroxy-1-methyl-2(1H) naphthalenone(32) gave only a 35% yield of the expected epoxide 33. A substantial quantity of a white solid mp 115-18^{o} was also obtained. No carbonyl band was present in its IR spectrum. The exact constitution of this material remains uncertain, but the following dimeric structure seems to fit the available data:



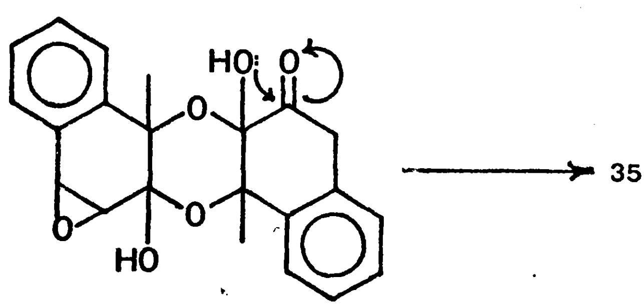
35

This species arises from (double) hemi-ketal formation between the following molecules:

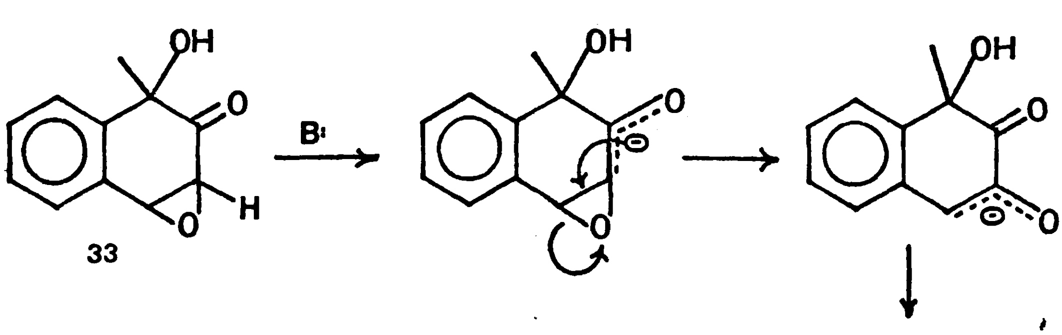


33 36

The α-ketol so produced could exist as the hydroxy epoxide:



The genesis of 36 might be explained by the following scheme:



33

36

The removal of a proton such as H_3 in 33 by base is not novel.

None of the other epoxidations tabulated gave rise to a product analogous to 35, though on the basis of the above scheme there is no reason why such a product should form only when C_1 bears methyl and hydroxyl groups. Only epoxidation of 1-acetoxy-1-methyl-2 (1H) naphthalenone 31 gave traces of a white solid mp about 120^o. This very minor product may be the same as 35, but the small quantities isolated make identification impossible.

There seems to be no good reason why only one (trans) epoxide should form in these reactions. Both faces of these enones are accessible and no great thermodynamic difference between the cis and trans isomers is evident from an inspection of their structures.

The conclusion which can be drawn from this work is that under alkaline conditions epoxidation of 1-alkyl-1-hydroxy-2 (1H) naphthalenones and their esters and ethers does give only one epoxide in which the epoxide oxygen is on the face opposite to the oxygen function originally present. Changing the size of the alkyl group from methyl to isopropyl has no effect on this unique outcome nor does changing the oxygen function from OH to OAc or OCH_3.

The problem of establishing a simple criterion or rule for assigning the stereochemistry of these epoxides remains unresolved. The use of NMR shift reagents[48] and of ^{13}C spectra proved unproductive of a solution.

Two shift reagents were employed (in $CDCl_3$ at 100 MHz; 0, 0.2, 0.4, 0.6M in shift reagent). $Eu(dpm)_3$ reacted with the trans epoxy ketol 14 and also with 13. No meaningful spectra were obtained with this reagent. When $Eu(fod)_3$ was employed, meaningful spectra were obtained, in which a plot of $\Delta\delta$ vs $[Eu(fod)_3]$ gave straight lines (all protons except aromatics and OH) for the trans epoxy ketol 14 and trans epoxy acetate 16. However, no obvious diagnostic criterion could be extracted from these spectra which could be related to their trans stereochemistry and applied to distinguish cis from trans isomers. Doubt about the exact locus (both in space and site of co-ordination) of the shift reagent with respect to the molecule makes interpretation difficult.

The ^{13}C spectra of trans epoxy ketol 14 and of ketol 13 were recorded, but interpreting the spectrum of 14 in terms of its stereochemistry proved difficult. Again no diagnostic link between the stereochemistry of the molecule and its spectrum could be discerned.

EXPERIMENTAL

Melting points (mp) were recorded on a Riechert microscope hot-stage, and are uncorrected.

Proton magnetic resonance (PMR) spectra were recorded on a Varian T-60 (60MHz) spectrometer in deuterochloroform with tetramethyl-silane (TMS) as internal standard at 0 ppm (δ).

Infra-red (I.R.) spectra were recorded on a Perkin-Elmer 257 spectrophotometer. Letters in parenthesis after a peak indicate its approximate appearance and relative intensity, (s) strong; (m) medium; (b) broad; (sp) sharp.

Mass spectra (MS) were recorded on a G.E.C.-A.E.I. M.S.12 spectrometer.

Ultraviolet (U.V.) spectra were recorded over the range 450-200 nm as solutions in methanol, and are quoted as λ MAX values in nanometers (nm) followed by log ϵ values in parenthesis. Only signals above 250 nm are quoted. A Pye-Unicam S.P.800 spectrometer was employed.

Analyses were carried out by Mrs. W. Harkness, and are given as percentages (%).

Preparative chromatography was conducted on plates coated with 1 mm of Merck Hf 254 fluorescent silica. Microslides were used for analytical tlc.

The organic phase of extractions was dried by shaking with saturated brine followed by anhydrous magnesium sulphate. Evaporation of solvents was conducted on a rotary evaporator (Büchi) under a water-pump vacuum over a

.../

hot-water bath.

Exceptions to any of these conditions are noted at the appropriate points.

Reduction of 1-hydroperoxy-1-isopropyl-2 (1H) naphthalenone(17) by dimethyl sulphide.

6g (0.0275 mole) of 1-hydroperoxy-1-isopropyl-2(1H) naphthalenone (17) (mp 136-40^{o}) was dissolved in 300 ml of methanol or ethanol in a 500 ml conical flask equipped with a magnetic stirrer, and 6 ml (0.082 mole) of dimethyl sulphide was added. After a few minutes stirring the stopper was removed and a nitrogen stream blown through until most of the excess dimethyl sulphide had been removed.

The reaction mixture was then poured into 500 ml of water in a conical flask and cooled in an ice-salt mixture. 1-Hydroxy-1-isopropyl-2 (1H) naphthalenone(13) separated as white crystals, which were filtered off and washed with distilled ice-water. After overnight dessication 5.02 g, 91%, mp 82-6^{o} (lit.[49] 88-9^{o}), was obtained. The spectral characteristics were identical to those of authentic material.

PMR: 0.9, two doublets, J = 7Hz, 6H, non-equivalent isopropyl CH_3; 2.1, septet J = 7Hz, 1H, CH_3-C<u>H</u>-CH_3; 3.9, singlet, vanishes on D_2O shake, 1H, OH; 6.2, doublet, J = 10Hz, 1H, H_3; 7.8 - 8.2, multiplet, 5H, aromatic.

IR: 3460 (s), OH; 1655 (s), C = O; 1620 (m), enone C = C; 770 (s), 4 adjacent aromatic H.

MS: m/e 202.

UV: 312 (3.72).

^{13}C: 16.79, $\underline{C}H_3CHCH_3$; 17.54, $CH_3CH\underline{C}H_3$; 40.58, $CH_3\underline{C}HCH_3$; 82.37, C_1; 123.14, C_9 or C_{10}; 127.07-129.72, aromatic C; 143.55, C_3; 145.77, C_4; 206.40, C_2.

These values are given as ppm downfield from TMS. ^1H decoupled. Recorded in $CDCl_3$.

Epoxidation of 1-isopropyl-1-hydroxy-2 (1H) naphthalenone(13) [36]

0.202g (10^{-3} mole) of 1-isopropyl-1-hydroxy-2 (1H) naphthalenone (13) was dissolved in 10 ml ethanol in a conical flask equipped with a magnetic stirrer. To this was added 0.1g of sodium carbonate in 1 ml water followed by 2 ml of 28% hydrogen peroxide.

The mixture was stirred for about 1h and 20 ml of water then added. The cloudiness which formed was dispersed by gentle warming. This solution was cooled overnight. The epoxide crystallised as a white solid which was filtered off and washed with cold water (145 mg; 67%; mp 72-3^o (lit.[36] 61-2^o)). Spectra of this compound were identical to those of authentic material. The mother liquors were extracted with ether and the ether layer washed and dried. Removal of the solvent left a clear oil (47.5 mg; 22%) whose spectra were also identical to authentic trans 1-isopropyl-1-hydroxy-2 (1H) naphthalenone-3,4-epoxide (14):

PMR: 0.9, non-equivalent isopropyl methyls, 6H, doublets, J = 7Hz; 2.6, septet, J = 7Hz, 1H, CH; 3.7 singlet, 1H, vanishes on D_2O shake, OH; 3.9 and 4.3, AM system, J = 4Hz, epoxide H; 7.2 - 7.7, multiplet, 4H, aromatic.

IR: 3401 (s,sp), OH; 1704 (s, sp), C = O, 762 (m, sp), 4 adjacent aromatic H.

MS: m/e 218

UV: 294 (2.24), 275.8 (2.69), 269 (2.72), 263.5 (2.65).

^{13}C: 15.75, $\underline{C}H_3CHCH_3$; 17.73, $CH_3CH\underline{C}H_3$; 37.77, $CH_3\underline{C}HCH_3$; 52.91, C_4; 60.10, C_3; 81.82, C_1; 127.78 - 129.17, aromatic C; 143.31, C; 193.20, C_2.

<u>Epoxidation of 1-acetoxy-1-isopropyl-2 (1H) naphthalenone(15)</u>[36]

102 mg (0.427×10^{-3} mole, mp 77 - 80°) of 1-acetoxy-1-isopropyl 2 (1H) naphthalenone(15) was dissolved in 8 ml ethanol and 0.3 m acetone. To this was added 0.015g (1.42×10^{-4} mole) of anhydrous AR sodium carbonate in 1.5 ml water, then 2 ml of 28% hydrogen peroxide solution.

The solution was heated to about 60° and stirred magnetically for 6h. The reaction mixture was then cooled and 15 ml water added. Further cooling on an ice-bath led to the formation of white crystals which were filtered off and washed with cold water (30 mg; 27%, mp 111-6°). Ether extraction of the mother liquors of the reaction gave a pale yellow oil (66 mg) which was separated by preparative chromatography (20% EtOAc in 60-80 petrol) into two bands. The more polar comprised 7 mg (ca 7%) of a white solid which on crystallisation from aq. ethanol melted 111-16° and was identical (tlc) to the white crystals of that melting point isolated previously. The less polar band (29 mg, 31%) was isolated as an oil whose spectra were identical to those of trans 1-isopropyl-1-hydroxy-2 (1H) naphthalenone-3,4 -epoxide(14).

The material mp 111-16^{o} was shown to be trans 1-acetoxy-1-isopropyl-2 (1H) naphthalenone-3,4-epoxide(16) by the following spectra:

PMR: 0.9, doublet, J = 7Hz, 3H, isopropyl CH_3; 1.0, doublet, J = 7Hz, 3H, isopropyl CH_3; 2.1, singlet, 3H, CH_3-CO; 2.45, septet, J = 7Hz, isopropyl CH; 3.8 and 4.3, AM system, J = 4Hz, epoxide H; 7.2 - 7.7, multiplet, 4H, aromatics.

IR: 1749 (s,sp), C = O acetate 1724 (s,sp), C = O ketone; 1235 (s,sp), C - O acetate; 767 (s,sp), 4 adjacent aromatic H.

MS: m/e 260.

UV: 304 (2.15), 275.5 (2.38), 269 (2.51), 264.5 (2.51).

<u>Epoxidation of 1-acetoxy-1-isopropyl-2 (1H) naphthalenone (15) at room temperature.</u>

62 mg (0.26×10^{-3} mole) of 1-acetoxy-1-isopropyl-2 (1H) naphthalenone(15) was dissolved in 5 ml ethanol and 0.2 ml acetone. To this solution was added 1 ml of 28% hydrogen peroxide and 0.01g of sodium carbonate dissolved in 1 ml water.

The reaction mixture was stirred at room temperature and its course followed on tlc. Under these conditions, the reaction was much slower than at 60^{o}. After 16h, spots corresponding to starting material, epoxy acetate, and trans hydroxy epoxide were evident. After about 48h all the starting material seemed to have been consumed, and 10 ml of water was added to the reaction mixture. A cloudiness which formed was dispersed by gentle warming, and overnight cooling led to the formation of white needles which were filtered off and washed with cold water (24.8 mg; 36%, mp 111-16^{o}). The properties of these crystals were identical in all respects to trans 1-acetoxy-1-isopropyl-2 (1H) naphthalenone-3,4-epoxide (16) isolated from the epoxidation at 60^{o}.

The aqueous mother liquors were then extracted with ether, washed and dried. Removal of the solvent left a clear oil (23 mg; 43%) whose spectra were identical to those of trans 1-hydroxy-1-isopropyl-2 (1H) naphthalenone-3,4-epoxide (14).

<u>Hydrolysis of trans 1-acetoxy-1-isopropyl-2 (1H) naphthalenone-3,4-epoxide (16)</u>[36]

30 mg (0.116 x 10^{-3} mole) of 1-acetoxy-1-isopropyl-2 (1H) naphthalenone-3,4-epoxide (16) was dissolved in 5 ml ethanol. To this was added 0.07g of AR sodium carbonate as a solution in 1 ml water. The temperature was raised to about 50^{o} and held overnight. Tlc then showed the reaction to be complete, only one product having formed. 10 ml of water was added, then the solution was extracted with ether, dried and evaporated to give a clear oil which solidified on standing. This solid was crystallised from aqueous ethanol to give 20.7 mg (0.95 x 10^{-4} mole; 82%), mp 72-3^{o} (lit[36] 61-2^{o}). This material was identical in all respects to trans 1-isopropyl-1-hydroxy-2 (1H) naphthalenone-3,4-epoxide (14).

<u>Preparation of 1-isopropyl-1-trimethylsilyloxy-2 (1H) naphthalenone (30)</u>

0.101g (0.5 x 10^{-3} mole) of 1-hydroxy-1-isopropyl-2 (1H) naphthalenone (13) was dissolved in 2 ml of N - TMS imidazole and allowed to stand at ambient temperature overnight.

The reaction mixture was poured into water (about 10 ml) then extracted with ether and the ether layer dried and evaporated to yield a yellow oil (152 mg) which tlc (30% EtOAc in 60-80 petrol) showed to comprise one substance less polar than the starting material, with the following characteristics:

PMR: 0.1, singlet, 9H, $(CH_3)_3Si$; 0.8, non-equivalent isopropyl methyls, doublets, J = 7Hz, 6H; 2.0, septet, J = 7Hz, 1H, CH; 6.1, doublet, J = 10Hz, 1H, H_3; 7.1 - 7.6, multiplet, 5H aromatic H.

IR: 2970 (m), aliphatic CH; 1685 (s), C = 0; 1252 (s,sp); 760 (m), 4 adjacent aromatic H. (thin film).

MS: m/e 274.

UV: 311 (3.79) (ethanol).

Reaction of 1-isopropyl-1-trimethylsilyloxy-2 (1H) naphthalenone (30) with sodium carbonate.

10 mg of 1-isopropyl-1-trimethylsilyloxy-2 (1H) naphthalenone (30) was dissolved in 1 ml ethanol and 10 mg of anhydrous sodium carbonate added as a solution in 1 ml water. This solution was stirred at ambient temperature for 48h, during which tlc showed no evidence of hydrolysis.

Epoxidation of 1-isopropyl-1-trimethylsilyloxy-2 (1H) naphthalenone (30).

137 mg (0.5×10^{-3} mole) of 1-isopropyl-1-trimethylsilyloxy-2 (1H) naphthalenone (30) (yellow oil) was dissolved in 5 ml ethanol with 0.2 ml acetone. To this was added 1 ml of 28%

hydrogen peroxide and 0.05g (0.47×10^{-3} mole) of anhydrous sodium carbonate dissolved in 0.5 ml water.

The solution was stirred at room temperature but no evidence of reaction was apparent (tlc) after 1h. After overnight stirring (19h) observable amounts of a more polar product appeared, but after 46h much starting material still remained.

The reaction mixture was then poured into 20 ml water and extracted with ether. The ether extract was dried and evaporation left a colourless oil (88 mg) which was separated by chromatography (30%EtOAc in 60-80 petrol). This gave two bands, the less polar (23 mg; 17% of starting material) being identical in all respects to starting 1-isopropyl-1-trimethylsilyloxy-2 (1H) naphthalenone(30). The more polar band (59.2 mg; 55%) was identical to trans 1-hydroxy-1-isopropyl-2 (1H) naphthalenone-3,4-epoxide(14) prepared previously.

<u>Reaction of 1-hydroxy-1-isopropyl-2 (1H) naphthalenone(13) with m-chloroperbenzoic acid</u>

a) At room temperature.

0.202g (10^{-3} mole) of 1-hydroxy-1-isopropyl-2 (1H) naphthalenone (13)was dissolved in 10 ml 1,2 dichloroethane (DCE) with 0.207g (1.2×10^{-3} mole) of m-chloroperbenzoic acid (MCPBA).

The reaction was stirred magnetically at room temperature and followed by tlc, which, after 8 days showed one product forming, but in very small amounts. The reaction mixture was then extracted with ether, the ether layer shaken with bicarbonate, washed and dried. Evaporation of the organic solvents left a pale yellow oil (0.2g) which was separated by chromatography (30% EtOAc in 60-80 petrol) to give two bands. The less polar band (0.18g) was shown by tlc and PMR to be a mixture of the starting material, 2-hydroxy-2-isopropyl-1 (2H) naphthalenone (21) and a third product. The more polar band (14.3 mg; 6.5% conversion) was subsequently shown by its PMR spectrum and tlc behaviour to be cis 2-hydroxy-2-isopropyl-1(2H)naphthalenone-3,4-epoxide (28).

b) At 90^{o} in the presence of 2,2' thiobis (4-methyl-6-t-butyl-phenol) (TBP)[43].

0.857g (4.25×10^{-3} mole) of 1-hydroxy-1-isopropyl-2 (1H) naphthalenone (13) was dissolved with 0.876g (5.1×10^{-3} mole; 1.2 equivalents) of MCPBA in 20 ml DCE. To this was added 10mg (approx.) of TBP (about 1% by weight of MCPBA).

The solution was heated to gentle reflux under a water condenser, and aliquots of the inhibitor (TBP) were added every 3h. The continuing presence of peracid in solution was confirmed at these times by means of starch-iodide papers.

After 24h starch-iodide tests were negative, tlc showed that products were forming but that starting material remained. A sample of the reaction mixture (100 mg) was extracted and separated by chromatography (20% EtOAc in 60-80 petrol). This gave three bands, the second of which corresponded in Rf and stain to the starting material (30%). The PMR spectrum showed it to be a mixture of starting material and 2-hydroxy-2-isopropyl-1 (2H) naphthalenone (21). The least polar band had the following spectrum.

0.6, doublet, J = 7Hz, 3H, CH_3; 1.1, doublet J = 7Hz, 3H, CH_3; 2.55, septet, J = 7Hz, 1H, $(CH_3)_2CH$; 4.2, singlet, vanishes on D_2O shake, OH; 6.2 and 6.5, AB system, J = 7Hz, epoxide H; 7.0 - 7.7, multiplet, 3H, H_5-H_7; 7.9 d x d, J = 8Hz, J_m = 2Hz, 1H, H_8.

The constitution of this material remains uncertain.

The most polar band (35%) was cis-2-hydroxy-2-isopropyl-1 (2H) naphthalenone-3,4-epoxide (28). The oil solidified on standing and was crystallised from petrol with a few drops of ethanol, mp 123-4^o (needles). (lit[36] 123^o)

PMR: 0.7, doublet, J = 7Hz, 3H, CH_3; 1.0, doublet, J = 7Hz, 3H, CH_3; 1.7, septet, J = 7Hz, 1H, $(CH_3)_2CH$; 3.8, singlet, vanishes on D_2O shake, 1H, OH, 3.9 and 4.1, AB system, J = 4Hz, epoxide H; 7.3 - 7.8, multiplet, 4H, aromatic.

IR: 3450 (s), OH; 1700 (s), C = O; 1606 (s, sp), aromatic C = C; 767 (s,sp), 4 adjacent aromatic H.

MS: 175 (M - 43).

UV: 291 (3.13), 250.7 (3.85) (ethanol).

$C_{13}H_{14}O_3$ requires: C 71.54 H 6.47

found: C 71.67 H 6.47

To the main body of the reaction mixture was added 0.875g (0.51 x 10^{-3} mole) of MCPBA and reflux was again commenced with addition of TBP at appropriate intervals. Within 24h all of the starting material had gone (tlc) and the reaction mixture was partitioned between ether and water, the ether layer extracted with bicarbonate, washed and dried.

Evaporation of the solvents left a yellow oil(1.09g) which was separated by column chromatography(Mallinckrodt Silicic acid 100 Mesh; 12% EtOAc in 60-80 petrol). This gave three eluates, the first and last of which were identical to the compound of undetermined constitution whose PMR spectrum is given on p. 58 and cis 2-isopropyl-2-hydroxy-1 (2H) naphthalenone-3,4 -epoxide(28)(31%) respectively. The intermediate eluate mp 109-10^{o}(needles from petrol with a few drops of ethanol)(18%) is assigned as 2-keto-3-hydroxy-3-isopropyl -2,3-dihydro-benzo(f)oxepin-4,5-epoxide(29), on the basis of the following:

PMR: 0.8, doublet, J=6.5 Hz, 3H, CH_3; 1.15, doublet, J=6.5 Hz, 3H, CH_3; 2.75, septet, J=6.5 Hz, 1H, $(CH_3)_2CH$; 4.0, singlet, 1H, vanishes on D_2O shake, OH; 4.3, doublet, J=2 Hz, 1H, epoxide; 5.6, doublet, J=2 Hz, 1H, epoxide; 7.3 - 8.0, multiplet, 4H, aromatic.

IR: 3520 (m, sp), OH; 1730(s, sp) C=O; 753 (s, sp), 4 adjacent H.

MS: m/e 234

UV: 272 (3.48), 265 (3.55), 260 (3.50)

$C_{13}H_{14}O_4$ requires: C 66.66 H 6.05
found: C 66.51 H 6.02

<u>Attempted epoxidation of 1-hydroxy-1-isopropyl-2(1H)naphthalenone(13) in the presence of bases.</u>[50]

a) Potassium carbonate.

101 mg(0.5x10^{-3}mole) of 13 was dissolved in 5ml DCE with 102 mg(0.6x10^{-3}mole) of MCPBA. To this was added 330 mg(2.4x10^{-3} mole of AR anhydrous potassium carbonate.

The mixture was heated to reflux with vigorous magnetic stirring, a few milligrams of TBP being added. After about 1h, starch-iodide tests showed that no peracid remained in the reaction mixture, and tlc showed only starting material. The reaction mixture was filtered and the filtrate partitioned between ether and water, the ethereal layer shaken with bicarbonate, washed and dried. Evaporation of the solvents left a pale yellow oil (quantitative recovery) whose PMR spectrum was consistent with a 1:1 mixture of starting material and 2-hydroxy-2-isopropyl-1 (2H) naphthalenone(21).

b) Disodium hydrogen orthophosphate.

An exactly similar experiment to (a) was performed with disodium hydrogen orthophosphate (AR anhydrous) as a base and again the peracid rapidly vanished (starch-iodide) from solution with complete absence of product formation. A quantitative mass balance was recovered.

<u>Approximate decomposition rate of MCPBA in the presence of potassium carbonate in refluxing DCE</u>

0.204g (1.2×10^{-3} mole) of MCPBA was dissolved in 3 ml DCE with a few milligrams of TBP to prevent thermal decomposition.

A quenching (reducing) solution was prepared by dissolving 1.66g (10^{-2} mole) of potassium iodide in 100 ml of distilled water. A thiosulphate standard of 0.2×10^{-2} M was prepared from a "Convol" vial. Starch indicator was employed for the titrations.

An oil bath was preheated to 90°, the flask containing the peracid solution inserted, and allowed to come to thermal equilibrium, as was a second solution prepared by adding 0.663g (4.8×10^{-3} mole) of anhydrous potassium carbonate to 17 ml of DCE. The peracid solution was transferred by means of a Pasteur pipette to the carbonate suspension, 1 ml aliquots being extracted at intervals of 1 minute, quenched in 2 ml of the potassium iodide solution and titrated against standard thiosulphate. Vigorous magnetic stirring ensured that reasonably accurate end points were obtained.

These titrations showed that the concentration of peracid under these conditions drops to less than half of the original in 5 min from 6.0×10^{-2} M to 2.6×10^{-2} M.

<u>Epoxidation of 1-hydroxy-1-isopropyl-2 (1H) naphthalenone (13) with t-butylhydroperoxide.</u>

a) With molybdenum hexacarbonyl[46].

To a solution of 1-hydroxy-1-isopropyl-2 (1H) naphthalenone (13)(202 mg; 10^{-3} mole) in 5 ml benzene was added 3.4 mg (1.27×10^{-5} mole) of molybdenum hexacarbonyl.

t-Butyl hydroperoxide was obtained by extracting Koch-Light pract. (70% + 30% di-t-butyl peroxide) into 15% KOH and precipitating the hydroperoxide by means of ammonium chloride.

166 mg (1.84×10^{-3} mole) of the liquid so obtained was added dropwise to the enone as a solution in 5 ml benzene and the reaction mixture purged with nitrogen and put under a positive pressure before being heated to reflux. The pale yellow solution was held at reflux for 24 hours when tlc showed that all the starting material had been consumed. Evaporation to about half the volume resulted in the formation of white crystals (0.154g; 70%) which were filtered off and crystallised

from petrol with a few drops of ethanol, mp 123-4°. The spectral properties and tlc behaviour of this material were identical to those of cis 2-hydroxy-2-isopropyl-1(2H) naphthalenone-3,4-epoxide(28) already described. A mixed melting point of the material obtained in this reaction with that obtained previously exhibited no depression.

b) With Triton B[51].

To 5 ml of dry AR benzene was added 0.2 ml (2×10^{-3} mole) of t-butyl-hydroperoxide (purified as described in (a) above) and 2 drops (about 1% molar) of Triton B (40% w/w in methanol). A solution of 202 mg (10^{-3} mole) of 1-hydroxy-1-isopropyl-2 (1H) naphthalenone in 5 ml benzene was added to the hydroperoxide, the resultant solution becoming pale yellow. The reaction mixture was raised to reflux and followed on tlc, but no reaction appeared to be taking place. After 5 days only one spot, corresponding to starting material, was evident.

<u>Synthetic approaches to 1-isopropyl-1-methoxy-2 (1H) naphthalenone (18)</u>

a) 202 mg (10^{-3} mole) of 1-hydroxy-1-isopropyl-2 (1H) naphthalenone (13) was dissolved in 10 ml anhydrous ether and cooled to -70° on a methanol/dry-ice bath. To this solution was added 0.4 ml (1.1×10^{-3} mole) of n-butyl lithium (20% solution in hexane) followed by 0.14 ml (2×10^{-3} mole) of methyl iodide.

The solution was stirred at -70° for about 30 min but tlc showed no evidence of reaction. Another 1.1 equivalent of n-butyl lithium was added and the solution allowed to rise to room temperature. After 60 min at room temperature, tlc showed that the starting material had been consumed. The reaction mixture was partitioned between ether and water, the ether layer dried and evaporated to yield a brown oil (0.28g) which on standing formed into whitish crystals. These were purified by crystallisation from 60-80 petrol. 50 mg of these crystals were chromatographed (50% ethyl acetate in 60-80 petrol) giving two bands of which the less polar (6.1 mg) was not further studied. The more polar band (28.3 mg) had a PMR spectrum consistent with a mixture of diols (see Results & Discussion for details).

b)[52] To a hexane-washed suspension (60% in oil) of sodium hydride (44 mg; 10^{-3} mole) in 5 ml of dry THF was added 202 mg (10^{-3} mole) of 1-hydroxy-1-isopropyl-2 (1H) naphthalenone (13)as a solution in 5 ml dry THF.

The colour of the solution immediately changed from pale yellow to deep maroon, with gas evolution. 0.3 ml (4×10^{-3} mole) of methyl iodide was then added and the reaction allowed to stir overnight (22h) at room temperature, then partitioned between ether and water. The aqueous layer assumed the maroon colour. The pale-yellow ethereal layer was dried and evaporated to yield a brown oil (0.16g) which was separated by chromatography (20% EtOAc in 60-80 petrol) into two bands. The less polar of these (51 mg) had the following spectra:

PMR: 0.8, doublet, J = 6.5Hz, 3H, CH_3; 1.05, doublet, J = 6.5Hz, 3H, CH_3; 2.15, septet, J = 6.5Hz, 1H; $(CH_3)_2CH$; 3.2, singlet, 3H, OCH_3; 6.2, doublet, J = 10Hz, 1H, HC = CH; 6.9, doublet, J = 10Hz, 1H, CH = CH; 7.1 - 7.8, multiplet, 3H, aromatic

H_5-H_7; 8.1, dxd, Jo = 7.5Hz, Jm = 2Hz, 1H, H_8.

MS: m/e 216.

This is taken to be consistent with 2-isopropyl-2-methoxy-1 (2H) naphthalenone. The more polar of the two bands (82 mg) had a PMR spectrum consistent with a mixture of starting material 13 and 2-hydroxy-2-isopropyl-1 (2H) naphthalenone (21) but with a strong singlet at 3.1, suggesting a methyl ether and a doublet, J = 10Hz at 6.15, distinguishable from the doublet corresponding to H_4 of the starting material. These peaks seem to be consistent with the presence of 1-isopropyl-1-methoxy-2 (1H) naphthalenone (18) in the mixture. All attempts to resolve this mixture chromatographically using a variety of solvents proved fruitless.

c) Di-isopropylamide/methyl iodide/THF[53]

A solution of di-isopropylamide (ca 1M) was prepared by dissolving 0.154 ml (1.1×10^{-3} mole) of di-isopropylamine in 1 ml dry THF then adding 0.3 ml (1.1×10^{-3} mole) of n-butyl lithium (20% solution in hexane) at ambient temperature. This solution was cooled to -78^{o} on a drikold -acetone bath, and 202 mg (10^{-3} mole) of 1-hydroxy-1-isopropyl-2 (1H) naphthalenone (13) was added as a solution in 1 ml THF, followed immediately by 0.075 cc (1.2×10^{-3} mole) of methyl iodide and 0.23 ml of hexamethylphosphoric triamide (HMPT) in 1 ml THF.

The resultant solution was stirred at -70^{o} for 2h and at -40^{o} for a further 1h, finally being allowed to rise to room temperature before being poured into water and extracted with ether. The ether extract was dried and evaporated to leave a pale yellow oil (0.214g) whose PMR spectrum was consistent with starting material and 2-hydroxy-2-isopropyl-1 (2H) naphthalenone(21). No evidence of methylated material was found.

Attempts to mask the carbonyl group of 1-hydroxy-1-isopropyl-2 (1H) naphthalenone(13)

a) Ethylene glycol/p-toluene sulphonic acid (PTSA)[39]

202 mg (10^{-3} mole) of ketol 13 was dissolved in 15 ml of dry benzene with 1.6g (2.56×10^{-2} mole) of dry redistilled ethylene glycol and 5 mg of PTSA.

The mixture was refluxed for 4h when tlc showed a large number of products and considerable tarring. The reaction mixture was partitioned between ether and water and the ether layer dried and evaporated to leave a brown tarry oil which proved intractable. The PMR spectrum of this material was uninformative.

b) Ethylene glycol/oxalic acid/acetonitrile[40].

202 mg (10^{-3} mole) of 1-hydroxy-1-isopropyl-2 (1H) naphthalenone (13) was dissolved in 15 ml of acetonitrile with 0.85g (0.94×10^{-2} mole) of anhydrous oxalic acid and 2.26g (3.65×10^{-2} mole) of dry, redistilled ethylene glycol.

The solution was stirred at room temperature, slight heat being needed to dissolve the last traces of oxalic acid. After 48h tlc showed no evidence of reaction and the acetonitrile was removed under vacuum into a toxic-solvent trap. The residue was rinsed into a separating funnel first with ether then water and partitioned, the ether layer dried and evaporated to yield a pale yellow oil (0.18g; 90% recovery) which PMR showed to be a mixture of starting material 13 and 2-hydroxy-2-isopropyl-1 (2H) naphthalenone (21)

Synthetic approaches to 1-hydroxy-1-methyl-2 (1H) naphthalenone (32)

Periodate oxidation of 1-methyl-2-naphthol[29a].

a) Using 100% excess periodate

0.158g (10^{-3} mole) of 1-methyl-2-naphthol was placed in a 100 ml conical flask with 15 ml distilled water, and sufficient acetone was added to dissolve the naphthol (about 10 ml). To this mixture was added 0.428g (2×10^{-3} mole) of sodium meta periodate in 2 ml water.

The reaction was stirred at room temperature and followed on tlc. After 3h substantial amounts of starting material remained and the reaction was left stirring overnight (total reaction time 21h) in order to consume all the 1-methyl-2-naphthol.

The amber solution was then partitioned between ether and water, the ether layer dried and evaporated to yield a brown oil (146 mg) which partly crystallised. These crystals were filtered off (19 mg) and the residual oil extracted with bicarbonate. Acidification of the bicarbonate extract led to the precipitation of a white solid (18 mg, total yield 20%) which was recrystallised from aq. ethanol in combination with the first crop of crystals to give needles mp 141-3^{o} (lit[54] 143-4^{o}). This compound is assigned as o-acetyl-cinnamic acid on the basis of the following data:

PMR: 2.6, singlet, 3H, CH_3COAr; 5.95, doublet, J = 12Hz, 1H, $CH = CH\text{-}CO_2H$; 7.2 - 7.9, multiplet, 5H, aromatic + $CH = CHCO_2H$; 10.65, broad, vanishes on D_2O shake, 1H, CO_2H.

IR: 2950(b), OH acid; 1700 (s,sp) C = O, acid; 1680 (s,sp), C = O aromatic ketone; 1630 (s,sp), 1572 (m, sp), both C = C; 760 (m,sp), 4 adjacent aromatic H.

MS: 145; M-45.

UV: 290 (shoulder, 3.34).

The neutral oily residue (100 mg) of the bicarbonate extraction was chromatographed (30% EtOAc in 60-80 petrol) which gave, apart from base-line residue, one main band and a second less polar band which was not present in sufficient amounts to characterise, but probably comprised residual 1-methyl-2-naphthol.

The main band (52 mg; 30%) was a pale yellow oil, which solidified on standing and was crystallised from aq. ethanol as white/pale yellow plates, mp 85 - 90^{o} (lit.[28,34] 88-9^{o}). This compound, assigned as 1-hydroxy-1-methyl-2 (1H) naphthalenone (32) had the following spectra.

PMR: 1.55, singlet, 3H, CH_3; 3.7, sharp singlet, 1H, vanishes on D_2O shake, OH; 6.2, doublet, J = 10Hz, 1H, H_3; 7.2 - 7.7, multiplet, 5H, H_4 and aromatic H.

IR: 3419 (s,sp), OH; 1658 (s,sp), C = O; 768 (m,sp), 4 adjacent aromatic H.

MS: m/e 174

UV: 308 (3.78)

b) Using 5% molar excess periodate.

0.158g (10^{-3} mole) of 1-methyl-2-naphthol was dissolved in a solution of 10 ml acetone and 10 ml water. 0.235g (1.05×10^{-3} mole) of sodium meta periodate was added as a solution in 5 ml water. The mixture was stirred at room temperature until starch-iodide tests showed that all the periodate had been consumed (22h). Tlc of the amber-yellow solution showed that substantial amounts of 1-methyl-2-naphthol remained in the amber solution.

c) Wessely acetoxylation of 1-methyl-2-naphthol.

158 mg (10^{-3} mole) of 1-methyl-2-naphthol was dissolved in 10 ml glacial acetic acid with 0.668g (1.5×10^{-3} mole) of freshly crystallised lead tetra-acetate (white needles from glacial acetic acid/acetic anhydride). 2 ml of acetic anhydride was also added.

The reaction mixture was stirred at room temperature for 30 min when tlc showed that all the 1-methyl-2-naphthol had been consumed, and that one (more polar) product had formed.

Ethylene glycol was added to destroy residual LTA, followed by saturated aq sodium bicarbonate (care!). When the acetic acid had been neutralised the solution was saturated with sodium chloride and extracted repeatedly with ether. The combined ether layers were washed with water, dried and evaporated to give a pale yellow crystalline solid. This was recrystallised from aq methanol as white plates

(192 mg; 89%) mp 131-3^{o} (lit.[28] 129 - 30^{o}). 1-Acetoxy-1-methyl -2 (1H) naphthalenone(31) had the following characteristics:

PMR: 1.5, singlet, 3H, CH_3; 2.1, singlet, 3H, CH_3COO; 6.3, doublet, J = 10Hz, 1H, H_3; 7.2 - 7.6, multiplet, 5H, aromatics + H_4.

IR: 1749 (s,sp), C = 0 acetate; 1685 (s,sp) C = 0 ketone; 1253 (s), 1242 (s), both C - 0 acetate; 765 (s,sp), 4 adjacent aromatic H.

MS: m/e 216.

UV: 304 (4.0).

Hydrolysis of 1-acetoxy-1-methyl-2 (1H) naphthalenone(31).

0.218g (10^{-3} mole) of 1-acetoxy-1-methyl-2 (1H) naphthalenone (31) was dissolved in 5 ml ethanol and 0.53g (5×10^{-3} mole) of anhydrous sodium carbonate added as a solution in 2 ml water.

The reaction mixture was heated to about 40^{o} and held at that temperature under a water condenser for 6h, when tlc showed the reaction to be complete.

The reaction mixture was cooled and sufficient water added to dissolve the carbonate residues. The solution was then saturated with solid sodium chloride and extracted thoroughly with ether, the combined ether layers dried and evaporated to give a clear oil which slowly formed into crystals. These grew from hexane (aqueous methanol can also be employed) as white plates (160mg; 92%) mp 88-90^{o} (lit[28, 34] 88-9^{o}). The spectral properties of this material were identical to those of 1-hydroxy-1-methyl-2 (1H) naphthalenone(32) previously isolated.

Epoxidation of 1-hydroxy-1-methyl-2 (1H) naphthalenone (32).

0.181g (1.04 x 10^{-3} mole) of 1-hydroxy-1-methyl-2 (1H) naphthalenone (32) was dissolved in 5 ml ethanol and 0.55 g (5.2 x 10^{-3} mole) of anhydrous sodium carbonate added as a solution in 2 ml water, followed by 1 ml of 28% hydrogen peroxide.

The mixture was stirred at room temperature and after a few minutes the faint yellow colour of the solution was discharged. Tlc showed only one spot (Rf identical to starting material but stain distinctively different).

Sufficient water was added to dissolve the carbonate then the solution was saturated with sodium chloride. A white solid (35) precipitated. This was filtered off and washed thoroughly with cold water (98 mg, mp 115-18^{o}). This compound had the following characteristics:

PMR: 1.7, two nearly equivalent singlets, 6H; 2.7, doublet J = 4Hz, 1H, epoxide; 3.1, broad, vanishes on D_2O shake, 1H, OH; 3.8, doublet, J = 4Hz, 1H, epoxide; 4.2, singlet, 2H; 6.0, sharp singlet, vanishes on D_2O shake, 1H, OH; 7.4 - 7.8, multiplet, 6H; aromatic.

IR: 3415 (s,sp), 3280 (s), both OH; 1150 (s), 1090, 1078, 1065, 1042, 1028, 1012, all (s); 908(s); 805 (m); 762 (s).

MS: m/e 380

UV: 300, 275, 268, 263

$C_{22}H_{20}O_6$ requires C 69.46 H 5.30
found C 70.61 H 5.95

The filtrate was then extracted with ether (3 x 2 ml), dried and evaporated to yield a colourless oil (70 mg, 35%) which was assigned as 1-hydroxy-1-methyl-1 (2H) naphthalenone-3,4-epoxide (33) on the following data:

PMR: 1.65, singlet, 3H, CH_3; 3.7 broad, 1H, vanishes on D_2O shake, OH; 3.8, doublet, J = 4Hz, 1H, H_4, 4.2 doublet, J = 4Hz, 1H, H_3; 7.2 - 7.7, multiplet, 4H, aromatic.

IR: 3430 (s,b), OH; 3030 (w,b), aromatic H; 2965 (w,sp) 2925 (w,sp)both CH_3 stretch; 1720 (s,sp), C = O; 1182 (m, sp), C - O stretch; 760 (s,sp), 4 adjacent aromatic H. (thin film)

MS: m/e 190.

UV: 269 (2.64), 261 (shoulder, 2.65).

$C_{11}H_{10}O_3$ requires C 69.46 H 5.30

found C H

Epoxidation of 1-acetoxy-1-methyl-2 (1H) naphthalenone (31)

0.109g (0.5 x 10^{-3} mole) of 1-acetoxy-1-methyl-2 (1H) naphthalenone (31) was dissolved in 10 ml ethanol and 0.265g (2.5 x 10^{-3} mole) of anhydrous sodium carbonate added as a solution in 1 ml water with 1 ml 28% hydrogen peroxide.

The reaction was stirred at room temperature and tlc showed that within 4h all the starting material had been consumed. The residual hydrogen peroxide was destroyed by the addition of aq potassium iodide solution, and the reaction mixture thoroughly extracted with ether, saturated with sodium chloride and extracted again. The combined ether layers were dried and evaporated to give a clear oil (67 mg, 70%), whose spectra were identical to those of 1-hydroxy-1-methyl-2 (1H) naphthalenone-3,4-epoxide (33) previously isolated. No evidence of acetylated material was found.

The aqueous phase of the extraction was acidified and re-extracted with ether. The ether was then dried and evaporated to give about 10 mg of crystalline material melting in the region of 120^{o}. This material was not further studied, but is possibly the same compound (35) isolated in the epoxidation of 1-hydroxy-1-methyl-2 (1H) naphthalenone (32).

Synthetic approaches to 1-methoxy-1-methyl-2 (1H) naphthalenone (22) employing thallium trinitrate trihydrate (TTN)[30].

a) At room temperature.

To a solution of 1-methyl-2-naphthol (170 mg; 1.08×10^{-3} mole) in 5 ml of a 1:1 mixture of trimethylorthoformate and methanol was added 0.53g (1.19×10^{-3} mole) of thallium trinitrate trihydrate ($Tl(NO_3)_3 \cdot 3H_2O$) in 5 ml of the methanol/orthoformate solution.

A white precipitate formed at once from the yellow solution and tlc showed that all the 1-methyl-2-naphthol had been consumed.

The solution was then pipetted off from the $TlNO_3$ precipitate, which was rinsed with ether and the rinsings combined with the reaction solution and allowed to stand in contact with water in order to hydrolyse the trimethylorthoformate present.

The resultant solution was partitioned and the aqueous layer extracted with ether. The combined ether extracts were washed, dried and evaporated to leave a yellow oil (207 mg). PMR of this oil appeared to indicate a mixture (approximately 1:1) of 1-methoxy-1-methyl-2 (1H) naphthalenone(22) and one other compound, which was tentatively assigned as 1-methyl-1-nitrato-2 (1H) naphthalenone (23). The bands corresponding to this latter compound were: 1.55, singlet, 3H, CH_3; 6.3, doublet, J = 9.5Hz, 1H, H_3; 7.2 - 7.7, aromatic H. All the remaining bands were subsequently assigned with certainty to 22 .

The yellow oil (mixture) was then stirred at room temperature for 1h with 5% sodium methoxide in methanol, partitioned between ether and water, the ether extract dried and evaporated to give a second yellow oil whose PMR indicated that the 1-nitrato species (23) had been consumed. Those signals corresponding to 1-methoxy-1-methyl enone (22) remained, but a new set of peaks, which had been entirely absent from the spectrum of the original mixture were evident. When this second yellow oil was allowed to stand in ether solution deposition of white crystals (70 mg) took place. These were filtered off and recrystallised from petrol with a few drops of ethanol, mp 165-7^{o}. This compound had the following characteristics:

PMR: 1.55, singlet, 3H, CH_3; 4.0, singlet, 3H, CH_3; 5.7, singlet, 1H; 7.25 - 8.0, multiplet, 5H, aromatic; 9.2, singlet, 1H, vanishes on D_2O shake.

IR: 3240 (b,m), OH; 1635 (s,sp); 1608 (s), 1558 (s); 1240 (s,sp), 1226 (s,sp); 1093 (m, sp); 1069 (m,sp); 968 (m,sp); 815 (m, sp); 804 (m, sp); 769 (m, sp); 755 (m,sp); 718 (m, sp).

MS:

UV: 304

Analysis gave: C 63.9 H 5.82.

After this compound mp 165-7^{o} had been filtered off, the residual oil (116 mg) was chromatographed (35% EtOAc in 60/80 petrol). This gave one main band (81 mg) and a second (more polar) band. The main band was a yellow oil which solidified on standing into crystalline masses. Recrystallised from hexane as pale yellow nucleii mp 67-8^{o} (71 mg; 35% overall yield). 1-Methoxy-1-methyl-2 (1H) naphthalenone (22) had the following characteristics:

PMR: 1.5, singlet, 3H, CH_3; 3.08, singlet, 3H, OCH_3; 6.2, doublet, J = 10Hz, 1H, H_3; 7.3 - 7.7, multiplet, 5H, aromatics + H_4.

IR: 3040 (w), aryl C - H; 2980 (m,sp), 2912 (m,sp), both CH_3 stretch; 2812 (m,sp), OCH_3; 1665 (very s), C = O; 1617 (s,sp), 1565 (m,sp), both C = C; 1440(m), 1392 (m,sp), CH_3 deformation; 1100 (s) C - O stretch; 760 (s,sp), 4 adjacent aromatic H. (Thin film).

MS: m/e 188.

UV: 312 (3.71)

$C_{12}H_{12}O_2$ requires: C 76.57 H 6.43

found: C 76.51 H 6.63

b) At -30^{o}

An identical reaction to that described in a) above was performed, but with the reactants cooled to -78^{o} in a dry-ice/acetone bath. No precipitate of thallous nitrate was seen until the temperature was allowed to rise to -40^{o}. The bath temperature was held between -40^{o} and -30^{o} for 1h, during which period the precipitate of thallous nitrate was substantially augmented. The temperature was then allowed to rise to ambient, and the reaction solution worked-up, in the way described in a). A yellow oil resulted, whose PMR spectrum differed from that of the material isolated in a) and assigned as a mixture of 1-methoxy-1-methyl enone (22) and 1-methyl-1-nitrato enone (23) only in the relative intensities of the two sets of peaks. In the mixture from the low temperature reaction the peaks assigned to the 1-nitrato compound 23 were present to the extent of about half the intensity of the peaks corresponding to 1-methoxy-1-methyl enone (22).

Treatment of the mixture with 5% sodium methoxide discharged the peaks corresponding to the 1-nitrato species 23 but as in a) appreciable quantities of the white solid mp 165-70^{o} were produced.

<u>Epoxidation of 1-methoxy-1-methyl-2 (1H) naphthalenone (22).</u>

To a methanolic solution of 1-methoxy-1-methyl-2 (1H) naphthalenone (22) (94 mg, 0.5×10^{-3} mole in 4 ml methanol) was added an aqueous solution of 1 ml 28% hydrogen peroxide and 64 mg (1.2×10^{-3} mole) of anhydrous sodium carbonate in 1 ml water.

A precipitate of sodium carbonate formed immediately, and tlc showed the reaction was complete within 5 min (it is probably almost instantaneous). Only one product seemed to have formed.

The reaction mixture was then poured into water and extracted with ether. The aqueous phase was then saturated with sodium chloride and re-extracted. The combined ether extracts were washed with water, dried and evaporated to yield a white crystalline solid (88 mg, 86%) mp 111-4^{o}. Recrystallised from hexane and a few drops of ether mp 116-7^{o}. This material assigned as 1-methoxy-1-methyl-2 (1H) naphthalenone-3,4-epoxide was the only product formed and had the following characteristics:

PMR: 1.65, singlet, 3H, CH_3; 3.0, singlet, 3H, OCH_3; 3.8, doublet, J = 4Hz, 1H, H_4; 4.25, doublet, J = 4Hz, 1H, H_3, 7.3 - 7.7, multiplet, 4H, aromatics.

IR: 1725 (s,sp), C = O; 1232 (m,sp), C - O; 770 (s,sp), 4 adjacent aromatic H.

MS: m/e 204.

UV: 315 (1.89),276 (2.4), 270 (2.51), 264.5 (2.49).

$C_{12}H_{12}O_3$ requires: C 70.58% H 5.92%

found: C 70.28% H 6.02%

<u>Synthesis of 1-ethyl-2-naphthol</u>[55]

400 mg (2.15 x 10^{-3} mole) of 1-acetyl-2-naphthol (mp 63-5^{o} from petrol) was dissolved in 10 ml of dry xylene in a 50 ml 3-necked flask equipped with a magnetic stirrer and a nitrogen inlet.

The flask was cooled on ice and 2 ml of sodium dihydrobis

(2 methoxyethoxy) aluminate (SDA; 70% in benzene; 6.9×10^{-3} mole) added dropwise with vigorous magnetic stirring and a steady nitrogen flow. The strong yellow colour which formed initially subsided, and when the solution was clear and colourless a further 10 ml of dry xylene was added and the apparatus placed under a water condenser. The temperature was raised to reflux (with a pause at 80° to allow the benzene to distil out) and held there for 2h.

The reaction mixture was cooled and residual SDA destroyed by the addition of dilute sulphuric acid. The solvent was decanted off the precipitated solids into a separating funnel where it was extracted (2 x 50 ml) with 15% aqueous KOH. Both the xylene solution and the base were thoroughly purged with nitrogen before being allowed to come in contact.

The KOH layer was then acidified as quickly as possible, and a white flocculent precipitate of 1-ethyl-2-naphthol formed (260 mg; 70%, mp = 103-4° lit[56] 103-4°). This compound had the following characteristics:

PMR: 1.25, triplet, J = 7.5Hz, 3H, CH_3CH_2; 3.05, quartet, J = 7.5Hz, 2H, CH_3CH_2; 4.5, broad, vanishes on D_2O shake, 1H, OH; 6.8 - 8.0, multiplet, 6H, aromatics.

IR: 3430 (s,b), OH; 1622 (m,sp), 1597 (s,sp), both aromatic C = C; 1194 (s,sp); 1140 (s,sp), C - O stretch; 811 (s,sp), 2 adjacent aromatic H; 745 (s,sp), 4 adjacent aromatic H.

MS: m/e 172

UV: 333 (2.7), 326 (shoulder, 2.62), 290 (2.86), 279 (2.95), 269 (2.84).

Synthesis of 1-acetoxy-1-ethyl-2 (1H) naphthalenone

1-ethyl-2-naphthol (200 mg; 1.16×10^{-3} mole) was dissolved in a mixture of 7 ml of dry glacial acetic acid and 3 ml of acetic anhydride. To this solution was added 0.52g (1.28×10^{-3} mole) of freshly crystallised lead tetra-acetate (LTA). The solution was pale yellow.

The reaction mixture was stirred at room temperature and tlc showed the reaction to be complete within 45 min, only one product (slightly more polar) forming.

The reaction was terminated by the addition of ethylene glycol followed by 10 ml water. Solid sodium bicarbonate was carefully added to neutralise the acetic acid, then the resulting solution was extracted with ether (3 x 50 ml) and the ethereal layer washed with water, dried and evaporated to give a red-brown oil which grew from aqueous ethanol as white crystals, mp 88-90^{o} (190 mg, 72%). 1-Ethyl-1-acetoxy-2 (1H) naphthalenone had the following spectra:

PMR: 0.7, triplet, J = 8Hz, 3H, CH_3CH_2; 2.0, quartet, J = 8Hz, 2H, CH_3CH_2; 2.1, singlet, 3H, CH_3CO; 6.3, doublet, J = 10Hz, 1H, H_3; 7.2 - 7.5, 5H, aromatics + H_4.

IR: 1740 (s,sp), C = O acetate; 1665 (s,sp), C = O ketone; 1250 (s,sp) C - O acetate.

MS: m/e 230

UV: 308.5 (4.07).

$C_{14}H_{14}O_3$ requires: C 73.03 H 5.92

found: C H

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